CAPSID POLYPEPTIDES AND METHODS OF USE THEREOF

1. CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of U.S. provisional application no. 63/551,418, filed February 8, 2024, and U.S. provisional application no. 63/707,055, filed October 14, 2024, the contents of each of which are incorporated herein in their entireties by reference thereto.

2. SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML Sequence Listing, created on February 6, 2025, is named DYN-005WO_SL.xml and is 97,346 bytes in size.

3. BACKGROUND

[0003] Dependoparvoviruses, e.g., adeno-associated dependoparvoviruses, e.g., adeno-associated viruses (AAVs), are of interest as vectors for delivering various payloads to cells, including in human subjects.

4. SUMMARY

[0004] The present disclosure relates, in part, to improved dependoparvovirus capsid polypeptides, such as VP1, VP2 and/or VP3 capsid polypeptides, methods of producing a dependoparvovirus comprising capsid polypeptides, compositions for use in the same, as well as viral particles produced by the same. In certain aspects, the present disclosure relates to viral particles comprising the improved dependoparvovirus capsid polypeptides, with increased central nervous system (CNS) biodistribution and/or transduction as compared to viral particles, e.g., without the mutations in the improved dependoparvovirus capsid polypeptides. In certain aspects, the present disclosure relates to viral particles comprising the improved dependoparvovirus capsid polypeptides, with increased muscle biodistribution and/or transduction as compared to viral particles, e.g., without the mutations in the improved dependoparvovirus capsid polypeptides. In certain aspects, the present disclosure relates to viral particles comprising the improved dependoparvovirus capsid polypeptides, with increased skeletal muscle biodistribution and/or transduction as compared to viral particles, e.g., without the mutations in the improved dependoparvovirus capsid polypeptides. In certain aspects, the present disclosure relates to viral particles comprising the improved dependoparvovirus capsid polypeptides, with increased cardiac muscle biodistribution and/or transduction as compared to viral particles, e.g., without the mutations in the improved dependoparvovirus capsid polypeptides.

[0005] The present disclosure provides a capsid polypeptide comprising a threonine at a position corresponding to Q579 of the VP1 capsid polypeptide of SEQ ID NO:1, a valine at a position corresponding to Q592 of the VP1 capsid polypeptide of SEQ ID NO:1, an alanine at a position corresponding to T593 of the VP1 capsid polypeptide of SEQ ID NO:1, an alanine at a position corresponding to W595 of the VP1 capsid polypeptide of SEQ ID NO:1, a leucine at a position corresponding to V596 of the VP1 capsid polypeptide of SEQ ID NO:1, a serine at a position corresponding to N598 of the VP1 capsid polypeptide of SEQ ID NO:1, and an alanine at a position corresponding to I601 of the VP1 capsid polypeptide of SEQ ID NO:1.

[0006] In some embodiments, the capsid polypeptide comprises an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to a VP1 polypeptide of SEQ ID NO:12 or to a VP2 or VP3 portion thereof. In some embodiments, the percentage sequence identity is calculated excluding any targeting peptide sequence insertion(s) in the capsid polypeptide sequence relative to the reference polypeptide sequence. In other embodiments, the percentage sequence identity is calculated including any targeting peptide sequence insertion(s) in the capsid polypeptide sequence relative to the reference polypeptide sequence.

[0007] An exemplary VP1 amino acid sequence of the disclosure is set forth in SEQ ID NO:12. Additional exemplary capsid polypeptides are disclosed in Section 6.2 and numbered embodiments 1 to 130.

[0008] The present disclosure further provides a nucleic acid comprising a nucleotide sequence encoding a capsid polypeptide as provided for herein, e.g., a capsid polypeptide disclosed in Section 6.2 or any one of numbered embodiments 1 to 130. In some embodiments, the nucleic acid molecule comprises a nucleotide sequence of SEQ ID NO:13, a fragment thereof (e.g., a fragment thereof encoding a VP2 or VP3 polypeptide), or a variant of any of the foregoing having at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity thereto. In some embodiments, the percentage sequence identity is calculated excluding any nucleotide sequence(s) encoding targeting peptide sequence insertion(s). In some embodiments, the percentage sequence identity is calculated including any nucleotide sequence(s) encoding targeting peptide sequence insertion(s) relative to the polypeptide encoded by the nucleotide sequence of SEQ ID NO:13. In some embodiments, the nucleic acid is a vector, e.g., a plasmid. Exemplary nucleic acids are disclosed in Section 6.2 and numbered embodiments 131 to 150.

[0009] The present disclosure further provides a dependoparvovirus particle comprising a capsid polypeptide and/or a nucleic acid described herein, e.g., a capsid polypeptide disclosed in Section 6.2 or any one of numbered embodiments 1 to 130 and/or a nucleic acid described herein, e.g., a nucleic acid disclosed in Section 6.2 or any one of numbered embodiments 131 to 150 or a nucleic acid comprising a transgene / payload as disclosed in Section 6.6.1. In some embodiments, the dependoparvovirus is an adeno-associated dependoparvovirus (AAV). In some embodiments, the AAV is AAV9, e.g., a variant AAV9. In some embodiments, the AAV comprises a capsid polypeptide comprising the amino acid sequence of SEQ ID NO:12 or the VP2 or VP3 portion thereof and a nucleic acid comprising AAV inverted terminal repeat sequences (ITRs) and a heterologous transgene operably linked to one or more regulatory elements (e.g., a promoter), e.g., for delivery of the transgene to a cell (e.g., human cell) when used for gene therapy. Exemplary virus particles are disclosed in Section 6.3 and numbered embodiments 151 to 188. In some embodiments, the virus particles have one or more characteristics disclosed in Section 6.4 and numbered embodiments 151 to 188.

[0010] In some embodiments, the disclosure is directed, in part, to a cell, cell-free system, or other translation system comprising a nucleic acid or vector described herein, e.g., comprising a sequence encoding a capsid polypeptide having one or more mutations described herein, for example a capsid polypeptide disclosed in Section 6.2 or any one of numbered embodiments 1 to 130. In some embodiments, the cell, cell-free system, or other translation system comprises a dependoparvovirus particle described herein, e.g., wherein the particle comprises a nucleic acid comprising a sequence

encoding a capsid polypeptide, e.g., a capsid polypeptide disclosed in Section 6.2 or any one of numbered embodiments 1 to 130 and/or a nucleic acid described herein, e.g., a nucleic acid disclosed in Section 6.2 or any one of numbered embodiments 131 to 150 or a nucleic acid comprising a transgene as disclosed in Section 6.6.1. Exemplary cells, cell-free and other translation systems and their use to produce dependoparvovirus particles are disclosed in Section 6.5 and in numbered embodiments 1291 to 1301 and 1305 to 1316.

[0011] The present disclosure further provides methods of using a dependoparvovirus disclosed herein, e.g., for delivering a payload to a cell or treating a disease or condition in a subject. The methods typically comprise contacting the cell or administering to the subject a dependoparvovirus particle described herein in an amount effective to treat the disease or condition. Exemplary methods are disclosed in Section 6.6 and numbered embodiments 189 to 1290. The dependoparvovirus particles may be in the form of a composition, e.g., a pharmaceutical composition comprising the dependoparvovirus particles and a pharmaceutically acceptable carrier or excipient, for example as described in Section 6.6.2 and numbered embodiment 1302. The disclosure further provides compositions disclosed herein for use in treating a disease or condition in a subject and for use in the manufacture of a medicament for use in treating a disease or condition in a subject. Exemplary compositions for use are described in numbered embodiments 1303 and 1304.

[0012] Additional features, advantages and applications of the capsid polypeptides, nucleic acids, dependoparvovirus particles of the disclosure and methods of their production and use are more particularly described below.

5. BRIEF DESCRIPTION OF THE DRAWINGS

[0013] **FIGS. 1A-1C**. Illustration of exemplary AAV serotype alignments. Amino acids that are present only in VP1 polypeptides are in normal text; amino acids that are present only in VP1 and VP2 polypeptides are in bold; amino acids that are present in VP1, VP2 and VP3 polypeptides are underlined. FIGs. 1A-1C disclose SEQ ID NOS: 5, 3, 1, 7 and 9, respectively, in order of appearance.

[0014] **FIG. 2**: Transduction rates for V1 relative to VAR-1 in cell types of the prefrontal cortex, obtained via single nuclei RNA sequencing and analysis (Example 1).

[0015] **FIG. 3**: Transduction rates for V1 relative to VAR-1 in cell types of the motor cortex, obtained via single nuclei RNA sequencing and analysis (Example 1).

[0016] **FIG. 4**: Transduction rates for V1 relative to VAR-1 in cell types of the putamen, obtained via single nuclei RNA sequencing and analysis (Example 1).

[0017] **FIGS. 5A-5B:** Payload gene expression normalized to endogenous RPP30 expression (FIG. 5A) and vector genome biodistribution (FIG. 5B) in NHPs (Example 2).

[0018] **FIGS. 6A-6H**: Tissue immunofluorescence images and quantified values of transduction in various NHP tissues. FIG. 6A shows V1 distribution and tissue-specific marker staining in muscle tissues. FIG. 6B shows V1 distribution and tissue-specific marker staining in brain tissues. FIG. 6C shows the percentage of cardiomyocyte nuclei transduced. FIG. 6D shows the percentage of all nuclei transduced in cardiac muscle tissues. FIG. 6E shows the percentage of myofibers transduced. FIG. 6F shows the percentage of all nuclei transduced in skeletal muscle tissues. FIG. 6G shows the percentage of cells

transduced in brain tissues. FIG. 6H shows the percentage of Fox3+ neurons transduced in brain tissues. (Example 2).

6. DETAILED DESCRIPTION

6.1. Definitions

[0019] Unless otherwise defined herein, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. Exemplary methods and materials are described below, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present disclosure. In case of conflict, the present specification, including definitions, will control. Generally, nomenclature used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics, analytical chemistry, synthetic organic chemistry, medicinal and pharmaceutical chemistry, and protein and nucleic acid chemistry and hybridization described herein are those well-known and commonly used in the art. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Throughout this specification and embodiments, the words "have" and "comprise," or variations such as "has," "having," "comprises," or "comprising," will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. All publications and other references mentioned herein are incorporated by reference in their entirety. Although a number of documents are cited herein, this citation does not constitute an admission that any of these documents forms part of the common general knowledge in the art.

[0020] **A, An, The:** As used herein, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

[0021] **About, Approximately:** As used herein, the terms "about" and "approximately" shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees of error are within 15 percent (%), typically, within 10%, and more typically, within 5% of a given value or range of values. Any disclosure herein of a value preceded by the term "about" or "approximately" is also a disclosure of the value per se. For example, disclosure of "about 10 µg/ml" is a disclosure of the value "10 µg/ml."

[0022] **CNS:** As used herein, "CNS" means one or more regions of the central nervous system. In embodiments, the CNS includes one or more of: brain and spinal cord.

[0023] **Corresponds to:** As used herein, the term "corresponds to" as used in reference to a position in a sequence, such as an amino acid or nucleic acid sequence, can be used in reference to an entire capsid polypeptide or polynucleotide sequence, such as the full-length sequence of the capsid polypeptide that comprises a VP1, VP2, and VP3 polypeptide, or a nucleic acid molecule encoding the same. In some embodiments, the term "corresponds to" can be used in reference to a region or domain of the capsid polypeptide. For example, a position that corresponds to a position in the VP1 section of the reference capsid polypeptide can correspond to the VP1 portion of the polypeptide of the variant capsid polypeptide. Thus, when aligning the two sequences to determine whether a position

corresponds to another position the full-length polypeptide can be used or domains (regions) can be used to determine whether a position corresponds to a specific position. In some embodiments, the region is the VP1 polypeptide. In some embodiments, the region is the VP2 polypeptide. In some embodiments, the region is the VP3 polypeptide. In some embodiments, when the reference polypeptide is the wild-type sequence (e.g., full-length or region) of a certain serotype of AAV, the variant polypeptide can be of the same serotype with a mutation made at such corresponding position as compared to the reference sequence (e.g., full-length or region). In some embodiments, the variant capsid polypeptide is a different serotype as compared to the reference sequence.

[0024] Dependoparvovirus capsid: As used herein, the term "dependoparvovirus capsid" refers to an assembled viral capsid comprising dependoparvovirus polypeptides. In some embodiments, a dependoparvovirus capsid is a functional dependoparvovirus capsid, e.g., is fully folded and/or assembled, is competent to infect a target cell, or remains stable (e.g., folded/assembled and/or competent to infect a target cell) for at least a threshold time.

[0025] Dependoparvovirus particle: As used herein, the term "dependoparvovirus particle" refers to an assembled viral capsid comprising dependoparvovirus polypeptides and a packaged nucleic acid, e.g., comprising a payload, one or more components of a dependoparvovirus genome (e.g., a whole dependoparvovirus genome), or both. In some embodiments, a dependoparvovirus particle is a functional dependoparvovirus particle, e.g., comprises a desired payload, is fully folded and/or assembled, is competent to infect a target cell, or remains stable (e.g., folded/assembled and/or competent to infect a target cell) for at least a threshold time.

[0026] Dependoparvovirus X particle/capsid: As used herein, the term "dependoparvovirus X particle/capsid" refers to a dependoparvovirus particle/capsid comprising at least one polypeptide or polypeptide encoding nucleic acid sequence derived from a naturally occurring dependoparvovirus X species or serotype. For example, a dependoparvovirus B particle refers to a dependoparvovirus particle comprising at least one polypeptide or polypeptide encoding nucleic acid sequence derived from a naturally occurring dependoparvovirus B sequence. Derived from, as used in this context, means having at least 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% identity to the sequence in question. Correspondingly, an AAVX particle/capsid, as used herein, refers to an AAV particle/capsid comprising at least one polypeptide or polypeptide encoding nucleic acid sequence derived from a naturally occurring AAV X serotype. For example, an AAV9 particle refers to an AAV particle comprising at least one polypeptide or polypeptide encoding nucleic acid sequence derived from a naturally occurring AAV9 sequence. Sometimes, a dependoparvovirus X capsid is referred to as "Wild Type" or "wt" when such capsid comprises capsid polypeptides from a specified sequence identifier associated with such dependoparvovirus X capsid. Thus, for example, the terms wild-type AAV9 capsid or wtAAV9 capsid (or simply wtAAV9) are used interchangeably and refer to a capsid that comprises capsid polypeptides of SEQ ID NO:1 (e.g., a VP1 capsid of SEQ ID NO:1 and VP2 and VP3 portions thereof).

[0027] Edit Distance: Sequences disclosed herein may be described in terms of "edit distance." The minimum number of sequence edits, i.e., additions, substitutions, or deletions of a single amino acid (for amino acid sequence) or a single nucleotide (for nucleotide sequences), which change one sequence into another sequence is the edit distance between the two sequences. The term "edit distance" is often used interchangeably with the term "Levenshtein distance."

[0028] Exogenous: As used herein, the term "exogenous" refers to a feature, sequence, or component present in a circumstance (e.g., in a nucleic acid, polypeptide, or cell) that does not naturally occur in said circumstance. For example, a nucleic acid sequence encoding a polypeptide can comprise an exogenous codon (e.g., codon encoding for an amino acid that does not naturally occur in that position, for example in a reference sequence), such as provided for herein. Use of the term exogenous in this fashion means that the codon in question at this position does not occur naturally, e.g., is not present in AAV9, e.g., is not present in SEQ ID NO:1. In some embodiments, the codon replaces an endogenous codon. In some embodiments, the exogenous codon is inserted into the nucleic acid sequence, for example, relative to a reference sequence. A person of skill will readily understand that a sequence (e.g., a codon) can be exogenous when provided in a particular sequence (e.g., that does not naturally comprise the codon at the site in question) but may not be exogenous in a second sequence (e.g., that does naturally comprise that particular codon at the site in question).

[0029] Functional: As used herein in reference to a polypeptide component of a dependoparvovirus capsid (e.g., Cap (e.g., VP1, VP2, and/or VP3) or Rep), the term "functional" refers to a polypeptide which provides at least 50, 60, 70, 80, 90, or 100% of the activity of a naturally occurring version of that polypeptide component (e.g., when present in a host cell). For example, a functional VP1 polypeptide can stably fold and assemble into a dependoparvovirus capsid (e.g., that is competent for packaging and/or secretion). As used herein in reference to a dependoparvovirus capsid or particle, "functional" refers to a capsid or particle comprising one or more of the following production characteristics: comprises a desired payload, is fully folded and/or assembled, is competent to infect a target cell, or remains stable (e.g., folded/assembled and/or competent to infect a target cell) for at least a threshold time.

[0030] Mutation Difference: As used herein with respect to a polypeptide sequence, means a single amino acid mutation (e.g., substitution, insertion or deletion) present in a subject polypeptide sequence, relative to a reference polypeptide sequence. In various embodiments, the reference polypeptide sequence is a polypeptide of any one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:12, or a VP2 or VP3 portion thereof. In a preferred embodiment, the reference polypeptide is a polypeptide of SEQ ID NO:1. In various embodiments, the subject polypeptide is SEQ ID NO:12 or a VP2 or VP3 portion thereof.

[0031] Mutation Set: As used herein, the term "mutation set" refers to the complete set of single amino acid mutations (substitutions, deletions and/or insertions) in a variant capsid polypeptide sequence (e.g., a polypeptide sequence of SEQ ID NO:12 or a VP2 or VP3 portion thereof) relative to a reference sequence (e.g., a wild-type reference sequence). In some embodiments, the reference sequence is wild-type AAV9 VP1 capsid polypeptide (SEQ ID NO:1) or a VP2 or VP3 portion thereof. In some cases, part of the mutation set (i.e., more than one single amino acid mutation) is notated collectively, however, it will be understood that even when referred to in this way, the mutation set is a collection of single amino acid mutations. For example, an insertion of amino acid 1, 2, and 3 between amino acid N at position nn and amino acid W at position ww of a reference sequence may be notated as "Nnn_3aa_Www_123," and it will be understood that each of amino acids 1, 2 and 3 represent separate single amino acid mutations within the mutation set. In some embodiments, a variant capsid polypeptide of the disclosure comprises a mutation set not consisting solely of a mutation set present in a capsid polypeptide of SEQ ID NO:12.

[0032] Nucleic Acid: As used herein, in its broadest sense, the term "nucleic acid" refers to any compound and/or substance that is or can be incorporated into an oligonucleotide chain. In some embodiments, a nucleic acid is a compound and/or substance that is or can be incorporated into an oligonucleotide chain via a phosphodiester linkage. As will be clear from context, in some embodiments, "*nucleic acid*" refers to an individual nucleic acid monomer (e.g., a nucleotide and/or nucleoside); in some embodiments, "*nucleic acid*" refers to an oligonucleotide chain comprising individual nucleic acid monomers or a longer polynucleotide chain comprising many individual nucleic acid monomers. In some embodiments, a "*nucleic acid*" is or comprises RNA; in some embodiments, a "*nucleic acid*" is or comprises DNA. In some embodiments, a nucleic acid is, comprises, or consists of one or more natural nucleic acid residues. In some embodiments, a nucleic acid is, comprises, or consists of one or more nucleic acid analogs. In some embodiments, a nucleic acid is, comprises, or consists of one or more modified, synthetic, or non-naturally occurring nucleotides. In some embodiments, a nucleic acid analog differs from a nucleic acid in that it does not utilize a phosphodiester backbone. For example, in some embodiments, a nucleic acid is, comprises, or consists of one or more "peptide nucleic acids", which are known in the art and have peptide bonds instead of phosphodiester bonds in the backbone, are considered within the scope of the present invention. Alternatively or additionally, in some embodiments, a nucleic acid has one or more phosphorothioate and/or 5'-N-phosphoramidite linkages rather than phosphodiester bonds. In some embodiments, a nucleic acid has a nucleotide sequence that encodes a functional gene product such as an RNA or protein. In some embodiments, a nucleic acid is partly or wholly single stranded; in some embodiments, a nucleic acid is partly or wholly double stranded.

[0033] Or: Unless indicated otherwise, an "or" conjunction is intended to be used in its correct sense as a Boolean logical operator, encompassing both the selection of features in the alternative (A or B, where the selection of A is mutually exclusive from B) and the selection of features in conjunction (A or B, where both A and B are selected). In some places in the text, the term "and/or" is used for the same purpose, which shall not be construed to imply that "or" is used with reference to mutually exclusive alternatives.

[0034] Percent Identity: Sequences disclosed herein may be described in terms of "percent identity" (% identity). For calculating percent identity between two amino acid sequences or two nucleic acid sequences, the two sequences to be compared are aligned using the EMBOSS Needle Pairwise Sequence Alignment software tool based on the Needleman and Wunsch algorithm (Needleman & Wunsch, 1970, J. Mol. Biol. 48(3):443-53) (available at www.ebi.ac.uk/Tools/psa/emboss_needle/) using the following parameters: Matrix: BLOSUM62 (for amino acid sequences) or DNAfull (for DNA sequences); Gap Open: 10; Gap Extend: 0.5; End Gap Penalty: false; End Gap Open: 10; and End Gap Extend: 0.5. Percent identity is determined by dividing the number of amino acid or nucleotide matches in the alignment by the length of the alignment and multiplying by 100. For example, if an alignment of two amino acid sequences has 95 matching amino acids and an alignment length of 100 amino acids, the two sequences have 95% identity.

[0035] When calculating percent identity of two capsid polypeptides, one or both of which contain(s) one or more targeting peptide insertions, percent identity can be determined without removing the targeting peptide insertion sequence(s) from the capsid polypeptide sequence(s) or, alternatively, percent identity can be determined after removing the targeting peptide insertion sequence(s) from the capsid polypeptide sequence(s). For example, if a first capsid polypeptide has an identical sequence to a

second capsid polypeptide, except that the first capsid polypeptide has a 7-mer targeting peptide insertion, the two capsid polypeptides have less than 100% sequence identity when percent identity is determined without removal of the targeting peptide insertion sequence from the first capsid polypeptide sequence, whereas the two capsid polypeptides have 100% sequence identity when the targeting peptide insertion sequence is removed from the first capsid polypeptide sequence prior to calculating percent identity. References herein to percent identity of capsid polypeptides without mention of a targeting peptide refer to percent identity of the capsid polypeptides determined following removal of targeting polypeptide insertion sequence(s), if any, present in both capsid polypeptides, unless required otherwise by context. References herein to percent identity calculated "taking targeting peptide insertions into account" means that the percent identity is calculated without removal of targeting polypeptide insertion sequence(s), if any, present in both capsid polypeptides. References herein to percent identity calculated "without taking targeting peptide insertions into account" means that the percent identity is calculated following removal of targeting polypeptide insertion sequence(s), if any, present in both capsid polypeptides.

[0036] PNS: as used herein, "PNS" means one or more regions of the peripheral nervous system that does not include the CNS. In embodiments, the PNS includes dorsal root ganglia. In embodiments, the PNS includes sensory neurons and motor neurons.

[0037] Polypeptide, peptide, and protein: The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids.

[0038] Targeting Peptide: As used herein, a "targeting peptide" refers to a peptide inserted into, or attached to, a capsid polypeptide to alter the tropism of the capsid polypeptide. A targeting peptide can be inserted into an AAV capsid sequence for enhanced targeting to a desired cell-type, tissue, or organ, for example for enhanced targeting to the CNS. A targeting peptide is typically 3 to 20 amino acids in length, for example, 3 to 12 amino acids, 4 to 10 amino acids, 5 to 12 amino acids, 5 to 10 amino acids, or 7 to 10 amino acids in length.

[0039] Treating: As used herein, the term "treating a disease or condition" refers to treating a manifest disease or condition, for example, where the subject is already suffering from one or more symptoms of the disease or condition, or refers to treating a pre-manifest disease or condition, for example, where the subject is identified as having a disease or condition but is not yet exhibiting one or more symptoms of the disease or condition. Pre-manifest conditions may be identified by, for example, genetic testing.

[0040] Variant: As used herein, a "variant capsid polypeptide" refers to a polypeptide that differs from a reference sequence (e.g., SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:7, SEQ ID NO:9 or SEQ ID NO:11, preferably SEQ ID NO:1, or sequence subunit thereof such as a VP2 or VP3 portion thereof). The variant capsid polypeptide can, for example, comprise a mutation (e.g., substitution, deletion, or insertion). In some embodiments, the variant is about, or at least, 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to the reference sequence. It will be clear to the skilled artisan from this disclosure that any capsid polypeptide, for example any capsid polypeptide disclosed herein, for example, a capsid polypeptide of SEQ ID NO:12, is a variant capsid polypeptide with respect to another capsid polypeptide having a different amino acid

sequence, e.g., another capsid polypeptide with a reference sequence as set forth above. Thus, the term "variant capsid polypeptide" herein means, and is used interchangeably with, "capsid polypeptide," and does not require any comparison to a specific reference sequence. In some embodiments, the reference sequence is a polypeptide comprising SEQ ID NO:1. In some embodiments, the reference sequence comprises or consists of a VP1, VP2 or VP3 polypeptide, e.g., of SEQ ID NO:1. In some contexts used herein, the term "variant" refers to a virus particle that includes a variant capsid polypeptide, e.g., described herein.

6.2. Capsid Polypeptides and Nucleic Acids Encoding the Same

[0041] The disclosure is directed, in part, to a variant capsid polypeptide, and to a nucleic acid comprising a sequence encoding the variant capsid polypeptide, wherein the variant capsid polypeptide comprises a mutation (insertion, deletion, or substitution) as compared to the wild-type sequence. In some embodiments, the wild-type sequence is SEQ ID NO:1. The disclosure is directed, in part, to a variant capsid polypeptide comprising SEQ ID NO:1 with mutations as compared to SEQ ID NO:1, and nucleic acid molecules encoding the variant capsid polypeptide. A mutation can be, for example, an insertion, deletion, or substitution as compared to the wild-type sequence. In some embodiments, the wild-type sequence is SEQ ID NO:1.

[0042] Mutations associated with Variant 1 ("V1") (corresponding to a capsid polypeptide of SEQ ID NO:12) are shown in Table 1 in relation to a VP1 polypeptide of SEQ ID NO:1.

TABLE 1

Capsid polypeptide	Q579	Q592	T593	W595	V596	N598	I601	Edit distance to SEQ ID NO:1
V1	T	V	A	A	L	S	A	7

[0043] In some embodiments, the disclosure provides a variant capsid polypeptide (and nucleic acids encoding said capsid polypeptide) that comprises all of the mutation differences associated with the variant capsid polypeptide of SEQ ID NO:12 or comprises mutations which corresponds to all of the mutation differences associated with the variant capsid polypeptide of SEQ ID NO:12.

[0044] In some embodiments, the variant capsid polypeptide is, but for the mutation differences described in or corresponding to the mutation differences associated with a capsid polypeptide described herein, e.g., associated with SEQ ID NO:12, at least 90%, at least 95%, 96%, 97%, 98%, 99%, or 100% identical to a reference AAV serotype described herein.

[0045] In some embodiments, the variant capsid polypeptide described herein is, but for the mutation differences associated with a capsid polypeptide described herein, e.g., associated with SEQ ID NO:12, or which correspond to the mutation differences associated with a capsid polypeptide described herein, e.g., associated with SEQ ID NO:12, comprised within such variant capsid polypeptide, at least 90%, at least 95%, 96%, 97%, 98%, 99%, or 100% identical to a capsid polypeptide of SEQ ID NO:1 (e.g., a VP1, VP2 or VP3 sequence of SEQ ID NO:1).

[0046] In some embodiments, the variant capsid polypeptide described herein is, but for the mutation differences associated with a capsid polypeptide described herein, e.g., associated with SEQ ID NO:12,

or which correspond to the mutation differences associated with a capsid polypeptide described herein, e.g., associated with SEQ ID NO:12, comprised within such variant capsid polypeptide, at least 90%, at least 95%, 96%, 97%, 98%, 99%, or 100% identical to a capsid polypeptide of SEQ ID NO:3 (e.g., a VP1, VP2 or VP3 sequence of SEQ ID NO:3).

[0047] In some embodiments, the variant capsid polypeptide described herein is, but for the mutation differences associated with SEQ ID NO:12, or which correspond to the mutation differences associated with SEQ ID NO:12, comprised within such variant capsid polypeptide, at least 90%, at least 95%, 96%, 97%, 98%, 99%, or 100% identical to a capsid polypeptide of SEQ ID NO:5 (e.g., a VP1, VP2 or VP3 sequence of SEQ ID NO:5).

[0048] In some embodiments, the variant capsid polypeptide described herein is, but for the mutation differences associated with SEQ ID NO:12, or which correspond to the mutation differences associated with SEQ ID NO:12, comprised within such variant capsid polypeptide, at least 90%, at least 95%, 96%, 97%, 98%, 99%, or 100% identical to a capsid polypeptide of SEQ ID NO:7 (e.g., a VP1, VP2 or VP3 sequence of SEQ ID NO:7).

[0049] In some embodiments, the variant capsid polypeptide described herein is, but for the mutation differences associated with SEQ ID NO:12, or which correspond to the mutation differences associated with SEQ ID NO:12, comprised within such variant capsid polypeptide, at least 90%, at least 95%, 96%, 97%, 98%, 99%, or 100% identical to a capsid polypeptide of SEQ ID NO:9 (e.g., a VP1, VP2 or VP3 sequence of SEQ ID NO:9).

[0050] In some embodiments, the variant capsid polypeptide described herein is, but for the mutation differences associated with SEQ ID NO:12, or which correspond to the mutation differences associated with SEQ ID NO:12, comprised within such variant capsid polypeptide, at least 90%, at least 95%, 96%, 97%, 98%, 99%, or 100% identical to a capsid polypeptide of SEQ ID NO:11 (e.g., a VP1, VP2 or VP3 sequence of SEQ ID NO:11).

[0051] In some embodiments, a variant capsid polypeptide is provided that comprises a variant capsid polypeptide that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to a variant capsid polypeptide as provided herein.

[0052] In some embodiments, a variant capsid polypeptide is provided that comprises a variant capsid polypeptide that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical (not including targeting peptide insertions) to a variant capsid polypeptide as provided herein.

[0053] In some embodiments, the variant capsid polypeptide comprises a VP1, VP2, VP3, or any combination thereof, that is each at least, or about, 95, 96, 97, 98 or 99% identical to a polypeptide of SEQ ID NO:12, and comprises all of the mutation differences of SEQ ID NO:12.

[0054] In some embodiments, the variant capsid polypeptide comprises a VP1, VP2, VP3, or any combination thereof, that is each at least, or about, 95, 96, 97, 98 or 99% identical (not including target peptide insertions) to a polypeptide of SEQ ID NO:12, and comprises all of the mutation differences of SEQ ID NO:12.

[0055] In some embodiments, the variant capsid polypeptide comprises a VP1, VP2, VP3, or any combination thereof, that each has about 1 to about 20 mutations as compared to a polypeptide of SEQ ID NO:12, and comprises all of the mutation differences of such SEQ ID NO:12. In some embodiments the variant capsid polypeptide comprises a VP1, VP2, VP3, or any combination thereof, that each has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mutations as compared to a polypeptide of SEQ ID NO:12, and comprises all of the mutation differences of such SEQ ID NO:12.

[0056] In some embodiments, the variant capsid polypeptide comprises a VP1, VP2, VP3, or any combination thereof, that each has about 1 to about 10 mutations as compared to a polypeptide of SEQ ID NO:12, and comprises all of the mutation differences of such SEQ ID NO:12.

[0057] In some embodiments, the variant capsid polypeptide comprises a VP1, VP2, VP3, or any combination thereof, that each has 1 to 5 mutations as compared to a polypeptide of SEQ ID NO:12, and comprises all of the mutation differences of SEQ ID NO:12.

[0058] In aspects, provided herein are nucleic acid molecules encoding a variant capsid polypeptide as provided herein. In aspects, the nucleic acid molecule comprises sequence encoding a variant capsid polypeptide (e.g., a VP1, VP2 or VP3 capsid polypeptide) of SEQ ID NO:12, or fragment thereof. In aspects, the nucleic acid molecule comprises SEQ ID NO:13, or fragment thereof (e.g., a VP1-encoding, VP2-encoding or VP3-encoding fragment thereof).

[0059] In some embodiments, the nucleic acid molecule encodes a variant capsid polypeptide that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to a variant capsid polypeptide as provided herein.

[0060] In some embodiments, the nucleic acid molecule or the nucleic acid molecule encoding the reference polypeptide for purposes of % identity, comprises a nucleotide sequence of SEQ ID NO:13.

[0061] In some embodiments, the nucleic acid molecule or the nucleic acid molecule encoding the reference polypeptide for purposes of % identity, comprises a nucleotide sequence that encodes a sequence of a variant capsid polypeptide, e.g., as described herein, e.g., encodes SEQ ID NO:12.

[0062] In some embodiments, the variant capsid polypeptide, or the reference polypeptide for purposes of % identity, comprises a sequence of SEQ ID NO:12, that is encoded by a nucleotide sequence of SEQ ID NO:13, respectively.

[0063] In some embodiments, the variant capsid polypeptide is a VP1 capsid polypeptide. In some embodiments, the variant capsid polypeptide is a VP2 capsid polypeptide. In some embodiments, the variant capsid polypeptide is a VP3 capsid polypeptide. With respect to reference sequence SEQ ID NO:1, a VP1 capsid polypeptide comprises amino acids 1-736 of SEQ ID NO:1. With respect to reference sequence SEQ ID NO:1, a VP2 capsid polypeptide comprises amino acids 138-736 of SEQ ID NO:1. With respect to reference sequence SEQ ID NO:1, a VP3 capsid polypeptide comprises amino acids 203-736 of SEQ ID NO:1.

[0064] With respect to a variant capsid polypeptide sequence of SEQ ID NO:12, a VP1 capsid polypeptide comprises all of the amnio acids of SEQ ID NO:12. With respect to a sequence of SEQ ID NO:12, a VP2 capsid polypeptide comprises, e.g., consists of, a sequence that begins with the threonine corresponding to the threonine at position 138 of SEQ ID NO:1, and continuing to the C-terminus of SEQ

ID NO:12. With respect to a sequence of SEQ ID NO:12, a VP3 capsid polypeptide comprises, e.g., consists of, a sequence that begins with the methionine corresponding to methionine at position 203 of SEQ ID NO:1 and continuing to the C-terminus of SEQ ID NO:12.

[0065] In some embodiments, the nucleic acid molecule encodes a variant capsid polypeptide that has at least 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99%, or 100% identity to a VP1, VP2, or VP3 sequence of SEQ ID NO:12.

[0066] In some embodiments, the nucleic acid molecule encodes a variant capsid polypeptide that has at least 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99%, or 100% identity (not including targeting peptide insertions) to a VP1, VP2, or VP3 sequence of SEQ ID NO:12.

6.2.1. Variant Capsid Polypeptides (Corresponding Positions)

[0067] The mutations to capsid polypeptide sequences described herein are described in relation to a position and/or amino acid at a position within a reference sequence, e.g., SEQ ID NO:1. Thus, in some embodiments, the capsid polypeptides described herein are variant capsid polypeptides of the reference sequence, e.g., SEQ ID NO:1, e.g., include capsid polypeptides comprising at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to the reference capsid polypeptide sequence (e.g., reference capsid polypeptide VP1, VP2 and/or VP3 sequence), e.g., SEQ ID NO:1 (or VP2 or VP3 sequence comprised therein) and include the mutations described herein.

[0068] It will be understood by the skilled artisan, and without being bound by theory, that each amino acid position within a reference sequence corresponds to a position within the sequence of other reference capsid polypeptides such as capsid polypeptides derived from dependoparvoviruses with different serotypes. Such corresponding positions are identified using sequence alignment tools known in the art. A particularly preferred sequence alignment tool is EMBOSS Needle Pairwise Sequence Alignment software tool based on the Needleman and Wunsch algorithm (Needleman & Wunsch, 1970, J. Mol. Biol. 48(3):443-53) (available at www.ebi.ac.uk/Tools/psa/emboss_needle/). An alignment of exemplary reference capsid polypeptides is shown in FIGS.1A-1C. Thus, in some embodiments, the variant capsid polypeptides of the invention include variants of reference capsid polypeptides that include mutations described herein in such reference capsid polypeptides at positions corresponding to the position of the mutations described herein in relation to a different reference capsid polypeptide. Thus, for example, a mutation described as XnnnY relative to SEQ ID NO:1 (where X is the amino acid present at position nnn in SEQ ID NO:1 and Y is the amino acid mutation at that position, e.g., described herein), the disclosure provides variant capsid polypeptides comprising at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to a reference capsid polypeptide sequence (e.g., reference capsid polypeptide VP1, VP2 and/or VP3 sequence) other than SEQ ID NO:1 (or VP2 or VP3 sequence comprised therein) and further comprising the disclosed mutation at a position corresponding to position nnn of SEQ ID NO:1 (e.g., comprising Y at the position in the new variant capsid polypeptide sequence that corresponds to position nnn of SEQ ID NO:1). As described above, such corresponding position is determined using a sequence alignment tool, such as, for example, the clustal omega tool described above. Examples of corresponding amino acid positions of exemplary known AAV serotypes is provided in FIG.1A-1C. In some embodiments, the variant is a variant of the

AAV9 capsid polypeptide, which can be referred to as a "AAV9 variant capsid polypeptide" or "variant AAV9 capsid polypeptide."

[0069] Thus, in some embodiments, the disclosure provides variant capsid polypeptide sequences that are variants of a reference sequence other than SEQ ID NO:1, e.g., a reference sequence other than SEQ ID NO:1 as described herein, which include mutations corresponding to the mutations described herein. Such variants include mutations corresponding to all of the mutations associated with SEQ ID NO:12.

[0070] The variant capsid polypeptides described herein are optionally variants of reference capsids serotypes known in the art. Non-limiting examples of such reference AAV serotypes include AAV1, AAVrh10, AAV-DJ, AAV-DJ8, AAV5, 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.eB, AAVPHP.S/G2A12, AAVG2A15/G2A3 (G2A3), AAVG2B4 (G2B4), AAVG2B5 (G2B5), PHP.S, AAV2, AAV2G9, AAV3, AAV3a, AAV3b, AAV3-3, AAV4, AAV4-4, AAV6, AAV6.1, AAV6.2, AAV6.1.2, AAV7, AAV7.2, AAV8, AAV9.11, AAV9.13, AAV9, AAV9 K449R (or K449R AAV9), AAV9.16, AAV9.24, AAV9.45, AAbiodisV9.47, 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/r11.64, 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, 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, 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 (also referred to as AAVrh74), AAVrh8R, AAVrh8R A586R mutant, AAVrh8R R533A mutant, AAAV, 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, 7m8, Spark100, AAVMYO and variants thereof.

[0071] In some embodiments, the reference AAV capsid sequence comprises an AAV2 sequence. In some embodiments, the reference AAV capsid sequence comprises an AAV5 sequence. In some embodiments, the reference AAV capsid sequence comprises an AAV8 sequence. In some embodiments, the reference AAV capsid sequence comprises an AAV9 sequence. In some embodiments, the reference AAV capsid sequence comprises an AAVrh74 sequence. While not wishing to be bound by theory, it is understood that a reference AAV capsid sequence comprises a VP1 region. In certain embodiments, a reference AAV capsid sequence comprises a VP1, VP2 and/or VP3 region, or any combination thereof. A reference VP1 sequence may be considered synonymous with a reference AAV capsid sequence.

[0072] The wild-type reference sequence of AAV9, SEQ ID NO:1 is as follows:

MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLVLPGYKYLGPGNGLDKGEPVNA
ADAAALEHDKAYDQQLKAGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQAKKRLLEPLGLVEEAA
K**TAPGKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVPDPQPIGEPPAAPSGVGSLT**M
ASGGGAPVADNNEGADGVGSSSGNWHCDSQWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSN
DNAYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTDNNGVKTIANNLT
STVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMIPQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTG
NNFQFSYEFENVPFHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGSGQNQQTLKFSVAGPSNMAVQGRN
YIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRNSLMNPGPAMASHKEGEDRFFPLSGSLIFGK
QGTGRDNVDADKVMITNEEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQDRDV
YLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPADPPTAFNKDKLNSFITQYSTGQVSVEI
EWELQKENSKRWNPEIQYTSNYYKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL (SEQ ID NO:1)

[0073] Unless otherwise noted, SEQ ID NO:1 is the reference sequence. In the sequence above, the sequence found in VP1, VP2 and VP3 is underlined (e.g., a VP3 capsid polypeptide includes, e.g., consists of, amino acids corresponding to amino acids 203-736 of SEQ ID NO:1), the sequence found in both VP1 and VP2 is in bold (e.g., a VP2 capsid polypeptide includes, e.g., consists of, the sequence corresponding to amino acids 138-736 of SEQ ID NO:1) and the sequence that is not underlined or bold is found only in VP1 (e.g., a VP1 capsid polypeptide includes, e.g., consists of, amino acids corresponding to amino acids 1-736 of SEQ ID NO:1).

[0074] The wild-type reference sequence of SEQ ID NO:1 can be encoded by a reference nucleic acid molecule sequence of SEQ ID NO:2.

[0075] An exemplary reference sequence of wild-type AAV2, SEQ ID NO:3 (wild-type AAV2) is as follows:

MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLVLPGYKYLGPFNGLDKGEPVNE
ADAAALEHDKAYDRQLDSGDNPYLKYNHADAEFQERLKEDTSFGGNLGRAVFQAKKRVLEPLGLVEEP
VKT**APGKKRPVEHSPVEPDSSSGTGKAGQQPARKRLNFGQTGDADSVPDPQPLGQPPAAPSGLGTN**
TMATGSGAPMADNNEGADGVGNSSGNWHCDSTWMGDRVITTSTRTWALPTYNNHLYKQISSQSGASN
DNHYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTQNDGTTTIANNLT
STVQVFTDSEYQLPYVLGSAHQGCLPPFPADVFMVPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRT
GNNFTFSYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTNTPSGTTTQSRLQFSQAGASDIRDQS
RNWLPGPCYRQQRVSKTSADNNNSEYSWTGATKYHLNGRDSLVNPGPAMASHKDDEEKFFPQSGVLI
FGKQGSEKTNVDIEKVMITDEEEIRTTNPVATEQYGSVSTNLQRGNRQAATADVNTQGVLPGMVWQDR
DVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPPPQILIKNTPVPANPSTTFSAAKFASFITQYSTGQVSV
EIEWELQKENSKRWNPEIQYTSNYNKSVNVDFTVDTNGVYSEPRPIGTRYLTRNL (SEQ ID NO:3)

[0076] In the sequence above, the sequence found in VP1, VP2 and VP3 is underlined (e.g., a VP3 capsid polypeptide includes, e.g., consists of, amino acids corresponding to amino acids 203-735 of SEQ

ID NO:3), the sequence found in both VP1 and VP2 is in bold (e.g., a VP2 capsid polypeptide includes, e.g., consists of, the sequence corresponding to amino acids 138-735 of SEQ ID NO:3) and the sequence that is not underlined or bold is found only in VP1 (e.g., a VP1 capsid polypeptide includes, e.g., consists of, amino acids corresponding to amino acids 1-735 of SEQ ID NO:3).

[0077] An example nucleic acid sequence encoding SEQ ID NO:3 is SEQ ID NO:4.

[0078] An exemplary reference sequence of wild type AAV5, SEQ ID NO:5 (wild-type AAV5), is as follows:

MSFVDHPPDWLEEVGEGLREFLGLEAGPPKPKPNQQHQDQARGLVLPGYNYLGPGNGLDRGEPVNRA
DEVAREHDISYNEQLEAGDNPYLKYNHADAEFQEKLADDTSFGGNLGKAVFQAKKRVLEPFGLVEEGAK
TAPTGKRIDDHFPKRKKARTEEDSKPSTSSDAEAGPSGSQQLQIPAQPASSLGADTMSAGGGGPLGD
NNQGADGVGNASGDWHCDSTWMGDRVVTKSTRTWVLPSYNNHQYREIKSGSVDGSNANAYFGYSTP
WGYFDFNRFHSHWSPRDWQRLINNYWGFRPRSLRVKIFNIQVKEVTVQDSTTTIANNLTSTVQVFTDDD
YQLPYVVGNGTEGCLPAFPPQVFTLPQYGYATLNRDNTENPTERSSFFCLEYFPSKMLRTGNNFEFTYN
FEEVPFHSSFAPSQNLFKLANPLVDQYLYRFVSTNNTGGVQFNKNLAGRYANTYKNWFPGPMGRTQG
WNLGSGVNRASVSAFATTNRMELEGASYQVPPQPNGMTNNLQGSNTYALENTMIFNSQPANPGTTATY
LEGNMLITSESETQPVNRVAYNVGGQMATNNQSSTTAPATGTYNLQEIVPGSVWMERDVYLQGPIWAKI
PETGAHFHPSPAMGGFGLKHPPPMMLIKNTPVPGNITSFSDVPVSSFITQYSTGQVTVEMEWELKKENS
KRWNPEIQYTNNYNDPQFVDFAPDSTGEYRTTRPIGTRYLTRPL (SEQ ID NO:5)

[0079] In the sequence above, the sequence found in VP1, VP2 and VP3 is underlined (e.g., a VP3 capsid polypeptide includes, e.g., consists of, amino acids corresponding to amino acids 193-724 of SEQ ID NO:5), the sequence found in both VP1 and VP2 is in bold (e.g., a VP2 capsid polypeptide includes, e.g., consists of, the sequence corresponding to amino acids 137-724 of SEQ ID NO:5) and the sequence that is not underlined or bold is found only in VP1 (e.g., a VP1 capsid polypeptide includes, e.g., consists of, amino acids corresponding to amino acids 1-724 of SEQ ID NO:5).

[0080] An example nucleic acid sequence encoding SEQ ID NO:5 is SEQ ID NO:6.

[0081] An exemplary reference sequence of wild-type AAV8, SEQ ID NO:7 (wild-type AAV8), is as follows:

MAADGYLPDWLEDNLSEGIREWWALKPGAPKPKANQQKQDDGRGLVLPGYKYLGPFNGLDKGEPVNA
ADAAALEHDKAYDQQLQAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQAKKRVLEPLGLVEEG
AK**TAPGKKRPVEPSPQRSPDSSTGIGKKGQQPARKRLNFGQTGDSESVPDPQPLGEPPAAPSGVGPN
T**MAAGGGAPMADNNEGADGVGSSSGNWHCDSTWLGDRVITTSTRTWALPTYNNHLYKQISNGTSGGA
TNDNTYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLSFKLFNIQVKEVTQNEGTKTIANN
LTSTIQVFTDSEYQLPYVLGSAHQGCLPPFPADVFMIPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRT
GNNFQFTYTFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQTTGGTANTQTLGFSQGGPNTMANQ
AKNWLPGPCYRQQRVSTTTGQNNNSNFAWTAGTKYHLNGRNSLANPGIAMATHKDDEERFFPSNGILIF
GKQNAARDNADYSDVMLTSEEEIKTTNPVATEEYGIVADNLQQQNTAPQIGTVNSQGALPGMVWQNRD
VYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPPQILIKNTPVPADPPTTFNQSKLNSFITQYSTGQVSVE
IEWELQKENSKRWNPEIQYTSNYYKSTSVDFAVNTEGVYSEPRPIGTRYLTRNL (SEQ ID NO:7)

[0082] In the sequence above, the sequence found in VP1, VP2 and VP3 is underlined (e.g., a VP3 capsid polypeptide includes, e.g., consists of, amino acids corresponding to amino acids 204-738 of SEQ ID NO:7), the sequence found in both VP1 and VP2 is in bold (e.g., a VP2 capsid polypeptide includes, e.g., consists of, the sequence corresponding to amino acids 138-738 of SEQ ID NO:7) and the sequence that is not underlined or bold is found only in VP1 (e.g., a VP1 capsid polypeptide includes, e.g., consists of, amino acids corresponding to amino acids 1-738 of SEQ ID NO:7).

[0083] An example nucleic acid sequence encoding SEQ ID NO:7 is SEQ ID NO:8.

[0084] An exemplary reference sequence of wild-type AAVrh74, SEQ ID NO:9 (wild-type AAVrh74), is as follows:

MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDNGRGLVLPGYKYLGPFNGLDKGEPVNA
ADAAALEHDKAYDQQLQAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQAKKRVLEPLGLVESP
VKT**APGKKRPVEPSPQRSPDSSTGIGKKGQQPAKKRLNFGQTGDSESVPDPQPIGEPPAGPSGLGSG**
TMAAGGGAPMADNNEGADGVGSSSGNWHCDSTWLGDRVITTSTRTWALPTYNNHLYKQISNGTSGGS
TNDNTYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTQNEGTKTIANN
LTSTIQVFTDSEYQLPYVLGSAHQGCLPPFPADVFMIPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRT
GNNFEFSYNFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQSTGGTAGTQQLLFSQAGPNNMSAQ
AKNWLPGPCYRQQRVSTTLSQNNNSNFAWTGATKYHLNGRDSLVNPGVAMATHKDDEERFFPSSGVL
MFGKQGAGKDNVDYSSVMLTSEEEIKTTNPVATEQYGVVADNLQQQNAAPIVGAVNSQGALPGMVWQ
NRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPPQILIKNTPVPADPPTTFNQAKLASFITQYSTGQV
SVEIEWELQKENSKRWNPEIQYTSNYYKSTNVDFAVNTEGTYSEPRPIGTRYLTRNL (SEQ ID NO:9)

[0085] An alternative exemplary reference sequence of SEQ ID NO:11 (alternate wild-type AAVrh74) is as follows:

MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDNGRGLVLPGYKYLGPFNGLDKGEPVNA
ADAAALEHDKAYDQQLQAGDNPYLRYNHADAEFQERLQEDTSFGGNLGRAVFQAKKRVLEPLGLVESP
VKT**APGKKRPVEPSPQRSPDSSTGIGKKGQQPAKKRLNFGQTGDSESVPDPQPIGEPPAGPSGLGSG**
TMAAGGGAPMADNNEGADGVGSSSGNWHCDSTWLGDRVITTSTRTWALPTYNNHLYKQISNGTSGGS
TNDNTYFGYSTPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTQNEGTKTIANN
LTSTIQVFTDSEYQLPYVLGSAHQGCLPPFPADVFMIPQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRT
GNNFEFSYNFEDVPFHSSYAHSQSLDRLMNPLIDQYLYYLSRTQSTGGTAGTQQLLFSQAGPNNMSAQ
AKNWLPGPCYRQQRVSTTLSQNNNSNFAWTGATKYHLNGRDSLVNPGVAMATHKDDEERFFPSSGVL
MFGKQGAGKDNVDYSSVMLTSEEEIKTTNPVATEQYGVVADNLQQQNAAPIVGAVNSQGALPGMVWQ
NRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPPQILIKNTPVPADPPTTFTKAKLASFITQYSTGQV
SVEIEWELQKENSKRWNPEIQYTSNYYKSTNVDFAVNTEGTYSEPRPIGTRYLTRNL (SEQ ID NO:11)

[0086] In the sequences above (SEQ ID NO:9 or SEQ ID NO:11), the sequence found in VP1, VP2 and VP3 is underlined (e.g., a VP3 capsid polypeptide includes, e.g., consists of, amino acids corresponding to amino acids 204-738 of SEQ ID NO:9), the sequence found in both VP1 and VP2 is in bold (e.g., a VP2 capsid polypeptide includes, e.g., consists of, the sequence corresponding to amino acids 138-738 of SEQ ID NO:9) and the sequence that is not underlined or bold is found only in VP1 (e.g., a VP1 capsid polypeptide includes, e.g., consists of, amino acids corresponding to amino acids 1-738 of SEQ ID NO:9).

[0087] An example nucleic acid sequence encoding SEQ ID NO:9 is SEQ ID NO:10.

[0088] 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 (i.e. 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. Where the Met/AA-clipping is incomplete, a mixture of one or more (one, two or three) VP capsid proteins comprising the viral capsid can be produced, some of which include a Met1/AA1 amino acid (Met+/AA+) and some of

which 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. According to the present disclosure, references to capsid polypeptides is not limited to either clipped (Met-/AA-) or unclipped (Met+/AA+) and, in context, also refer to independent capsid polypeptides, viral capsids comprised of a mixture of capsid proteins, and/or polynucleotide sequences (or fragments thereof) which encode, describe, produce or result in capsid polypeptides of the present disclosure. A direct reference to a "capsid polypeptide" (such as VP1, VP2 or VP3) also comprise VP capsid proteins which include a Met1/AA1 amino acid (Met+/AA+) as well as corresponding VP capsid polypeptide which lack the Met1/AA1 amino acid as a result of Met/AA-clipping (Met-/AA-). 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 polypeptides which include a Met1/AA1 amino acid (Met+/AA+) should be understood to teach the VP capsid polypeptides 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). 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 is also 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 can 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. 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-). 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-).

[0089] In some embodiments, the reference AAV capsid sequence comprises 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 those described above.

[0090] In some embodiments, the reference AAV capsid sequence is encoded by a nucleotide 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 above. In certain embodiments, the reference sequence is not an AAV capsid sequence and is instead a different vector (e.g., lentivirus, plasmid, etc.).

[0091] In some embodiments, a nucleic acid of the disclosure (e.g., encoding an AAV9 variant capsid protein) comprises conventional control elements or sequences which are operably linked to the nucleic acid molecule in a manner which permits transcription, translation and/or expression in a cell transfected with the nucleic acid (e.g., a plasmid vector comprising said nucleic acid) or infected with a virus comprising said nucleic acid. As used herein, "operably linked" sequences include both expression control sequences that are contiguous with the gene of interest and expression control sequences that act in trans or at a distance to control the gene of interest.

[0092] Expression control sequences include efficient RNA processing signals such as splicing and polyadenylation (polyA) signals; appropriate transcription initiation, termination, promoter and enhancer sequences; sequences that stabilize cytoplasmic mRNA; sequences that enhance protein stability; sequences that enhance translation efficiency (e.g., Kozak consensus sequence); and in some embodiments, sequences that enhance secretion of the encoded transgene product. Expression control sequences, including promoters which are native, constitutive, inducible and/or tissue-specific, are known in the art and can be utilized with the compositions and methods disclosed herein.

[0093] In some embodiments, the native promoter for the transgene is used. Without wishing to be bound by theory, the native promoter can mimic native expression of the transgene, or provide temporal, developmental, or tissue-specific expression, or expression in response to specific transcriptional stimuli. In some embodiments, the transgene is operably linked to other native expression control elements, such as enhancer elements, polyadenylation sites or Kozak consensus sequences, e.g., to mimic the native expression.

[0094] In some embodiments, the transgene is operably linked to a tissue-specific promoter, e.g., a promoter active specifically in one or more CNS cell types. In some embodiments, the transgene is operably linked to a promoter active in muscle (*e.g.*, skeletal muscle and/or cardiac muscle). The promoter active in skeletal muscle can be specific to skeletal muscle, or expressed more broadly in other muscle types (e.g., cardiac muscle, smooth muscle). In some embodiments, the transgene is operably linked to a promoter active in cardiac muscle. The promoter active in cardiac muscle can be specific to cardiac muscle, or expressed more broadly in other muscle types (e.g., skeletal muscle, smooth muscle).

[0095] In some embodiments, a vector, e.g., a plasmid, carrying a transgene includes a selectable marker or a reporter gene. Such selectable reporters or marker genes can be used to signal the presence of the vector, e.g., plasmid, in bacterial cells. Other components of the vector, e.g., plasmid, include an origin of replication. Selection of these and other promoters and vector elements are conventional and many such sequences are available (see, e.g., Sambrook et al, and references cited therein).

[0096] In some embodiments, the viral particle comprising a variant capsid polypeptide, e.g., a variant capsid polypeptide described herein, exhibits increased CNS transduction as compared to a viral particle with the wild-type capsid polypeptide (SEQ ID NO:1).

[0097] In some embodiments, the viral particle comprising a variant capsid polypeptide, e.g., a variant capsid polypeptide described herein, exhibits increased CNS transduction as compared to a viral particle with the VAR-1 capsid polypeptide (SEQ ID NO:38). In some embodiments, the viral particle comprising a variant capsid polypeptide, e.g., a variant capsid polypeptide described herein, exhibits increased transduction in one or more CNS regions (e.g., motor cortex, prefrontal cortex, putamen) and/or CNS cell types (e.g., astrocytes, excitatory neurons, interneurons, oligodendrocytes, medium spiny neurons) as compared to a viral particle with the VAR-1 capsid polypeptide (SEQ ID NO:38).

[0098] In some embodiments, the viral particle comprising a variant capsid polypeptide, e.g., a variant capsid polypeptide described herein, exhibits increased muscle transduction as compared to a viral particle with the wild-type capsid polypeptide (SEQ ID NO:1).

[0099] In some embodiments, the viral particle comprising a variant capsid polypeptide, e.g., a variant capsid polypeptide described herein, exhibits increased skeletal muscle transduction as compared to a viral particle with the wild-type capsid polypeptide (SEQ ID NO:1).

[0100] In some embodiments, the viral particle comprising a variant capsid polypeptide, e.g., a variant capsid polypeptide described herein, exhibits increased cardiac muscle transduction as compared to a viral particle with the wild-type capsid polypeptide (SEQ ID NO:1).

[0101] In some embodiments, the capsid polypeptide is an isolated or purified polypeptide (e.g., isolated or purified from a cell, other biological component, or contaminant). In some embodiments, the variant polypeptide is present in a dependoparvovirus particle, e.g., described herein. In some embodiments, the variant capsid polypeptide is present in a cell, cell-free system, or translation system, e.g., described herein.

[0102] In some embodiments, the capsid polypeptide is present in a dependoparvovirus B (e.g., AAV9) particle. In some embodiments, the capsid particle has increased CNS transduction. In some embodiments, the capsid particle has increased skeletal muscle transduction. In some embodiments, the capsid particle has increased cardiac muscle transduction.

[0103] In some embodiments, a dependoparvovirus particle comprises an amino acid sequence that has at least 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% identity to the amino acid sequences provided for herein (e.g., SEQ ID NO:12). In some embodiments, the variant capsid polypeptide comprises an amino acid sequence that differs by no more than 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acids from the amino acid sequence of a variant capsid polypeptide provided for herein.

6.2.1. Targeting Peptides

[0104] The capsid polypeptides of the disclosure can include (but do not necessarily include) a targeting peptide to alter the tropism of the capsid polypeptides, for example to enhance targeting to the CNS or muscle (e.g., skeletal or cardiac muscle). Thus, in some embodiments, a capsid polypeptide of the disclosure includes a targeting peptide. In other embodiments, a capsid polypeptide of the disclosure does not include a targeting peptide.

6.2.1.1. CNS Targeting Peptides

[0105] Various targeting peptides for enhancing CNS tropism, and which can be included in capsid polypeptides of the disclosure, are described in the art, for example in WO 2017/197355, WO 2019/006182, WO 2019/060454, WO 2012/145601, WO 2018/022905, WO 2021/243085, WO 2019/076856, WO2015/038958, WO 2015/191508, WO 2020/068990, WO 2020/210655, WO 2020/198737, WO 2020/028751, WO 2019/028306, WO 2017/100671 A1, WO 2020/028751 A2, WO 2020/072683 A1, WO 2020/160337 A1, WO 2020/223280 A1, WO 2021/025995 A1, WO 2021/202651 A1, WO 2021/230987 A1, WO 2022/235702 A1, WO 2020/014471, WO 2018/189244, WO 2019/141765, WO 2019/207132, WO 2019/210267, WO 2018/156654, WO 2010/093784, WO 2015/048534, WO 2017/058892, WO 2019/169132, WO 2021/108468, WO 2021/102234, WO 2022/173847, WO 2021/077000, WO 2020/160337, WO 2021/050974, WO 2021/222831, WO 2022/020616, WO 2020/193799, WO 2021/072197, WO 2022/126188, WO 2022/126189, WO 2021/165544, WO 2021/084133, WO 2022/040527, WO 2022/221400, WO 2022/221404, WO 2022/221420, WO 2021/216456, WO 2021/009684, WO 2021/242909, WO 2019/158619, WO 2021/226267, WO 2023/283962, WO 2021/219762, WO 2022/226374, WO 2022/226375, WO 2022/229703, and WO 2022/229702, the contents of which are incorporated herein by reference in their entireties. Targeting peptides are typically 3 to 20 amino acids in length. In some embodiments, a targeting peptide is 3 to 12 amino acids in length. In other embodiments, a targeting peptide is 5 to 12 amino acids in length. In other embodiments, a targeting peptide is 5 to 10 amino acids in length. In other embodiments, a targeting peptide is 7 to 10 amino acids in length. In some embodiments, a targeting peptide is 7 amino acids in length. In other embodiments, a targeting peptide is 9 amino acids in length.

[0106] In some embodiments, the targeting peptide comprises at least 3, 4, 5, 6, 7, 8, or 9 consecutive amino acids from the amino acid sequence of PLNGAVHLY (SEQ ID NO:16). In some embodiments, the targeting peptide comprises the amino acid sequence PLNGAVHLY (SEQ ID NO:16). In some embodiments, the targeting peptide comprises at least 3, 4, 5, 6, or 7 consecutive amino acids from the amino acid sequence of IVMNSLK (SEQ ID NO:17). In some embodiments, the targeting peptide comprises the amino acid sequence IVMNSLK (SEQ ID NO:17). In some embodiments, the targeting peptide comprises at least 3, 4, 5, 6, or 7 consecutive amino acids from the amino acid sequence of RDSPKGW (SEQ ID NO:18). In some embodiments, the targeting peptide comprises the amino acid sequence RDSPKGW (SEQ ID NO:18). In some embodiments, the targeting peptide comprises at least 3, 4, 5, 6, or 7 consecutive amino acids from the amino acid sequence of YSTDVRM (SEQ ID NO:19). In some embodiments, the targeting peptide comprises the amino acid sequence YSTDVRM (SEQ ID NO:19). In some embodiments, the targeting peptide comprises at least 3, 4, 5, 6, or 7 consecutive amino acids from the amino acid sequence of RESPRGL (SEQ ID NO:20). In some embodiments, the targeting peptide comprises the amino acid sequence RESPRGL (SEQ ID NO:20). In some embodiments, the targeting peptide comprises 4, 5, 6, or 7 consecutive amino acids from GNNTRSV (SEQ ID NO:21), GNNTRDT (SEQ ID NO:22) or TNSTRPV (SEQ ID NO:23). In some embodiments, the targeting peptide comprises the amino acid sequence GNNTRSV (SEQ ID NO:21). In some embodiments, the targeting peptide comprises the amino acid sequence GNNTRDT (SEQ ID NO:22). In some embodiments, the targeting peptide comprises the amino acid sequence TNSTRPV (SEQ ID NO:23).

6.2.1.2. Muscle Targeting Peptides

[0107] Various targeting peptides for enhancing muscle (e.g., skeletal and/or cardiac) tropism, and which can be included in capsid polypeptides of the disclosure, are described in the art, for example in WO 2020/206189A1, WO 2022/226374 A1, WO 2022/053630 A1, and WO 2019/207132 A1.

[0108] In some embodiments, the muscle targeting peptide comprises at least 3, 4, 5, 6, or 7 consecutive amino acids from the amino acid sequence ASSLNIA (SEQ ID NO:24).

[0109] In some aspects, the targeting peptide targets the insulin receptor (INSR). In some embodiments, the peptide targeting the INSR comprises an amino acid sequence having at least 80%, 87%, 91%, 94%, 97%, or 100% sequence identity to SLEEEWAQVECEVYGRGCPSGSLDESFYDWFERQL (SEQ ID NO:25), or which has at least 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 or 35 consecutive amino acids from the amino acid sequence SLEEEWAQVECEVYGRGCPSGSLDESFYDWFERQL (SEQ ID NO:25).

[0110] In some aspects, the targeting peptide targets muscle-specific kinase (MUSK). In some embodiments, the inserted MUSK-targeting peptide is from the acetylcholinesterase collagenic tail peptide (ColQ), e.g., a C-terminal portion of ColQ (ColQ CTD). In some embodiments, the ColQ CTD peptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to TPFYPVGYTVKQPGTCGDGVLQPGEECDDGNPDVSDGCIDCHRAYCGDGYRHQGVEDCDGSDFGYLT CETYLPGSYGDLRCTQYCSIDSTPCRYFT (SEQ ID NO:26), or which has at least 70, 80, 85, 90, 91, 92, 93, 94, 95, or 96 consecutive amino acids from the amino acid sequence TPFYPVGYTVKQPGTCGDGVLQPGEECDDGNPDVSDGCIDCHRAYCGDGYRHQGVEDCDGSDFGYLT CETYLPGSYGDLRCTQYCSIDSTPCRYFT (SEQ ID NO:26).

[0111] In some aspects, the targeting peptide targets integrin, for example via an RGD-motif. In some embodiments, the RGD peptide comprises a subsequence Y or F amino acid to produce an RGDY (SEQ ID NO: 40) or RGDF motif (SEQ ID NO: 41). In some embodiments, integrin targeting peptides have the motif $RGDX_1X_2X_3X_4$, with X_1 to X_4 each being any amino acid. In various aspects of SEQ ID NO:28, X_1, X_2, and X_3 are each independently selected from L, G, V, and A and/or X_4 is S, V, A, G, or L. In some embodiments, at least one of X_2 and X_3 is G. In some embodiments, the targeting peptide comprises the amino acid sequence RGDLGLS (SEQ ID NO: 28). In some embodiments, the targeting peptide comprises the amino acid sequence RGDLSTP (SEQ ID NO:29). In some embodiments, the targeting peptide comprises the amino acid sequence SNSRGDYNSL (SEQ ID NO:30). In some embodiments, the targeting peptide comprises the amino acid sequence ENRRGDFNNT (SEQ ID NO:31). In some embodiments, the targeting peptide comprises the amino acid sequence SRGDYNSL (SEQ ID NO:32). In some embodiments, the targeting peptide comprises the amino acid sequence RGDYNSL (SEQ ID NO:33). In some embodiments, the targeting peptide comprises the amino acid sequence RGDLST (SEQ ID NO: 34). In some embodiments, the targeting peptide comprises the amino acid sequence RGDYVGL (SEQ ID NO:35). In some embodiments, the targeting peptide comprises the amino acid sequence RGDAVGV (SEQ ID NO:36). The RGD peptides can be inserted in a linker, e.g., a flexible linker such as GGGS (SEQ ID NO: 42), scaffold. Other suitable linker scaffolds can be found in WO 2022/226374 A1, pages 26-28 of which are, scaffold. Other suitable linker scaffolds can be found in WO 2022/226374 A1, pages 26-28 of which are incorporated herein by reference.

[0112] In some embodiments, the muscle-targeting (e.g., skeletal and/or cardiac) peptide is present in, *e.g.*, inserted into, loop VIII of the capsid polypeptide. In some embodiments, the targeting peptide is inserted at any amino acid position corresponding to positions 586-592, inclusive, of SEQ ID NO:1. For example, the targeting peptide can be inserted between amino acids 588-589 of SEQ ID NO:1. In some embodiments, the targeting peptide is present, *e.g.*, inserted, immediately subsequent to the position corresponding to 586, 588, or 589 of SEQ ID NO:1. In some embodiments, the capsid polypeptide further comprises a deletion at the position corresponding to 587 and/or a deletion at the position corresponding to 588 of SEQ ID NO:1.

6.2.2. Nucleic Acids and Polypeptides

[0113] The disclosure is further directed, in part, to a nucleic acid comprising a sequence encoding a variant capsid polypeptide as provided for herein. In embodiments the nucleic acid encodes a VP1 variant capsid polypeptide, e.g., as described herein. In embodiments, the nucleic acid encodes a VP2 variant capsid polypeptide, e.g., as described herein. In embodiments, the nucleic acid encodes a VP3 variant capsid polypeptide, e.g., as described herein. In embodiments, the nucleic acid encodes a VP1, VP2 and VP3 variant capsid polypeptide, e.g., as described herein. In some embodiments, the variant capsid polypeptide comprises a sequence of SEQ ID NO:12. In some embodiments, the nucleic acid comprises a sequence of SEQ ID NO:13.

6.3. Dependoparvovirus Particles

[0114] The disclosure is also directed, in part, to a dependoparvovirus particle (e.g., a functional dependoparvovirus particle) comprising a nucleic acid or polypeptide described herein or produced by a method described herein.

[0115] Dependoparvovirus is a single-stranded DNA parvovirus that grows only in cells in which certain functions are provided, e.g., by a co-infecting helper virus. Several species of dependoparvovirus are known, including dependoparvovirus A and dependoparvovirus B, which include serotypes known in the art as adeno-associated viruses (AAV). At least thirteen serotypes of AAV that have been characterized. General information and reviews of AAV can be found in, for example, Carter, *Handbook of Parvoviruses*, Vol. 1, pp. 169-228 (1989), and Berns, *Virology*, pp. 1743-1764, Raven Press, (New York, 1990). AAV serotypes, and to a degree, dependoparvovirus species, are significantly interrelated structurally and functionally. (See, for example, Blacklowe, pp. 165-174 of *Parvoviruses and Human Disease*, J. R. Pattison, ed. (1988); and Rose, *Comprehensive Virology* 3:1-61 (1974)). For example, all AAV serotypes apparently exhibit very similar replication properties mediated by homologous rep genes; and all bear three related capsid proteins. In addition, heteroduplex analysis reveals extensive cross-hybridization between serotypes along the length of the genome, further suggesting interrelatedness. Dependoparvoviruses genomes also comprise self-annealing segments at the termini that correspond to "inverted terminal repeat sequences" (ITRs).

[0116] The genomic organization of naturally occurring dependoparvoviruses, e.g., AAV serotypes, is very similar. For example, the genome of AAV is a linear, single-stranded DNA molecule that is approximately 5,000 nucleotides (nt) in length or less. Inverted terminal repeats (ITRs) flank the unique coding nucleotide sequences for the non-structural replication (Rep) proteins and the structural capsid (Cap) proteins. Three different viral particle (VP) proteins form the capsid. The terminal approximately 145 nt of the genome are self-complementary and are organized so that an energetically stable

intramolecular duplex forming a T-shaped hairpin may be formed. These hairpin structures function as an origin for viral DNA replication, serving as primers for the cellular DNA polymerase complex. The Rep genes encode the Rep proteins: Rep78, Rep68, Rep52, and Rep40. Rep78 and Rep68 are transcribed from the p5 promoter, and Rep 52 and Rep40 are transcribed from the p19 promoter. The cap genes encode the VP proteins, VP1, VP2, and VP3. The cap genes are transcribed from the p40 promoter.

[0117] In some embodiments, a dependoparvovirus particle of the disclosure comprises a nucleic acid comprising a variant capsid polypeptide provided for herein. In some embodiments, the particle comprises a polypeptide as provided for herein.

[0118] In some embodiments, the dependoparvovirus particle of the disclosure is an AAV9 particle. In some embodiments, the AAV9 particle comprises a variant capsid polypeptide as provided for herein or a nucleic acid molecule encoding the same.

[0119] In some embodiments the dependoparvovirus particle comprises a variant capsid comprising a variant capsid polypeptide described herein. In embodiments, the dependoparvovirus particle comprises variant capsid polypeptide described herein and a nucleic acid molecule. In embodiments, the dependoparvovirus particle comprises variant capsid polypeptide described herein and a nucleic acid molecule comprising one or more inverted terminal repeat sequences (ITRs), for example, ITRs derived from an AAV9 dependoparvovirus or an AAV2 dependoparvovirus, one or more regulatory elements (for example, a promoter), and a payload (e.g., as described herein, e.g., a heterologous transgene). In embodiments, at least one of the ITRs is modified. In embodiments, the nucleic acid molecule is single-stranded. In embodiments, the nucleic acid molecule is double stranded, for example, self-complementary.

6.4. Improved Biodistribution and Transduction Characteristics

[0120] The disclosure is directed, in part, to nucleic acids, polypeptides, cells, cell free systems, translation systems, viral particles, and methods associated with using and making the same to produce viral particles that have increased distribution to tissues and cells of the CNS and/or CNS transduction as compared to a viral particle comprising a reference sequence that does not otherwise comprise the mutations described herein (or mutations corresponding thereto), for example, as compared with a viral particle comprising a capsid polypeptide sequence of SEQ ID NO:1. In some embodiments, a use of a viral particle comprising the variant capsid polypeptides as described in Section 6.2 or any one of numbered embodiments 1 to 130 (e.g., a viral particle as described in Section 6.3 or any one of numbered embodiments 151 to 188) leads to increased CNS biodistribution of the viral particle and/or increased transduction of a transgene virus particle in the cells of the CNS broadly or brain specifically, and, therefore, increased expression of the payload (transgene) in the CNS or brain. In some embodiments, use of a viral particle comprising the variant capsid polypeptides as described in Section 6.2 or any one of numbered embodiments 1 to 130 (e.g., a viral particle as described in Section 6.3 or any one of numbered embodiments 151 to 188) further leads to reduced (or non-increased) biodistribution of the viral particle and/or reduced (or non-increased) transduction of the transgene in one or more peripheral tissues, e.g., liver, spleen, dorsal root ganglia, or any combination of two or more of the foregoing peripheral tissue types. In certain embodiments, use of a viral particle comprising the variant capsid polypeptides as described in Section 6.2 or any one of numbered embodiments 1 to 130

(e.g., a viral particle as described in Section 6.3 or any one of numbered embodiments 151 to 188) leads to reduced biodistribution and/or reduced transduction of the transgene in liver tissue.

[0121] In some embodiments, biodistribution and transduction (*e.g.*, of the tissue types described in this section) are measured by relative quantification (e.g., via qPCR) of transgene mRNA in one or more samples isolated from the relevant tissue type, e.g., CNS, skeletal muscle, or cardiac muscle), for example using the procedures described in Section 8. In some embodiments, biodistribution and/or transduction of a virus particle having a variant capsid polypeptide can be measured using virus particles having a transgene operably linked to a promoter that is active in a target cell or tissue type of interest. In some embodiments, the promoter is a ubiquitous promoter. In other embodiments, the promoter is selective or specific to a target cell or tissue type (e.g., CNS and/or muscle (either broad muscle expression or skeletal muscle or cardiac muscle)), and, optionally, is less (or not) active in a cell or tissue type where transgene expression is not desired (e.g., liver, spleen, PNS, or any combination of two or all of the foregoing). A promoter that is selective for a first cell or tissue type over a second cell or tissue type is active in the first cell or tissue type and less active or silent in the second cell or tissue type. In some embodiments, the promoter is a CNS-specific or CNS-selective promoter. In some embodiments, the promoter is a muscle-specific promoter-specific or muscle-selective promoter. In some embodiments, the promoter is active in both CNS and muscle tissue. In some embodiments, biodistribution and/or transduction of a virus particle having a variant capsid polypeptide can be measured using virus particles having a transgene operably linked to a ubiquitous promoter or a CNS-specific promoter. For example, biodistribution can be measured using virus particles having a transgene operably linked to CBh promoter or a hSYN promoter. In various embodiments, the transgene is a transgene encoding a capsid polypeptide or any other suitable heterologous transgene, for example a nucleic acid sequence encoding a synthetic, mammalian or human therapeutic protein or nucleic acid (e.g., mRNA or RNAi) or reporter gene such as, for example a nucleic acid encoding a GFP or mCherry reporter.

[0122] In embodiments, the virus particle, e.g., as described herein, e.g., comprising a variant capsid polypeptide described herein, is capable of crossing the blood-brain barrier. In embodiments the virus particle, e.g., as described herein, e.g., comprising a variant capsid polypeptide described herein, exhibits increased crossing of the blood-brain barrier relative to a virus particle comprising a reference capsid polypeptide, e.g., a reference capsid polypeptide of SEQ ID NO:1. In embodiments, the virus particle, e.g., as described herein, e.g., comprising a variant capsid polypeptide described herein, exhibits increased transduction of neurons (e.g., excitatory neurons, interneurons, or medium spiny neurons), astrocytes, glial cells, oligodendrocytes or combinations thereof, relative to a virus particle comprising a reference capsid polypeptide, e.g., a reference capsid polypeptide of SEQ ID NO:1 or SEQ ID NO:38.

[0123] In some embodiments, a viral particle comprising the variant capsid polypeptide, e.g., the variant capsid polypeptide described herein, exhibits improved properties, e.g., improved biodistribution, transduction and/or production. Unless indicated otherwise, improvement rates are presented as fold-improvement over the rates exhibited by a virus particle comprising capsid polypeptides of SEQ ID NO:1. In some embodiments, improvement means an increase, e.g., in the case of CNS biodistribution or CNS

transduction. In other embodiments, improvement means a decrease, e.g., in the case of liver biodistribution or liver transduction.

[0124] In some embodiments, one or more improved properties (e.g., increased or decreased biodistribution and/or transduction) is exhibited in a mammal, e.g., a primate, e.g., a human. In embodiments, the increased or decreased biodistribution and/or transduction is exhibited upon administration of the virus particle or pharmaceutical composition comprising the virus particle, e.g., as described herein, by systemic administration, e.g., intravenous administration.

6.5. Methods of Making Compositions Described Herein

[0125] The disclosure is directed, in part, to a method of making a dependoparvovirus particle, e.g., a dependoparvovirus particle described herein. In some embodiments, a method of making dependoparvovirus particle comprises providing a cell, cell-free system, or other translation system, comprising a nucleic acid described encoding a variant capsid polypeptide provided for herein, or a polypeptide provided for herein (e.g., a variant capsid polypeptide); and cultivating the cell, cell-free system, or other translation system under conditions suitable for the production of the dependoparvovirus particle, thereby making the dependoparvovirus particle.

6.5.1. Host Cells

[0126] Aspects of the disclosure are directed to a host cell comprising a nucleic acid of the disclosure (e.g., encoding a variant capsid polypeptide as described in Section 6.2). A host cell of the disclosure, e.g., a host cell useful to general AAV virus particles comprising a variant AAV capsid as described herein, generally comprises one or more nucleic acids comprising a coding sequence encoding a variant capsid polypeptide of the disclosure (e.g., as described in Section 6.2), together with a payload (e.g., transgene) and one or more coding sequences encoding additional components useful for promoting packaging of the payload into a dependoparvovirus capsid. Additional components include, for example, coding sequences for a rep protein and dependoparvovirus inverted terminal repeats (ITRs), as well as helper sequences which promote dependoparvovirus particle production and/or secretion. Examples of helper sequences include E1a, E1b, E2a, E4, and VA. Such helper sequences may be included endogenously within the host cell (e.g., the host cell may be engineered to express such helper sequences, e.g., integrated into the host cell genome) or may be provided exogenously (e.g., transduced on the same or a different nucleic acid as the variant capsid polypeptide, payload, rep, and/or ITRs).

[0127] In some embodiments, the helper sequences include AdV5 helper sequences. An exemplary AdV5 genome is disclosed in the art as NCBI Reference Sequence AC_000008.1 (disclosed as SEQ ID NO:1 of PCT Patent Application Publication No. WO/2022/079429 A1). In some embodiments, a host cell disclosed herein comprises a portion of an AdV5 genome encoding for one or more helper protein sequences (e.g., E1a, E1b, E2a, E4) or RNA sequences (e.g., VA). In some embodiments, a host cell disclosed herein comprises a nucleic acid sequence encoding one or more AdV5 helper protein sequences. Certain exemplary AdV5 helper protein sequences are provided below.

[0128] AdV5 E1A:

MRHIICHGGVITEEMAASLLDQLIEEVLADNLPPPSHFEPPTLHELYDLDVTAPEDPNEEAVSQIFPDSVML
AVQEGIDLLTFPPAPGSPEPPHLSRQPEQPEQRALGPVSMPNLVPEVIDLTCHEAGFPPSDDEDEEGEE
FVLDYVEHPGHGCRSCHYHRRNTGDPDIMCSLCYMRTCGMFVYSPVSEPEPEPEPEPEPARPTRRPK

MAPAILRRPTSPVSRECNSSTDSCDSGPSNTPPEIHPVVPLCPIKPVAVRVGGRRQAVECIEDLLNEPGQ PLDLSCKRPRP (SEQ ID NO:43)

[0129] AdV5 E1B 19K:

MEAWECLEDFSAVRNLLEQSSNSTSWFWRFLWGSSQAKLVCRIKEDYKWEFEELLKSCGELFDSLNLG HQALFQEKVIKTLDFSTPGRAAAAVAFLSFIKDKWSEETHLSGGYLLDFLAMHLWRAVVRHKNRLLLLSS VRPAIIPTEEQQQQQEEARRRRQEQSPWNPRAGLDPRE (SEQ ID NO:44)

[0130] AdV5 E1B 55K:

MERRNPSERGVPAGFSGHASVESGCETQESPATVVFRPPGDNTDGGAAAAAGGSQAAAAGAEPMEP ESRPGPSGMNVVQVAELYPELRRILTITEDGQGLKGVKRERGACEATEEARNLAFSLMTRHRPECITFQ QIKDNCANELDLLAQKYSIEQLTTYWLQPGDDFEEAIRVYAKVALRPDCKYKISKLVNIRNCCYISGNGAE VEIDTEDRVAFRCSMINMWPGVLGMDGVVIMNVRFTGPNFSGTVFLANTNLILHGVSFYGFNNTCVEAW TDVRVRGCAFYCCWKGVVCRPKSRASIKKCLFERCTLGILSEGNSRVRHNVASDCGCFMLVKSVAVIKH NMVCGNCEDRASQMLTCSDGNCHLLKTIHVASHSRKAWPVFEHNILTRCSLHLGNRRGVFLPYQCNLS HTKILLEPESMSKVNLNGVFDMTMKIWKVLRYDETRTRCRPCECGGKHIRNQPVMLDVTEELRPDHLVL ACTRAEFGSSDEDTD (SEQ ID NO:45)

[0131] AdV5 E3 12.5K:

MLSGEAEQLRLKHLVHCRRHKCFARDSGEFCYFELPEDHIEGPAHGVRLTAQGELARSLIREFTQRPLLV ERDRGPCVLTVICNCPNLGLHQDLCCHLCAEYNKYRN (SEQ ID NO:46)

[0132] AdV5 E3 CR1-alpha0:

MNNSSNSTGYSNSGFSRIGVGVILCLVILFILILTLLCLRLAACCVHICIYCQLFKRWGRHPR (SEQ ID NO:47)

[0133] AdV5 E3 gp19K:

MIRYIILGLLTLASAHGTTQKVDFKEPACNVTFAAEANECTTLIKCTTEHEKLLIRHKNKIGKYAVYAIWQPG DTTEYNVTVFQGKSHKTFMYTFPFYEMCDITMYMSKQYKLWPPQNCVENTGTFCCTAMLITVLALVCTL LYIKYKSRRSFIEEKKMP (SEQ ID NO:48)

[0134] AdV5 E3 CR1-beta0:

MTNTTNAAAATGLTSTTNTPQVSAFVNNWDNLGMWWFSIALMFVCLIIMWLICCLKRKRARPPIYSPIIVL HPNNDGIHRLDGLKHMFFSLTV (SEQ ID NO:49)

[0135] AdV5 E3 RID-alpha:

MIPRVFILLTLVALFCACSTLAAVSHIEVDCIPAFTVYLLYGFVTLTLICSLITVVIAFIQCIDWVCVRFAYLRH HPQYRDRTIAELLRIL (SEQ ID NO:50)

[0136] AdV5 E3 RID-beta:

MKFTVTFLLIICTLSAFCSPTSKPQRHISCRFTRIWNIPSCYNEKSDLSEAWLYAIISVMVFCSTILALAIYPY LDIGWKRIDAMNHPTFPAPAMLPLQQVVAGGFVPANQPRPTSPTPTEISYFNLTGGDD (SEQ ID NO:51)

[0137] AdV5 E3 14.7K:

MTDTLDLEMDGIITEQRLLERRRAAAEQQRMNQELQDMVNLHQCKRGIFCLVKQAKVTYDSNTTGHRLS YKLPTKRQKLVVMVGEKPITITQHSVETEGCIHSPCQGPEDLCTLIKTLCGLKDLIPFN (SEQ ID NO:52)

[0138] AdV5 E4 ORF6/7:
MTTSGVPFGMTLRPTRSRLSRRTPYSRDRLPPFETETRATILEDHPLLPECNTLTMHNAWTSPSPPVKQ PQVGQQPVAQQLDSDMNLSELPGEFINITDERLARQETVWNITPKNMSVTHDMMLFKASRGERTVYSV CWEGGGRLNTRVL (SEQ ID NO:53)

[0139] AdV5 E4 34K:
MTTSGVPFGMTLRPTRSRLSRRTPYSRDRLPPFETETRATILEDHPLLPECNTLTMHNVSYVRGLPCSV GFTLIQEWVVPWDMVLTREELVILRKCMHVCLCCANIDIMTSMMIHGYESWALHCHCSSPGSLQCIAGG QVLASWFRMVVDGAMFNQRFIWYREVVNYNMPKEVMFMSSVFMRGRHLIYLRLWYDGHVGSVVPAMS FGYSALHCGILNNIVVLCCSYCADLSEIRVRCCARRTRRLMLRAVRIIAEETTAMLYSCRTERRRQQFIRAL LQHHRPILMHDYDSTPM (SEQ ID NO:54)

[0140] AdV5 E4 ORF4:
MVLPALPAPPVCDSQNECVGWLGVAYSAVVDVIRAAAHEGVYIEPEARGRLDALREWIYYNYYTERSKR RDRRRRSVCHARTWFCFRKYDYVRRSIWHDTTTNTISVVSAHSVQ (SEQ ID NO:55)

[0141] AdV5 E4 ORF3:
MIRCLRLKVEGALEQIFTMAGLNIRDLLRDILRRWRDENYLGMVEGAGMFIEEIHPEGFSLYVHLDVRAVC LLEAIVQHLTNAIICSLAVEFDHATGGERVHLIDLHFEVLDNLLE (SEQ ID NO:56)

[0142] AdV5 E4 ORFB:
MFERKMVSFSVVVPELTCLYLHEHDYDVLSFLREALPDFLSSTLHFISPPMQQAYIGATLVSIAPSMRVIIS VGSFVMVPGGEVAALVRADLHDYVQLALRRDLRDRGIFVNVPLLNLIQVCEEPEFLQS (SEQ ID NO:57)

[0143] AdV5 E4 ORF1:
MAAAVEALYVVLEREGAILPRQEGFSGVYVFFSPINFVIPPMGAVMLSLRLRVCIPPGYFGRFLALTDVNQ PDVFTESYIMTPDMTEELSVVLFNHGDQFFYGHAGMAVVRLMLIRVVFPVVRQASNV (SEQ ID NO:58)

[0144] In some embodiments, the helper sequences include AdV2 helper sequences. An exemplary AdV2 genome is disclosed in the art as NCBI Reference Sequence AC_000007.1 (disclosed as SEQ ID NO:2 of PCT Patent Application Publication No. WO/2022/079429 A1). In some embodiments, a host cell disclosed herein comprises a portion of an AdV2 genome encoding for one or more helper protein sequences (e.g., E1a, E1b, E2a, E4) or RNA sequences (e.g., VA). In some embodiments, a host cell disclosed herein comprises a nucleic acid sequence encoding one or more AdV2 helper protein sequences. Certain exemplary AdV2 helper protein sequences are provided below.

[0145] AdV2 E1A:
MRHIICHGGVITEEMAASLLDQLIEEVLADNLPPPSHFEPPTLHELYDLDVTAPEDPNEEAVSQIFPESVML AVQEGIDLFTFPPAPGSPEPPHLSRQPEQPEQRALGPVSMPNLVPEVIDLTCHEAGFPPSDDEDEEGEE FVLDYVEHPGHGCRSCHYHRRNTGDPDIMCSLCYMRTCGMFVYSPVSEPEPEPEPEPEPARPTRRPKL VPAILRRPTSPVSRECNSSTDSCDSGPSNTPPEIHPVVPLCPIKPVAVRVGGRRQAVECIEDLLNESGQP LDLSCKRPRP (SEQ ID NO:59)

[0146] AdV2 E1B 19K:
MEAWECLEDFSAVRNLLEQSSNSTSWFWRFLWGSSQAKLVCRIKEDYKWEFEELLKSCGELFDSLNLG HQALFQEKVIKTLDFSTPGRAAAAVAFLSFIKDKWSEETHLSGGYLLDFLAMHLWRAVVRHKNRLLLLSS VRPAIIPTEEQQQEEARRRRRQEQSPWNPRAGLDPRE (SEQ ID NO:60)

[0147] AdV2 E1B 55K:

MERRNPSERGVPAGFSGHASVESGGETQESPATVVFRPPGNNTDGGATAGGSQAAAAAGAEPMEPE
SRPGPSGMNVVQVAELFPELRRILTINEDGQGLKGVKRERGASEATEEARNLTFSLMTRHRPECVTFQQ
IKDNCANELDLLAQKYSIEQLTTYWLQPGDDFEEAIRVYAKVALRPDCKYKISKLVNIRNCCYISGNGAEV
EIDTEDRVAFRCSMINMWPGVLGMDGVVIMNVRFTGPNFSGTVFLANTNLILHGVSFYGFNNTCVEAWT
DVRVRGCAFYCCWKGVVCRPKSRASIKKCLFERCTLGILSEGNSRVRHNVASDCGCFMLVKSVAVIKHN
MVCGNCEDRASQMLTCSDGNCHLLKTIHVASHSRKAWPVFEHNILTRCSLHLGNRRGVFLPYQCNLSH
TKILLEPESMSKVNLNGVFDMTMKIWKVLRYDETRTRCRPCECGGKHIRNQPVMLDVTEELRPDHLVLA
CTRAEFGSSDEDTD (SEQ ID NO:61)

[0148] AdV2 E3 12.5K:

MTSGEAERLRLTHLDHCRRHKCFARGSGEFCYFELPEEHIEGPAHGVRLTTQVELTRSLIREFTKRPLLV
ERERGPCVLTVVCNCPNPGLHQDLCCHLCAEYNKYRN (SEQ ID NO:62)

[0149] AdV2 E3 CR1-alphap0:

MSNSSNSTSLSNFSGIGVGVILTLVILFILILALLCLRVAACCTHVCTYCQLFKRWGQHPR (SEQ ID NO:63)

[0150] AdV2 E3 gp19K:

MRYMILGLLALAAVCSAAKKVEFKEPACNVTFKSEANECTTLIKCTTEHEKLIIRHKDKIGKYAVYAIWQPG
DTNDYNVTVFQGENRKTFMYKFPFYEMCDITMYMSKQYKLWPPQKCLENTGTFCSTALLITALALVCTLL
YLKYKSRRSFIDEKKMP (SEQ ID NO:64)

[0151] AdV2 E3 CR1-beta0:

MTGSTIAPTTDYRNTTATGLTSALNLPQVHAFVNDWASLDMWWFSIALMFVCLIIMWLICCLKRRRARPPI
YRPIIVLNPHNEKIHRLDGLKPCSLLLQYD (SEQ ID NO:65)

[0152] AdV2 E3 RID alpha:

MIPRVLILLTLVALFCACSTLAAVAHIEVDCIPPFTVYLLYGFVTLILICSLVTVVIAFIQFIDWVCVRIAYLRHH
PQYRDRTIADLLRIL (SEQ ID NO:66)

[0153] AdV2 E3 RID beta:

MKRSVIFVLLIFCALPVLCSQTSAPPKRHISCRFTQIWNIPSCYNKQSDLSEAWLYAIISVMVFCSTIFALAIY
PYLDIGWNAIDAMNHPTFPVPAVIPLQQVIAPINQPRPPSPTPTEISYFNLTGGDD (SEQ ID NO:67)

[0154] AdV2 E3 14.7K:

MTESLDLELDGINTEQRLLERRKAASERERLKQEVEDMVNLHQCKRGIFCVVKQAKLTYEKTTTGNRLSY
KLPTQRQKLVLMVGEKPITVTQHSAETEGCLHFPYQGPEDLCTLIKTMCGIRDLIPFN (SEQ ID NO:68)

[0155] AdV2 E4 ORF6/7:

MTTSGVPFGMTLRPTRSRLSRRTPYSRDRLPPFETETRATILEDHPLLPECNTLTMHNAWTSPSPPVEQ
PQVGQQPVAQQLDSDMNLSELPGEFINITDERLARQETVWNITPKNMSVTHDMMLFKASRGERTVYSV
CWEGGGRLNTRVL (SEQ ID NO:69)

[0156] AdV2 E4 34K:

MTTSGVPFGMTLRPTRSRLSRRTPYSRDRLPPFETETRATILEDHPLLPECNTLTMHNVSYVRGLPCSV
GFTLIQEWVVPWDMVLTREELVILRKCMHVCLCCANIDIMTSMMIHGYESWALHCHCSSPGSLQCIAGG
QVLASWFRMVVDGAMFNQRFIWYREVVNYNMPKEVMFMSSVFMRGRHLIYLRLWYDGHVGSVVPAMS

FGYSALHCGILNNIVVLCCSYCADLSEIRVRCCARRTRRLMLRAVRIIAEETTAMLYSCRTERRRQQFIRAL LQHHRPILMHDYDSTPM (SEQ ID NO:70)

[0157] AdV2 E4 ORF4:
MVLPALPAPPVCDSQNECVGWLGVAYSAVVDVIRAAAHEGVYIEPEARGRLDALREWIYYNYYTERAKR RDRRRRSVCHARTWFCFRKYDYVRRSIWHDTTTNTISVVSAHSVQ (SEQ ID NO:71)

[0158] AdV2 E4 ORF3:
MIRCLRLKVEGALEQIFTMAGLNIRDLLRDILIRWRDENYLGMVEGAGMFIEEIHPEGFSLYVHLDVRAVCL LEAIVQHLTNAIICSLAVEFDHATGGERVHLIDLHFEVLDNLLE (SEQ ID NO:72)

[0159] AdV2 E4 ORF2:
MFERKMVSFSVVVPELTCLYLHEHDYDVLAFLREALPDFLSSTLHFISPPMQQAYIGATLVSIAPSMRVIIS VGSFVMVPGGEVAALVRADLHDYVQLALRRDLRDRGIFVNVPLLNLIQVCEEPEFLQS (SEQ ID NO:73)

[0160] AdV2 E4 ORF1:
MAAAVEALYVVLEREGAILPRQEGFSGVYVFFSPINFVIPPMGAVMLSLRLRVCIPPGYFGRFLALTDVNQ PDVFTESYIMTPDMTEELSVVLFNHGDQFFYGHAGMAVVRLMLIRVVFPVVRQASNV (SEQ ID NO:74)

[0161] Additional AAV helper sequences are recognized in the art and include, for example, those described in U.S. Patent Application Publication Nos. 2004/0248288 A1 and 2022/0259572A1, and in PCT Patent Application Publication Nos. WO/1997/017458 A1, WO/2024/143429 A1, and WO/2020/208379 A1, each of which is incorporated herein by reference.

[0162] Expression control sequences include efficient RNA processing signals such as splicing and polyadenylation (polyA) signals; appropriate transcription initiation, termination, promoter and enhancer sequences; sequences that stabilize cytoplasmic mRNA; sequences that enhance protein stability; sequences that enhance translation efficiency (e.g., Kozak consensus sequence); and in some embodiments, sequences that enhance secretion of the encoded transgene product. Expression control sequences, including promoters which are native, constitutive, inducible and/or tissue-specific, are known in the art and can be utilized with the compositions and methods disclosed herein.

[0163] In some embodiments, the native promoter for the transgene is used. Without wishing to be bound by theory, the native promoter can mimic native expression of the transgene, or provide temporal, developmental, or tissue-specific expression, or expression in response to specific transcriptional stimuli. In some embodiments, the transgene is operably linked to other native expression control elements, such as enhancer elements, polyadenylation sites or Kozak consensus sequences, e.g., to mimic the native expression.

[0164] In some embodiments, the transgene is operably linked to a tissue-specific promoter, e.g., a promoter active specifically in one or more CNS cell types or muscle cell types.

[0165] In some embodiments, a vector, e.g., a plasmid, carrying a transgene includes a selectable marker or a reporter gene. Such selectable reporters or marker genes can be used to signal the presence of the vector, e.g., plasmid, in bacterial cells. Other components of the vector, e.g., plasmid, include an origin of replication. Selection of these and other promoters and vector elements are conventional and many such sequences are available (see, e.g., Sambrook et al, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor, NY, and references cited therein).

[0166] In some embodiments, an insect cell may be used in production of the compositions described herein or in the methods of making a dependoparvovirus particle described herein. For example, an insect cell line used can be from *Spodoptera frugiperda*, such as Sf9, SF21, SF900+, drosophila cell lines, mosquito cell lines, e.g., *Aedes albopictus* derived cell lines, domestic silkworm cell lines, e.g., Bombyxmori cell lines, *Trichoplusia ni* cell lines such as High Five cells or Lepidoptera cell lines such as *Ascalapha odorata* cell lines. In some embodiments, the insect cells are susceptible to baculovirus infection, including High Five, Sf9, Se301, SeIZD2109, SeUCR1, SP900+, Sf21, BTI-TN-5B1-4, MG-1, Tn368, HzAml, BM-N, Ha2302, Hz2E5 and Ao38. Use of insect cells for expression of heterologous proteins is well recognized in the art, as are methods of introducing nucleic acids, such as vectors, e.g., insect-cell compatible vectors, into such cells and methods of maintaining such cells in culture. See, for example, O'Reilly et al., 1994, Baculovirus Expression Vectors, A Laboratory Manual. Oxford Univ. Press; Satnulski et al., 1989, J. Vir.63:3822-8; Kajigaya et al., 1991 PNAS 88:4646-50; Ruffin et al., 1992, J. Vir. 66:6922-30; Kimbauer et al ., 1996, Vir.21.9:37-44; Zhao et al., 2000, Vir.272:382-93; and U.S. Pat. No. 6,204,059, the contents of each of which are incorporated herein by reference in their entireties.

[0167] In certain embodiments, insect host cell systems, in combination with baculoviral systems (e.g., as described by Luckow et al., 1988, Bio/Technology 6:47) is used. In certain embodiments, the expression system is a Trichoplusia ni, Tn 5B1-4 insect cells/ baculoviral system, which can be used for production of high levels of proteins, as described in U.S. Pat. No. 6,660,521, incorporated herein by reference in its entirety.

[0168] Expansion, culture, transfection, infection, and storage of insect cells can be carried out in any cell culture media, cell transfection media or storage media known in the art. Nonlimiting examples of media are Hyclone SFX Insect Cell Culture Media, Expression System ESF AF Insect Cell Culture Medium, Basal IPL-41 Insect Cell Culture Media, ThermoFisher Sf90011 media, ThermoFisher Sf900111 media, and ThermoFisher Grace's Insect Media. Insect cell mixtures and/or media can also comprise appropriate formulation additives or elements, including but not limited to salts, acids, bases, buffers, and surfactants (such as Poloxamer 188/Pluronic F-68).

[0169] In some embodiments, the methods of the disclosure can be carried out with a mammalian cell type which allows for replication of dependoparvovirus or production of biologic products, and which can be maintained in culture. Host cells include cells derived from mammalian species including but not limited to, human, monkey, mouse, rat, rabbit, and hamster. Host cells can be of any suitable cell type, including but not limited to cell lines, fibroblasts, hepatocytes, tumor cells, and transformed cells. The mammalian cells used can be HEK293, HEK293T, HeLa, CHO, NS0, SP2/0, PER.C6, Vero, RD, BHK, HT 1080, A549, Cos-7, ARPE-19, MRC-5, WEH1, 3T3, 1.0T1/2, MDCK, COS 1, COS 7, BSC 1, BSC 40, BMT 10, W138, Saos, C2C12, HepG2, L cells, primary fibroblast, hepatocyte and myoblast cells derived from mammals, COS cells, C127, 3T3, CHO, HeLa cells, KB cells, BHK, and other mammalian cell lines as described in U.S. Pat. Nos. 6,156,303, 5,387,484, 5,741,683, 5,691,176, 6,428,988 and 5,688,676, 6,541,258, the contents of each of which are incorporated herein by reference.

[0170] In some embodiments, the host cell comprises a nucleic acid encoding a variant capsid polypeptide disclosed herein, where the nucleic acid is integrated into the host cell genome. Such host cells include adenovirus rep and cap genes integrated into the genome. Transcription of the integrated

rep and cap genes may be dependent upon introduction of certain helper virus sequences (e.g., adenovirus E4, E2a and/or VA RNA) into the cell by transduction or other suitable means. Example plasmid free host cells are described in U.S. Patent Application Publication No. 2022/0025396 A1, and U.S. Patent No. US 5,658,785, incorporated herein by reference.

[0171] In some embodiments, the host cells are trans-complementing packaging cell lines that provide functions deleted from a replication-defective helper virus, e.g., HEK293 cells or other Ea trans-complementing cells. In some embodiments, the packaging cell line 293-10-3 is used as described in U.S. Pat. No. 6,281,010, incorporated herein by reference.

[0172] In some embodiments, mammalian host cells (e.g. 293T cells) can be in an adherent state (e.g., adhered/attached to a suitable surface of a cell culture flask, vial, tray, well, tube, etc.). In other embodiments, mammalian host cells can be in a suspended state (e.g., suspended in a medium).

6.5.2. Viral Particle Production

[0173] In some embodiments, providing a cell comprising a nucleic acid described herein comprises introducing the nucleic acid to the cell, e.g., transfecting or transforming the cell with the nucleic acid. In embodiments, the nucleic acids of the disclosure are situated as a part of any genetic element (vector) which can be delivered to a host cell, e.g., naked DNA, a plasmid, phage, transposon, cosmid, episome, a protein in a non-viral delivery vehicle (e.g., a lipid-based carrier), virus, etc. which transfer the sequences carried thereon. Such a vector can be delivered by any suitable method, including transfection, liposome delivery, electroporation, membrane fusion techniques, viral infection, high velocity DNA- coated pellets, and protoplast fusion. A person of skill in the art possesses the knowledge and skill in nucleic acid manipulation to construct any embodiment of this invention and said skills include genetic engineering, recombinant engineering, and synthetic techniques. See, e.g., Sambrook et al, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor, NY.

[0174] In some embodiments, a vector of the disclosure comprises sequences encoding a dependoparvovirus variant capsid polypeptide as provided for herein or a fragment thereof. In some embodiments, a vector of the disclosure comprises sequences encoding a dependoparvovirus rep protein or a fragment thereof. Such a Rep coding region encodes at least for AAV Rep78, Rep68, Rep52, and Rep40, or functional homologs thereof. The Rep coding region is not required to include all wild-type genes but may be altered (e.g., by insertion, deletion, or mutation of one or more nucleotides) so long as the rep genes present provide for sufficient replication functions when expressed in the recombinant cell. The Rep coding region may be derived from any AAV serotype. In some embodiments, the Rep coding region is or comprises a rep gene encoding AAV2 Rep proteins, exemplary sequences of which are provided below.

[0175] AAV2 Rep78:

MPGFYEIVIKVPSDLDGHLPGISDSFVNWVAEKEWELPPDSDMDLNLIEQAPLTVAEKLQRDFLTEWRRV
SKAPEALFFVQFEKGESYFHMHVLVETTGVKSMVLGRFLSQIREKLIQRIYRGIEPTLPNWFAVTKTRNGA
GGGNKVVDECYIPNYLLPKTQPELQWAWTNMEQYLSACLNLTERKRLVAQHLTHVSQTQEQNKENQNP
NSDAPVIRSKTSARYMELVGWLVDKGITSEKQWIQEDQASYISFNAASNSRSQIKAALDNAGKIMSLTKTA
PDYLVGQQPVEDISSNRIYKILELNGYDPQYAASVFLGWATKKFGKRNTIWLFGPATTGKTNIAEAIAHTV
PFYGCVNWTNENFPFNDCVDKMVIWWEEGKMTAKVVESAKAILGGSKVRVDQKCKSSAQIDPTPVIVTS

NTNMCAVIDGNSTTFEHQQPLQDRMFKFELTRRLDHDFGKVTKQEVKDFFRWAKDHVVEVEHEFYVKK GGAKKRPAPSDADISEPKRVRESVAQPSTSDAEASINYADRYQNKCSRHVGMNLMLFPCRQCERMNQ NSNICFTHGQKDCLECFPVSESQPVSVVKKAYQKLCYIHHIMGKVPDACTACDLVNVDLDDCIFEQ (SEQ ID NO:75)

[0176] AAV2 Rep68:

MPGFYEIVIKVPSDLDGHLPGISDSFVNWVAEKEWELPPDSDMDLNLIEQAPLTVAEKLQRDFLTEWRRV SKAPEALFFVQFEKGESYFHMHVLVETTGVKSMVLGRFLSQIREKLIQRIYRGIEPTLPNWFAVTKTRNGA GGGNKVVDECYIPNYLLPKTQPELQWAWTNMEQYLSACLNLTERKRLVAQHLTHVSQTQEQNKENQNP NSDAPVIRSKTSARYMELVGWLVDKGITSEKQWIQEDQASYISFNAASNSRSQIKAALDNAGKIMSLTKTA PDYLVGQQPVEDISSNRIYKILELNGYDPQYAASVFLGWATKKFGKRNTIWLFGPATTGKTNIAEAIAHTV PFYGCVNWTNENFPFNDCVDKMVIWWEEGKMTAKVVESAKAILGGSKVRVDQKCKSSAQIDPTPVIVTS NTNMCAVIDGNSTTFEHQQPLQDRMFKFELTRRLDHDFGKVTKQEVKDFFRWAKDHVVEVEHEFYVKK GGAKKRPAPSDADISEPKRVRESVAQPSTSDAEASINYADRLARGHSL (SEQ ID NO:76)

[0177] AAV2 Rep52:

MELVGWLVDKGITSEKQWIQEDQASYISFNAASNSRSQIKAALDNAGKIMSLTKTAPDYLVGQQPVEDIS SNRIYKILELNGYDPQYAASVFLGWATKKFGKRNTIWLFGPATTGKTNIAEAIAHTVPFYGCVNWTNENFP FNDCVDKMVIWWEEGKMTAKVVESAKAILGGSKVRVDQKCKSSAQIDPTPVIVTSNTNMCAVIDGNSTT FEHQQPLQDRMFKFELTRRLDHDFGKVTKQEVKDFFRWAKDHVVEVEHEFYVKKGGAKKRPAPSDADI SEPKRVRESVAQPSTSDAEASINYADRYQNKCSRHVGMNLMLFPCRQCERMNQNSNICFTHGQKDCLE CFPVSESQPVSVVKKAYQKLCYIHHIMGKVPDACTACDLVNVDLDDCIFEQ (SEQ ID NO:77)

[0178] AAV2 Rep40:

MELVGWLVDKGITSEKQWIQEDQASYISFNAASNSRSQIKAALDNAGKIMSLTKTAPDYLVGQQPVEDIS SNRIYKILELNGYDPQYAASVFLGWATKKFGKRNTIWLFGPATTGKTNIAEAIAHTVPFYGCVNWTNENFP FNDCVDKMVIWWEEGKMTAKVVESAKAILGGSKVRVDQKCKSSAQIDPTPVIVTSNTNMCAVIDGNSTT FEHQQPLQDRMFKFELTRRLDHDFGKVTKQEVKDFFRWAKDHVVEVEHEFYVKKGGAKKRPAPSDADI SEPKRVRESVAQPSTSDAEASINYADRLARGHSL (SEQ ID NO:78)

[0179] In some embodiments the Rep coding region encodes for Rep sequences having at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% sequence identity to one or more AAV2 Rep proteins. In some embodiments, the Rep coding region comprises a nucleotide sequence encoding for a Rep78 protein having at least 80%, at least about 85%, at least about 90%, at least about 95%, at least 98%, at least 99%, or 100% sequence identity to AAV2 Rep78. In some embodiments, the Rep coding region comprises a nucleotide sequence encoding for a Rep68 protein having at least 80%, at least about 85%, at least about 90%, at least about 95%, at least 98%, at least 99%, or 100% sequence identity to AAV2 Rep68. In some embodiments, the Rep coding region comprises a nucleotide sequence encoding for a Rep52 protein having at least 80%, at least about 85%, at least about 90%, at least about 95%, at least 98%, at least 99%, or 100% sequence identity to AAV2 Rep52. In some embodiments, the Rep coding region comprises a nucleotide sequence encoding for a Rep40 protein having at least 80%, at least about 85%, at least about 90%, at least about 95%, at least 98%, at least 99%, or 100% sequence identity to AAV2 Rep40.

[0180] In some embodiments, the Rep coding sequence encodes for wild type Rep proteins. Alternatively, the Rep coding sequence may encode for one or more mutant Rep proteins having improved properties compared with wild type Rep proteins. Examples of such mutant Rep proteins are described in U.S. Patent No. 11,060,070, incorporated herein by reference.

[0181] Additional exemplary Rep gene and protein sequences are disclosed as SEQ ID NOs: 7 to 15 and 20 to 22 of PCT Patent Application Publication No. WO/2022/079429 A1, incorporated herein by reference.

[0182] In some embodiments, such vectors contain both dependoparvovirus cap and rep proteins. In vectors in which both AAV rep and cap are provided, in some embodiments, the dependoparvovirus rep and dependoparvovirus cap sequences are both of the same dependoparvovirus species or serotype origin, such as AAV9. Alternatively, the present embodiments also provides vectors in which the rep sequences are from a dependoparvovirus species or serotype which differs from that which is providing the cap sequences (e.g., AAV2 rep sequences and AAV9 cap sequences). In some embodiments, the rep and cap sequences are expressed from separate sources (e.g., separate vectors, or a host cell genome and a vector). In some embodiments, the rep sequences are fused in frame to cap sequences of a different dependoparvovirus species or serotype to form a chimeric dependoparvovirus vector.

[0183] In some embodiments, a vector of the disclosure comprises one or more helper sequences. Examples of helper sequences include E1a, E1b, E2a, E4, and VA. Certain exemplary helper protein sequences are provided in Section 6.5.1. Additional AAV helper sequences are recognized in the art and include, for example, those described in U.S. Patent Application Publication Nos. 2004/0248288 A1 and 2022/0259572A1, and in PCT Patent Application Publication Nos. WO/1997/017458 A1, WO/2024/143429 A1, and WO/2020/208379 A1, each of which is incorporated herein by reference.

[0184] In some embodiments, the vectors of the disclosure further contain a payload, e.g., a minigene comprising a selected transgene, e.g., flanked by dependoparvovirus 5' ITR and dependoparvovirus 3' ITR. In some embodiments, the ITR is from the same serotype as the variant capsid polypeptide. In some embodiments, the ITR is of a different serotype than the variant capsid polypeptide. In some embodiments, the viral genome comprises two ITR sequence regions, wherein the ITRs are of the same serotype as one another. In some embodiments, the viral genome comprises two ITR sequence regions, wherein 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. 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. Nonlimiting examples of ITR lengths are 102, 105, 130, 140, 141, 142, 145 nucleotides in length.

[0185] The vectors described herein, e.g., a plasmid, are useful for a variety of purposes, but are particularly well suited for use in production of recombinant dependoparvovirus particles comprising dependoparvovirus sequences or a fragment thereof, and in some embodiments, a payload.

[0186] In one aspect, the disclosure provides a method of making a dependoparvovirus particle (e.g., a dependoparvovirus B particle, e.g., an AAV9 particle), or a portion thereof. In some embodiments, the method comprises culturing a host cell which contains a nucleic acid sequence encoding a dependoparvovirus variant capsid protein as provided for herein, or fragment thereof; a functional rep gene (e.g., encoding Rep proteins as described herein); a payload, e.g., a minigene comprising dependoparvovirus inverted terminal repeats (ITRs) and a transgene; and sufficient helper functions to promote packaging of the payload, e.g., minigene, into the dependoparvovirus capsid. In some embodiments, the components necessary to be cultured in the host cell to package a payload, e.g., minigene, in a dependoparvovirus capsid are provided to the host cell in trans. In some embodiments, any one or more of the required components (e.g., payload (e.g., minigene), rep sequences, cap sequences, and/or helper functions) are provided by a host cell which has been engineered to stably comprise one or more of the required components using methods known to those of skill in the art. In some embodiments, a host cell which has been engineered to stably comprise the required component(s) comprises it under the control of an inducible promoter. In some embodiments, the required component(s) are under the control of a constitutive promoter. Examples of suitable inducible and constitutive promoters are provided herein and further examples are known to those of skill in the art. In some embodiments, a selected host cell which has been engineered to stably comprise one or more components comprises a component under the control of a constitutive promoter and another component under the control of one or more inducible promoters. For example, a host cell which has been engineered to stably comprise the required components is generated from 293 cells (e.g., which comprise helper functions under the control of a constitutive promoter), which comprises the rep and/or cap proteins under the control of one or more inducible promoters.

[0187] In some embodiments, the payload (e.g., minigene), rep sequences, cap sequences, and helper functions required for producing a dependoparvovirus particle of the disclosure are delivered to the packaging host cell in the form of any genetic element which transfers the sequences carried thereon (e.g., in a vector or combination of vectors). The genetic element may be delivered by any suitable method, including those described herein. Methods used to construct genetic elements, vectors, and other nucleic acids of the disclosure are known to those with skill and include genetic engineering, recombinant engineering, and synthetic techniques. See, e.g., Sambrook et al, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring Harbor, NY. Similarly, methods of generating rAAV virions are well known and the selection of a suitable method is not a limitation on the present disclosure. See, e.g., K. Fisher et al, J. Virol, 70:520-532 (1993) and US Patent 5,478,745. Unless otherwise specified, the dependoparvovirus ITRs, and other selected dependoparvovirus components described herein, are readily selected from among any dependoparvovirus species and serotypes, e.g., AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh74, or AAV9. ITRs or other dependoparvovirus components may be readily isolated using techniques available to those of skill in the art from a dependoparvovirus species or serotype. Dependoparvovirus species and serotypes may be isolated or obtained from academic, commercial, or public sources (e.g., the American Type Culture Collection, Manassas, VA). In some embodiments, the dependoparvovirus sequences may be obtained through synthetic or other suitable means by reference to published sequences such as are available in the literature or in databases such as, e.g., GenBank or PubMed.

[0188] Methods of expressing proteins (e.g., recombinant or heterologous proteins, e.g., dependoparvovirus polypeptides) in insect cells are well documented, as are methods of introducing nucleic acids, such as vectors, e.g., insect-cell compatible vectors, into such cells and methods of maintaining such cells in culture. See, for example, *METHODS IN MOLECULAR BIOLOGY*, ed. Richard, Humana Press, N J (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); Kirnbauer et al., *Vir.* 219:37-44 (1996); Zhao et al., *Vir.* 272:382-93 (2000); Samulski et al., and U.S. Pat. No. 6,204,059. In some embodiments, a nucleic acid construct encoding dependoparvovirus polypeptides (e.g., a dependoparvovirus genome) in insect cells is an insect cell-compatible vector. An "insect cell-compatible vector" as used herein refers to a nucleic acid molecule capable of productive transformation or transfection of an insect or insect cell. Exemplary biological vectors include plasmids, linear nucleic acid molecules, and recombinant viruses. Any vector can be employed as long as it is insect cell-compatible. The vector may integrate into the insect cell's genome or remain present extra-chromosomally. The vector may be present permanently or transiently, e.g., as an episomal vector. Vectors may be introduced by any means known in the art. Such means include but are not limited to chemical treatment of the cells, electroporation, or infection. In some embodiments, the vector is a baculovirus, a viral vector, or a plasmid. Methods of dependoparvovirus capsid (e.g., AAV) production in insect cells include, for example, those described in U.S. Patent Application Publication No. 2024/0093231 A1, U.S. Patent No. 11,306,291, Joshi et al., 2024, *Methods Mol Biol*, 2829:203-214, and Marwidi et al., 2024, *Mol Ther Methods Clin Dev.,* 32(2)101228, incorporated herein by reference.

[0189] In some embodiments, a nucleic acid sequence encoding a dependoparvovirus polypeptide is operably linked to regulatory expression control sequences for expression in a specific cell type, such as Sf9 or HEK cells. Techniques known to one skilled in the art for expressing foreign genes in insect host cells or mammalian host cells can be used with the compositions and methods of the disclosure. Methods for molecular engineering and expression of polypeptides in insect cells are described, for example, in Summers and Smith. *A Manual of Methods for Baculovirus Vectors and Insect Culture Procedures*, Texas Agricultural Experimental Station Bull. No. 7555, College Station, Tex. (1986); Luckow. 1991. In Prokop et al., *Cloning and Expression of Heterologous Genes in Insect Cells with Baculovirus Vectors' Recombinant DNA Technology and Applications,* 97-152 (1986); King, L. A. and R. D. Possee, *The baculovirus expression system*, Chapman and Hall, United Kingdom (1992); O'Reilly, D. R., L. K. Miller, V. A. Luckow, *Baculovirus Expression Vectors: A Laboratory Manual*, New York (1992); W. H. Freeman and Richardson, C. D., *Baculovirus Expression Protocols, Methods in Molecular Biology*, volume 39 (1995); U.S. Pat. No. 4,745,051; US2003148506; and WO 03/074714. Promoters suitable for transcription of a nucleotide sequence encoding a dependoparvovirus polypeptide include the polyhedron, p10, p35 or IE-1 promoters and further promoters described in the above references are also contemplated.

[0190] In some embodiments, providing a cell comprising a nucleic acid described herein comprises acquiring a cell comprising the nucleic acid.

[0191] Methods of cultivating cells, cell-free systems, and other translation systems are known to those of skill in the art. In some embodiments, cultivating a cell comprises providing the cell with suitable media and incubating the cell and media for a time suitable to achieve viral particle production.

[0192] In some embodiments, a method of making a dependoparvovirus particle further comprises a purification step comprising isolating the dependoparvovirus particle from one or more other components (e.g., from a cell or media component).

[0193] In some embodiments, production of the dependoparvovirus particle comprises one or more (e.g., all) of: expression of dependoparvovirus polypeptides, assembly of a dependoparvovirus capsid, expression (e.g., duplication) of a dependoparvovirus genome, and packaging of the dependoparvovirus genome into the dependoparvovirus capsid to produce a dependoparvovirus particle. In some embodiments, production of the dependoparvovirus particle further comprises secretion of the dependoparvovirus particle into the media. The dependoparvovirus particle can be isolated from the collected media. In other embodiments, dependoparvovirus particles are isolated from host cells. For instance, adherent host cells can subsequently be collected by scraping and/or pelleting and suspended cells can be collected by pelleting and transferred into a receptacle. Collection steps can be repeated as necessary for full collection of produced cells. If necessary, host cell lysis can be achieved by consecutive freeze-thaw cycles (−80°C to 37°C), chemical lysis (such as adding detergent, e.g., triton), mechanical lysis, or by allowing the cell culture to degrade after reaching ~0% viability. Cellular debris can be removed by centrifugation and/or depth filtration.

[0194] In some embodiments, and as described elsewhere herein, the nucleic acid molecule encoding the variant capsid polypeptide is disposed in a dependoparvovirus genome. In some embodiments, and as described elsewhere herein, the nucleic acid molecule encoding the variant capsid polypeptide is packaged into a dependoparvovirus particle along with the dependoparvovirus genome as part of a method of making a dependoparvovirus particle described herein. In other embodiments, the nucleic acid molecule encoding the variant capsid polypeptide is not packaged into a dependoparvovirus particle made by a method described herein.

[0195] In some embodiments, a method of making a dependoparvovirus particle described herein produces a dependoparvovirus particle comprising a payload (e.g., a payload described herein) and the variant capsid polypeptide. In some embodiments, the payload comprises a second nucleic acid (e.g., in addition to the dependoparvovirus genome), and production of the dependoparvovirus particle comprises packaging the second nucleic acid into the dependoparvovirus particle. In some embodiments, a cell, cell-free system, or other translation system for use in a method of making a dependoparvovirus particle comprises the second nucleic acid. In some embodiments, the second nucleic acid comprises an exogenous sequence (e.g., exogenous to the dependoparvovirus, the cell, or to a target cell or subject who will be administered the dependoparvovirus particle). In some embodiments, the exogenous sequence encodes an exogenous polypeptide. In some embodiments, the exogenous sequence encodes a therapeutic product.

[0196] In some embodiments, virus particles of the disclosure have a similar production efficiency to viral particles with a reference capsid polypeptide, for example, with the wild-type capsid polypeptide (SEQ ID NO:1). In some embodiments, production efficiency of viral particles of the disclosure is (a) at

least 0.1-fold, at least 0.2-fold, at least 0.3-fold, at least 0.4-fold, at least 0.5-fold, at least 0.6-fold, at least 0.7-fold, at least 0.8-fold, or at least 0.9-fold and/or (b) up to 1-fold, *e.g.*, as compared to a viral particle with a reference capsid polypeptide, for example, with the wild-type capsid polypeptide (SEQ ID NO:1), or the production efficiency is within any range bounded by a value in (a) and a value in (b). In some embodiments, production efficiency is at least 0.5-fold as compared to a viral particle with the wild-type capsid polypeptide (SEQ ID NO:1). Production efficiency can be evaluated by producing viral particles having a variant capsid with a genome encoding a unique barcode and a fluorescent reporter gene under the control of a ubiquitous (*e.g.*, CBh) or neuronal cell-type specific promoter (e.g., human synapsin) via transient triple transfection of adherent HEK293T followed by iodixanol gradient purification.

[0197] In some embodiments, a nucleic acid or polypeptide described herein is produced by a method known to one of skill in the art. In embodiments, the nucleic acids, polypeptides, and fragments thereof of the disclosure are produced by any suitable means, including recombinant production, chemical synthesis, or other synthetic means. Such production methods are within the knowledge of those of skill in the art and are not a limitation of the present invention.

[0198] Various methods and systems for dependoparvovirus production in host cells are recognized in the art and are contemplated herein including, for example, those described in U.S. Patent Application Publication Nos. 20220064671 A1, 20220259572 A1, 20220025396 A1 and PCT Patent Application Publication Nos. WO/1999/011764 A2, WO/2023/178220 A1, WO/2020/208379 A1, WO/2023/143063 A1, WO/2023/239627 A2, WO/2021/156609 A1, and WO/2021/113767 A1, each of which is incorporated herein by reference in its entirety.

6.6. Applications

[0199] The disclosure is directed, in part, to compositions comprising a nucleic acid, polypeptide, or particles described herein. The disclosure is further directed, in part, to methods utilizing a composition, nucleic acid, polypeptide, or particles described herein. As will be apparent based on the disclosure, nucleic acids, polypeptides, particles, and methods disclosed herein have a variety of utilities.

[0200] The disclosure is directed, in part, to a vector comprising a nucleic acid described herein, e.g., a nucleic acid encoding a variant capsid polypeptide. Many types of vectors are known to those of skill in the art. In some embodiments, a vector comprises a plasmid. In some embodiments, the vector is an isolated vector, e.g., removed from a cell or other biological components.

[0201] The disclosure is directed, in part to a cell, cell-free system, or other translation system, comprising a nucleic acid or vector described herein, e.g., a nucleic acid or vector comprising a nucleic acid molecule encoding a variant capsid polypeptide. In some embodiments, the cell, cell-free system, or other translation system is capable of producing dependoparvovirus particles comprising the variant capsid polypeptides. In some embodiments, the cell, cell-free system, or other translation system comprises a nucleic acid comprising a dependoparvovirus genome or components of a dependoparvovirus genome sufficient to promote production of dependoparvovirus particles comprising the variant capsid polypeptides.

[0202] In some embodiments, the cell, cell-free system, or other translation system further comprises one or more non-dependoparvovirus nucleic acid sequences that promote dependoparvovirus particle production and/or secretion. Said sequences are referred to herein as helper sequences. In some

embodiments, a helper sequence comprises one or more genes from another virus, e.g., an adenovirus or herpes virus. In some embodiments, the presence of a helper sequence is necessary for production and/or secretion of a dependoparvovirus particle. In some embodiments, a cell, cell-free system, or other translation system comprises a vector, e.g., plasmid, comprising one or more helper sequences.

[0203] In some embodiments, a cell, cell-free system, or other translation system comprises a first nucleic acid and a second nucleic acid, wherein the first nucleic acid comprises sequences encoding one or more dependoparvovirus genes (e.g., a Cap gene, a Rep gene, or a complete dependoparvovirus genome) and a helper sequence, and wherein the second nucleic acid comprises a payload. In some embodiments, a cell, cell-free system, or other translation system comprises a first nucleic acid and a second nucleic acid, wherein the first nucleic acid comprises sequences encoding one or more dependoparvovirus genes (e.g., a Cap gene, a Rep gene, or a complete dependoparvovirus genome) and a payload, and wherein the second nucleic acid comprises a helper sequence. In some embodiments, a cell, cell-free system, or other translation system comprises a first nucleic acid and a second nucleic acid, wherein the first nucleic acid comprises a helper sequence and a payload, and wherein the second nucleic acid comprises sequences encoding one or more dependoparvovirus genes (e.g., a Cap gene, a Rep gene, or a complete dependoparvovirus genome). In some embodiments, a cell, cell-free system, or other translation system comprises a first nucleic acid, a second nucleic acid, and a third nucleic acid, wherein the first nucleic acid comprises sequences encoding one or more dependoparvovirus genes (e.g., a Cap gene, a Rep gene, or a complete dependoparvovirus genome), the second nucleic acid comprises a helper sequence, and the third nucleic acid comprises a payload.

[0204] In some embodiments, the first nucleic acid, second nucleic acid, and optionally third nucleic acid are situated in separate molecules, e.g., separate vectors or a vector and genomic DNA. In some embodiments, one, two, or all of the first nucleic acid, second nucleic acid, and optionally third nucleic acid are integrated (e.g., stably integrated) into the genome of a cell.

[0205] In embodiments, a cell of the disclosure is generated by transfecting a suitable cell with a nucleic acid described herein. In some embodiments, a method of making a dependoparvovirus particle comprising a variant capsid polypeptide as provided for herein or improving a method of making a dependoparvovirus particle comprises providing a cell described herein. In some embodiments, providing a cell comprises transfecting a suitable cell with one or more nucleic acids described herein.

[0206] Many types and kinds of cells suitable for use with the nucleic acids and vectors described herein are known in the art. In some embodiments, the cell is a human cell. In some embodiments, the cell is an immortalized cell or a cell from a cell line known in the art. In some embodiments, the cell is an HEK293 cell. In some embodiments, the cell is an HEK293T cell.

6.6.1. Methods of delivering a payload

[0207] The disclosure is directed, in part, to a method of delivering a payload to a cell, e.g., a cell in a subject or in a sample. In some embodiments, a method of delivering a payload to a cell comprises contacting the cell with a dependoparvovirus particle comprising a variant capsid polypeptide (e.g., described herein) comprising the payload. The disclosure also includes a dependoparvovirus particle comprising a variant capsid polypeptide (e.g., described herein) comprising a payload described herein for use in the methods of delivering a payload described herein. In some embodiments, the

dependoparvovirus particle is a dependoparvovirus particle described herein and comprises a payload described herein. In some embodiments, the cell is a CNS cell (e.g., a neuron (e.g., an excitatory neuron, interneurons, or medium spiny neuron), astrocyte, glial cell, oligodendrocyte). In some embodiments, the cell is a skeletal muscle cell. Non-limiting examples of skeletal muscles include the biceps, the triceps, the quadriceps, the tibialis interior, the gastrocnemius muscle, and diaphragm. In some embodiments, the cell is a cardiac muscle cell. In some embodiments, the method is conducted ex vivo. In some embodiments, the cell is a cell in an ex vivo sample that has been obtained from a subject.

[0208] In some embodiments, the payload comprises a transgene. In some embodiments, the transgene is a nucleic acid sequence heterologous to the vector sequences flanking the transgene which encodes a polypeptide, RNA (e.g., a miRNA or siRNA) or other product of interest. In embodiments, the nucleic acid of the transgene is operatively linked to a regulatory component in a manner sufficient to promote transgene transcription, translation, and/or expression in a host cell.

[0209] In aspects, a transgene is any polypeptide- or RNA-encoding sequence and the transgene selected will depend upon the use envisioned. In some embodiments, a transgene comprises a reporter sequence, which upon expression produces a detectable signal. Such reporter sequences include, without limitation, DNA sequences encoding colorimetric reporters (e.g., β-lactamase, β-galactosidase (LacZ), alkaline phosphatase), cell division reporters (e.g., thymidine kinase), fluorescent or luminescence reporters (e.g., green fluorescent protein (GFP) or luciferase), resistance conveying sequences (e.g., chloramphenicol acetyltransferase (CAT)), or membrane bound proteins including to which high affinity antibodies directed thereto exist or can be produced by conventional means, e.g., comprising an antigen tag, e.g., hemagglutinin or Myc.

[0210] In some embodiments, a reporter sequence operably linked with regulatory elements which drive their expression, provide signals detectable by conventional means, including enzymatic, radiographic, colorimetric, fluorescence or other spectrographic assays, fluorescent activating cell sorting assays and immunological assays, including enzyme linked immunosorbent assay (ELISA), radioimmunoassay (RIA) and immunohistochemistry. In some embodiments, the transgene encodes a product which is useful in biology and medicine, such as RNA, proteins, peptides, enzymes, dominant negative mutants. In some embodiments, the RNA comprises a tRNA, ribosomal RNA, dsRNA, catalytic RNAs, small hairpin RNA, siRNA, trans-splicing RNA, and antisense RNAs. In some embodiments, the RNA inhibits or abolishes expression of a targeted nucleic acid sequence in a treated subject (e.g., a human or animal subject).

[0211] In some embodiments, the transgene is used to correct or ameliorate gene deficiencies. In some embodiments, gene deficiencies include deficiencies in which normal genes are expressed at less than normal levels or deficiencies in which the functional gene product is not expressed. In some embodiments, the transgene encodes a therapeutic protein or polypeptide which is expressed in a host cell. In some embodiments, a dependoparvovirus particle comprises or delivers multiple transgenes, e.g., to correct or ameliorate a gene defect caused by a multi-subunit protein. In some embodiments, a different transgene (e.g., each situated/delivered in a different dependoparvovirus particle, or in a single dependoparvovirus particle) is used to encode each subunit of a protein, or to encode different peptides or proteins, e.g., when the size of the DNA encoding the protein subunit is large, e.g., for immunoglobulin, platelet-derived growth factor, or dystrophin protein. In some embodiments, different subunits of a protein are encoded by the same transgene, e.g., a single transgene encoding each of the

subunits with the DNA for each subunit separated by an internal ribozyme entry site (IRES). In some embodiments, the DNA is separated by sequences encoding a 2A peptide, which self-cleaves in a post-translational event. See, e.g., Donnelly et al, *J. Gen. Virol.,* 78(Pt 1):13-21 (January 1997); Furler, et al, *Gene Ther.,* 8(11):864-873 (June 2001); Klump et al., *Gene Ther* 8(10):811-817 (May 2001) (incorporated herein by reference in its entirety).

[0212] In some embodiments, virus particles comprising a genome are provided, wherein the genome includes a nucleic acid expression construct. The nucleic acid expression construct can include a heterologous transgene and one or more regulatory elements.

[0213] In some embodiments, the regulatory elements include a promotor, e.g., a promoter that is active in a target cell or tissue type of interest. In some embodiments, the promoter is a ubiquitous promoter. In other embodiments, the promoter is selective or specific to a target cell or tissue type (e.g., CNS and/or muscle (e.g. broad muscle expression or skeletal muscle or cardiac muscle)), and, optionally, is less (or not) active in a cell or tissue type where transgene expression is not desired (e.g., liver, spleen, PNS, or any combination of two or all of the foregoing). A promoter that is selective for a first cell or tissue type over a second cell or tissue type is active in the first cell or tissue type and less active or silent in the second cell or tissue type. In some embodiments, the promoter is a CNS-specific or CNS-selective promoter. In some embodiments, the promoter is a muscle-specific promoter-specific or muscle-selective promoter. In some embodiments, the promoter is active in both CNS and muscle tissue.

[0214] In some embodiments, the promoter is a ubiquitous or constitutive promoter active in a mammalian cell, for example a human cell, for example, in a human cell type of interest. In some embodiments, the cell type is a CNS cell such as, for example, a neuronal cell, a glial cell, an endothelia cell, and the like. In some embodiments, the cell type is a skeletal muscle cell. In some embodiments, the cell type is a cardiac muscle cell. Examples of ubiquitous promoters include, but are not limited, to a CAG promoter (hybrid from a cytomegalovirus early enhancer element, a chicken-beta actin promoter, e.g., the first exon and the first intron of the chicken beta actin gene, and the splice acceptor of the rabbit beta globin gene), chicken-beta actin promoter, CBA promoter, CBh promoter, CB6 promoter, CMV promoter, human EF1-alpha promoter, PGK promoter, ubiquitin C (UBC) promoter and fragments thereof. In some embodiments, the promoter is a tissue-specific promoter, for example, a promoter specific in CNS tissue or cells of the CNS. Examples of CNS-specific promoters include but are not limited to a synapsin (SYN or SYN1) promoter, a neuron-specific enolase (NSE) promoter, a Ca^{2+}/calmodulin-dependent kinase subunit α (CaMKII) promoter, a synapsin I with a minimal CMV sequence (SynI-minCMV) promoter, a glial fibrillary acidic protein (GFAP) promoter, a internexin neuronal intermediate filament protein alpha (INA) promoter, a nestin (NES) promoter, a neurofilament light chain (NfL) promoter, a neurofilament heavy chain (NfH) promoter, a myelin-associated oligodendrocyte basic protein (MOBP) promoter, a myelin basic protein (MBP) promoter, a tyrosine hydroxylase (TH) promoter, a forkhead box A2 (FOXA2) promoter, a aldehyde dehydrogenase 1 family member L1 (ALDH1L1) promoter, a glutamate decarboxylase 2 (GAD2) promoter, a riken gene A930098C07Rik (A93) promoter, a somatostatin (SST) promoter, a platelet derived growth factor receptor alpha (PDGFRA) promoter, a glutamate receptor metabotropic 1 (GRM1) promoter, a C-type natriuretic peptide precursor (NPPC) promoter, a adrenomedullin (ADM) promoter, a type 2 lactosamine alpha-2,3-sialyltransferase (ST3GAL6) promoter, a ras responsive element binding protein 1 (RREB1) promoter, a deiodinase iodothyronine type II (DIO2)

promoter, an excitatory amino acid transporter 2 (EAAT2) promoter, a nuclear receptor subfamily 2 group F member 2 (NR2F2) promoter, a platelet-derived growth factor (PDGF) promoter, a methyl-CpG binding protein 2 (MeCP2) promoter, and mouse, primate or human homologs of any of the forgoing, and fragments (e.g., active fragments) of any of the foregoing. In embodiments, the CNS-specific promoter is a neuron specific promoter. In embodiments, the CNS-specific promoter is an astrocyte-specific promoter. In some embodiments, the promoter is a promoter specific in muscle tissue or muscle cells, e.g., a desmin, MCK, TNNT2, or smooth muscle 22 (SM22) promoter. Further exemplary muscle specific promoters are described below.

[0215] In some embodiments, the promoter is a CBh promoter. An exemplary CBh promoter sequence is set forth as SEQ ID NO:14. In some embodiments, the CBh promoter comprises a nucleotide sequence having at least 90%, at least 95%, at least 96%, at least 97%, or at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO:14

[0216] In other embodiments, the promoter is a synapsin promoter, for example a human synapsin promoter (hSYN). An exemplary hSYN promoter sequence is set forth as SEQ ID NO:15. In some embodiments, the hSYN promoter comprises a nucleotide sequence having at least 90%, at least 95%, at least 96%, at least 97%, or at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO:15.

[0217] In some embodiments, the nucleic acid expression construct comprises an intron. In embodiments, the intron is disposed between the promoter and the heterologous transgene. In some aspects, the intron is disposed 5' to the heterologous transgene on the expression construct, for example immediately 5' to the heterologous transgene or 100 nucleotides or less 5' to the heterologous transgene. In some aspects, the intron is a chimeric intron derived from human b-globin and Ig heavy chain (also known as b- globin splice donor/immunoglobulin heavy chain splice acceptor intron, or b-globin/IgG chimeric intron; Reed, R., et al. Genes and Development, 1989, incorporated herein by reference in its entirety). In other aspects, the intron is a VH4 intron or a SV40 intron.

[0218] As provided herein, in some embodiments, virus particles comprising a payload, wherein the payload includes a nucleic acid that includes a heterologous transgene are provided. In some embodiments, the heterologous transgene encodes an RNA interference agent, for example a siRNA, shRNA or other interfering nucleic acid.

[0219] In some embodiments, the payload includes a heterologous transgene that encodes a therapeutic polypeptide. In some aspects, the heterologous transgene is a human gene or fragment thereof. In some aspects, the therapeutic polypeptide is a human protein. In some embodiments, the heterologous transgene of the virus particle encodes a molecule useful in treating a disease, and the virus particle is administered to a patient in need thereof to treat said disease. In some aspects the payload comprises a molecule that is effective in treating chronic CNS disease, such as, for example, an RNA interference nucleotide (e.g., shRNA, siRNA or miRNA that inhibits APOL-1). Examples of diseases (and heterologous transgenes or molecules encoded by said heterologous transgenes) according to the present disclosure include: MPSI (alpha-L-iduronidase (IDUA)); MPS II – Hunter syndrome (iduronate-2-sulfatase (IDS)); Ceroid lipofuscinosis-Batten disease (CLN1, CLN2, CLN10, CLN13, CLN5, CLN11, CLN4, CNL14, CLN3, CLN6, CLN7, CLN8, CLN12); MPS IIIa - Sanfilippo Type A syndrome (heparin sulfate sulfatase (also called N-sulfoglucosamine sulfohydrolase (SGSH)); MPS IIIB – Sanfilippo Type b

syndrome (N-acetyl-alpha-D-glucosaminidase (NAGLU)); MPS VI - Maroteaux-Lamy syndrome (arylsulfatase B); MPS IV A - Morquio syndrome type A (GALNS); MPS IV B – Morquio syndrome type B (GLB1); chronic or neuropathic pain; Osteogenesis Imperfecgta Type I, II, III or IV (COL1Al and/or COL1A2); hereditary angioedema (SERPING1, C1NH); Osteogenesis Imperfecta Type V (IFITM5); Osteogenesis Imperfecta Type VI (SERPINF1); Osteogenesis Imperfecta Type VII (CRTAP); Osteogenesis Imperfecta Type VIII (LEPRE1 and/or P3H1); Osteogenesis Imperfecta Type IX (PPIB); Gaucher disease type I, II and III (Glucocerebrosidase; GBAl); Parkinson's Disease (Glucocerebrosidase; GBAl and/or dopamine decarboxylase); Pompe (acid maltase; GAA; hGAA); Metachromatic leukodystrophy (Aryl sulfatase A); MPS VII - Sly syndrome (beta-glucuronidase); MPS VIII (glucosamine-6-sulfate sulfatase); MPS IX (Hyaluronidase); maple syrup urine disease (BCKDHA, BCKDHB, and/or DBT); Niemann-Pick disease (Sphingomyelinase); Parkinson's disease (anti-alpha synuclein RNAi); Alzheimer's disease (anti-mutant APP RNAi); Niemann-Pick disease without sphingomyelinase deficiency (NPC1 or NPC gene encoding a cholesterol metabolizing enzyme); Tay-Sachs disease (alpha subunit of beta-hexosaminidase); Sandhoff disease (both alpha and beta subunit of beta-hexosaminidase); Fabry Disease (alpha-galactosidase); Fucosidosis (fucosidase (FUCAl)); Alpha-mannosidosis (alpha-mannosidase); Beta-mannosidosis (beta-mannosidase); Wolman disease (cholesterol ester hydrolase); Dravet syndrome (SCN1A, SCN1B, SCN2A, GABRG2); Parkinson's disease (Neurturin); Parkinson's disease (glial derived growth factor (GDGF)); Parkinson's disease (tyrosine hydroxylase); frontotemporal dementia (progranulin); Angleman syndrome (ubiquitin protein ligase 3A (UBE3A), gene editing systems targeting a UBE3A inhibitory RNA (UBE3A-anitsense transcript)); Parkinson's disease (glutamic acid decarboxylase; FGF-2; BDGF); Spinal Muscular Atrophy (SMN, including SMN1 or SMN2); Friedreich's ataxia (Frataxin); Amyotrophic lateral sclerosis (ALS) (SOD1 inhibitor, e.g., anti-SOD1 RNAi); Glycogen Storage Disease Ia (Glucose-6-phosphatase); XLMTM (MTMl); Crigler Najjar (UGTlAl); CPVT (CASQ2); spinocerebellar ataxia (ATXN2; ATXN3 or other ATXN gene; anti-mutant Machado-Joseph disease/SCA3 allele RNAi); Rett syndrome (MECP2 or fragment thereof); Achromatopsia (CNGB3, CNGA3, GNAT2, PDE6C); Choroidermia (CDM); Danon Disease (LAMP2); Cystic Fibrosis (CFTR or fragment thereof); Duchenne Muscular Dystrophy (Mini-/ Micro-Dystrophin Gene); SARS-Cov-2 infection (anti-SARS-Cov-2 RNAi, SARS-Cov-2 genome fragments or S protein (including variants)); Limb Girdle Muscular Dystrophy Type 2C - Gamma-sarcoglycanopathy (human-alpha-sarcoglycan); Advanced Heart Failure (SERCA2a); Rheumatoid Arthritis (TNFR:Fc Fusion; anti-TNF antibody or fragment thereof); Leber Congenital Amaurosis (GAA); X-linked adrenoleukodystrophy (ABCD1); Limb Girdle Muscular Dystrophy Type 2C - Gamma-sarcoglycanopathy (gamma-sarcoglycan); Angelman syndrome (UBE3A); Retinitis Pigmentosa (hMERTK); Age-Related Macular Degeneration (sFLT01); Phelan-McDermid syndrome (SHANK3; 22q13.3 replacement); Becker Muscular Dystrophy and Sporadic Inclusion Body Myositis (huFollistatin344); Parkinson's Disease (GDNF); Metachromatic Leukodystrophy – MLD (cuARSA); Hepatitis C (anti-HCV RNAi); Limb Girdle Muscular Dystrophy Type 2D (hSGCA); Human Immunodeficiency Virus Infections; (PG9DP); Acute Intermittant Porphyria (PBGD); Leber's Hereditary Optical Neuropathy (PIND4v2); Alpha-1 Antitrypsin Deficiency (alphaIAT); X-linked Retinoschisis (RS1); Choroideremia (hCHM); Giant Axonal Neuropathy (GAN); Hemophilia B (Factor IX); Homozygous FH (hLDLR); Dysferlinopathies (DYSF); Achromatopsia (CNGA3 or CNGB3); Progressive supranuclear palsy (MAPT; anti-Tau; anti-MAPT RNAi); Omithine Transcarbamylase deficiency (OTC); Hemophilia A (Factor VIII); Age-related macular degeneration

(AMD), including wetAMD (anti-VEGF antibody or RNAi); X-Linked Retinitis Pigmentosa (RPGR); Myotonic dystrophy Type 1 (DMPK; anti-DMPK RNAi, including anti-CTG trinucleotide repeat RNAi); Myotonic dystrophy Type 2 (CNBP); Facioscapulohumeral muscular dystrophy (D4Z4 DNA); oculopharynggeal muscular dystrophy (PABPN1; mutated PABPN1 inhibitor (e.g., RNAi)); Mucopolysaccharidosis Type VI (hARSB); Leber Hereditary Optic Neuropathy (ND4); X-Linked myotubular Myopathy (MTMI); Crigler-Najjar Syndrome (UGTIAI); Retinitis Pigmentosa (hPDE6B); Mucopolysaccharidosis Type 3B (hNAGLU); Duchenne Muscular Dystrophy (GALGT2); Alzheimer's Disease (NGF; ApoE4; ApoE2; ApoE3; Anti-ApoE RNAi, MAPT, anti-Tau antibody, anti-amyloid beta antibody (e.g., aducanumab)); multiple system atrophy; Familial Lipoprotein Lipase Deficiency (LPL); Alpha-1 Antitrypsin Deficiency (hAAT); Leber Congenital Amaurosis 2 (hRPE65v2); Batten Disease; Late Infantile Neuronal Lipofuscinosis (CLN2); Huntington's disease (HTT; anti-HTT RNAi); Fragile X syndrome (FMR1); Fragile X-associated tremor/ataxia syndrome (FMR1), Premature ovarian aging (FMR1), Polycystic ovarian syndrome (FMR1), Leber's Hereditary Optical Neuropathy (PIND4v2); Aromatic Amino Acid Decarboxylase Deficiency (hAADC); Retinitis Pigmentosa (hMERKTK); and Retinitis Pigmentosa (RLBPI). In some embodiments, the CNS disease is a tauopathy (e.g., Alzheimers' disease, progressive supranuclear palsy, frontotemporal dementia (Pick disease), corticobasal degeneration, argyrophilic grain disease, globular glial tauopathies, neurofibrillary tangle dementia, chronic traumatic encephalopathy (CTE), or aging-related tau astrogliopathy) and the payload is an anti-Tau antibody or antisense oligonucleotide targeting MAPT. In some aspects, the payload comprises a molecule that is effective in treating muscle-related disease. Exemplary, non-limiting muscle-related diseases are described below.

[0220] In some embodiments, the heterologous transgene encodes a therapeutic polypeptide. In some aspects, the heterologous transgene is a human gene or fragment thereof. In some aspects, the therapeutic polypeptide is a human protein. In some aspects, the heterologous transgene encodes an antibody or fragment thereof (for example an antibody light chain, an antibody heavy chain, a Fab or an scFv). Examples of antibodies or fragments thereof that are encoded by the heterologous transgene include but are not limited to: and an anti-Ab antibody (e.g., solanezumab, GSK933776, and lecanemab), anti-sortilin (e.g., AL-001), anti-Tau (e.g., ABBV-8E12, UCB-0107, and NI- 105), anti-SEMA4D (e.g., VX15/2503), anti-alpha synuclein (e.g., prasinezumab, NI-202, and MED-1341), anti- SOD1 (e.g., NI-204), anti-CGRP receptor (e.g., eptinezumab, fremanezumab, or galcanezumab), anti-VEGF (e.g., sevacizumab, ranibizumab, bevacizumab, and brolucizumab), anti-EpoR (e.g., LKA-651,), anti-ALKI (e.g., ascrinvacumab), anti-C5 (e.g., tesidolumab, ravulizumab, and eculizumab), anti-CD105 (e.g., carotuximab), anti-CCIQ (e.g., ANX-007), anti-TNFa (e.g., adalimumab, infliximab, and golimumab), anti-RGMa (e.g., elezanumab), anti-TTR (e.g., NI-301 and PRX-004), anti-CTGF (e.g., pamrevlumab), anti-IL6R (e.g., satralizumab, tocilizumab, and sarilumab), anti-IL6 (e.g., siltuximab, clazakizumab, sirukumab, olokizumab, and gerilimzumab), anti-IL4R (e.g., dupilumab), anti-IL17A (e.g., ixekizumab and secukinumab), anti-IL5R (e.g., reslizumab), anti-IL-5 (e.g., benralizumab and mepolizumab), anti-IL13 (e.g., tralokinumab), anti-IL12/IL23 (e.g., ustekinumab), anti-CD 19 (e.g., inebilizumab), anti-IL31RA (e.g., nemolizumab), anti-ITGF7 mAb (e.g., etrolizumab), anti-SOST mAb (e.g., romosozumab), anti-IgE (e.g., omalizumab), anti-TSLP (e.g., nemolizumab), anti-pKal mAb (e.g., lanadelumab), anti-ITGA4 (e.g., natalizumab), anti- ITGA4B7 (e.g., vedolizumab), anti-BLyS (e.g., belimumab), anti-PD-1 (e.g., nivolumab and pembrolizumab), anti-RANKL (e.g., denosumab), anti-PCSK9 (e.g., alirocumab and evolocumab),

anti-ANGPTL3 (e.g., evinacumab*), anti-OxPL (e.g., E06), anti-fD (e.g., lampalizumab), or anti-MMP9 (e.g., andecaliximab), optionally wherein the heavy chain (Fab and Fc region) and the light chain are separated by a self-cleaving furin (F)/F2A or furin (F)/T2A, IRES site, or flexible linker, for example, ensuring expression of equal amounts of the heavy and the light chain polypeptides.

[0221] In some embodiments, the virus particle comprises a heterologous transgene encoding a genome editing system. Examples include a CRISPR genome editing system (e.g., one or more components of a CRISPR genome editing system such as, for example, a guide RNA molecule and/or a RNA-guided nuclease such as a Cas enzyme such as Cas9, Cpf1 and the like), a zinc finger nuclease genome editing system, a TALEN genome editing system or a meganuclease genome editing system. In embodiments, the genome editing system targets a mammalian, e.g., human, genomic target sequence. In embodiments, the virus particle includes a heterologous transgene encoding a targetable transcription regulator. Examples include a CRISPR-based transcription regulator (for example, one or more components of a CRISPR-based transcription regulator, for example, a guide RNA molecule and/or a enzymatically-inactive RNA-guided nuclease/transcription factor ("TF") fusion protein such as a dCas9-TF fusion, dCpf1-TF fusion and the like), a zinc finger transcription factor fusion protein, a TALEN transcription regulator or a meganuclease transcription regulator.

[0222] In some embodiments, components of a therapeutic molecule or system are delivered by more than one unique virus particle (e.g., a population that includes more than one unique virus particles). In other embodiments, the therapeutic molecule or components of a therapeutic molecule or system are delivered by a single unique virus particle (e.g., a population that includes a single unique virus particle).

[0223] In embodiments, the transgene encodes any biologically active product or other product, e.g., a product desirable for study. Suitable transgenes may be readily selected by persons of skill in the art, such as those, but not limited to, those described herein.

[0224] Other examples of proteins encoded for by the transgene include, but are not limited to, colony stimulating factors (CSF); blood factors, such as β-globin, hemoglobin, tissue plasminogen activator or an analog thereof such as reteplase, lanoteplase or tenecteplase, and coagulation factors; interleukins; soluble receptors, such as soluble TNF-α. receptors, soluble VEGF receptors, soluble interleukin receptors (e.g., soluble IL-1 receptors and soluble type II IL-1 receptors), or ligand-binding fragments of a soluble receptor; growth factors, such as keratinocyte growth factor (KGF), stem cell factor (SCF), or fibroblast growth factor (FGF, such as basic FGF and acidic FGF); enzymes; chemokines,; enzyme activators, such as tissue plasminogen activator; angiogenic agents, such as vascular endothelial growth factors, glioma-derived growth factor, angiogenin, or angiogenin-2; anti-angiogenic agents, such as a soluble VEGF receptor; a protein vaccine; neuroactive peptides, such as nerve growth factor (NGF) or oxytocin; thrombolytic agents; tissue factors; macrophage activating factors; tissue inhibitors of metalloproteinases; or IL-1 receptor antagonists.

[0225] In embodiments, the disclosure provides a nucleotide sequence which encodes a molecule for the treatment of Alzheimer's disease. In embodiments, the molecule for the treatment of Alzheimer's disease comprises an inhibitory nucleic acid molecule (e.g., an antisense oligonucleotide or inhibitory RNA (e.g., siRNA, miRNA or shRNA molecule). In embodiments, the molecule for the treatment of Alzheimer's disease comprises an inhibitory nucleic acid molecule (e.g., an antisense oligonucleotide or

inhibitory RNA (e.g., siRNA, miRNA or shRNA molecule) targeting beta-amyloid, alpha-synuclein, Tau, TREM, e.g., TREM2, or an apolipoprotein (APO) E protein, e.g. APOE1, APOE2, APOE3 or APOE4.

[0226] In embodiments, the molecule for the treatment of Alzheimer's disease comprises a genome editing system (for example a zinc finger nuclease, a meganuclease, a TALEN, or an RNA-guided genome editing system (e.g. a Cas polypeptide and a guide RNA molecule). In embodiments the genome editing system targets a genetic region encoding a beta-amyloid protein or a Tau protein. In embodiments, the genome editing system targets MSA4.

[0227] In embodiments, the molecule for the treatment of Alzheimer's disease is an antibody or antigen-binding fragment thereof (e.g., as scFV). In embodiments, the molecule for the treatment of Alzheimer's disease is a human protein or fragment or variant thereof. In embodiments, the molecule for the treatment of Alzheimer's disease is an inhibitor of beta-amyloid aggregation. In embodiments, the molecule for the treatment of Alzheimer's disease is an inhibitor of alpha-synuclein. In embodiments, the molecule for the treatment of Alzheimer's disease is an anti-beta amyloid antibody, e.g., gantenerumab, crenezumab, aducanumab, lecanemab, bapineuzumab, solanezumab, donanemab or trontinemab (which is an anti-beta amyloid / anti-transferrin receptor bispecific antibody). In embodiments, the molecule for the treatment of Alzheimer's disease is a Tau inhibitor, e.g., an anti-tau antibody (e.g., semorinemab). In embodiments, the molecule for the treatment of Alzheimer's disease is an anti-TREM antibody or antigen-binding fragment thereof. In embodiments, the molecule for the treatment of Alzheimer's disease is human nerve growth factor or a fragment or variant thereof. In embodiments, the molecule for the treatment of Alzheimer's disease is human brain-derived neurotrophic factor or a fragment or variant thereof. In embodiments, the molecule for the treatment of Alzheimer's disease is human synapsin-caveolin-1 (SynCav1) or a fragment or variant thereof.

[0228] Accordingly, in certain aspects, is the disclosure provides a virus particle comprising (a) a variant capsid polypeptide described herein, e.g., a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Alzheimer's disease, for example as described herein, and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0229] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described in Section 6.2; (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Alzheimer's disease, for example as described herein, and (ii) a promoter operably linked to said nucleotide sequence.

[0230] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Alzheimer's disease, for example gantenerumab or an antigen binding fragment thereof, and (ii) a promoter operably

linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0231] In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Alzheimer's disease, for example crenezumab or an antigen binding fragment thereof, and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0232] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of myasthenia Gravis disease, for example an anti-IL-6 antibody (e.g., satralizumab) or antigen-binding fragment thereof, and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0233] In embodiments, the disclosure provides a nucleotide sequence which encodes a molecule for the treatment of Parkinson's disease. In embodiments, the molecule for the treatment of Parkinson's disease comprises an inhibitory nucleic acid molecule (e.g., an antisense oligonucleotide or inhibitory RNA (e.g., siRNA, miRNA or shRNA molecule). In embodiments, the molecule for the treatment of Parkinson's disease comprises an inhibitory nucleic acid molecule (e.g., an antisense oligonucleotide or inhibitory RNA (e.g., siRNA, miRNA or shRNA molecule) targeting SNCA. An exemplary accession number for human SNCA is set forth in Table 3, together with example antisense oligonucleotide targeting SNCA.

[0234] In embodiments, the molecule for the treatment of Parkinson's disease comprises a genome editing system (for example a zinc finger nuclease, a meganuclease, a TALEN, or an RNA-guided genome editing system (e.g. a Cas polypeptide and a guide RNA molecule). In embodiments the genome editing system targets a genetic region encoding an alpha-synuclein protein (e.g., SNCA gene).

[0235] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Parkinson's disease, for example an anti-alpha synuclein antibody (e.g., prasinezumab or BIIB054) or antigen-binding fragment thereof, and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence (e.g., a human GBA1 gene or fragment or variant thereof, e.g., a variant thereof having at least 90% or at least 95% sequence identity to human GBA1) encoding a molecule for the treatment of Parkinson's disease, for example human beta-glucocerebrosidase or a fragment thereof, and (ii) a promoter operably linked to said nucleotide sequence. An exemplary accession number for human GBA1 is set forth in Table 2. Example human GBA1 variants (e.g., single nucleotide polymorphism containing variants) are disclosed in PCT Patent Application Publication No. WO/2023/004370/A1, incorporated herein by reference in its entirety. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Parkinson's disease, for example an inhibitor of LRRK2, and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Parkinson's disease, for example a trophic factor (e.g., glial cell line-derived neurotrophic factor (GDNF) or cerebral dopamine neurotrophic factor (CDNF)) or a fragment thereof, and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Parkinson's disease, for example an antisense RNA (e.g., antisense RNA targeting alpha-synuclein, or SNCA, gene) or a fragment thereof, and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0236] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence (e.g., a human GBA gene, e.g., a human GBA1 gene) encoding a molecule for the treatment of Gaucher's disease, for example a human glucocerebrosidase (GCase, e.g. beta-glucosylceramidase-1) or fragment or variant thereof, and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide

sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0237] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of multiple sclerosis, for example an anti-CD20 antibody (e.g., ocrelizumab, rituximab, ofatumumab, or RG6035 / RO7121932 (an anti-CD20, anti-transferrin receptor bispecific antibody sometimes known as Brainshuttle (BS) CD20-Multiple Sclerosis) or antigen-binding fragment thereof, and (ii) a promoter operably linked to said nucleotide sequence. In embodiments the multiple sclerosis is relapsing remitting multiple sclerosis. In embodiments the multiple sclerosis is primary progressing multiple sclerosis. In embodiments the multiple sclerosis is secondary progressive multiple sclerosis. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0238] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Huntington's disease, for example an inhibitory nucleic acid directed to mutated huntingtin protein (HTT) (e.g., tominersen, WVE-120101 or WVE-120102), and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0239] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Phelan McDermid syndrome, for example human SHANK3 or fragment or variant thereof (e.g., a variant thereof having at least 90% or at least 95% sequence identity to human SHANK3), and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Phelan McDermid syndrome, for example a human growth hormone, e.g., human insulin like growth factor 1 (IGF-1), or fragment or variant thereof (e.g., a variant thereof having at least 90% or at least 95% sequence identity to human IGF-1), and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence,

and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0240] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of frontotemporal dementia, for example human progranulin or granulin, or fragment or variant thereof, and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of frontotemporal dementia, for example an anti-tau antibody (e.g., semorinemab), or fragment or variant thereof, and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of frontotemporal dementia, for example an inhibitory nucleic acid which targets SOD-1 (e.g., tofersen), and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0241] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of amyotrophic lateral sclerosis (ALS), for example an inhibitory nucleic acid which targets SOD-1 (e.g., tofersen), and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of ALS, for example an inhibitory nucleic acid which targets C9orf72 (e.g., BIIB078), and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of ALS, for example an inhibitory nucleic acid which targets ATXN2 (e.g., BIIB105), and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of ALS, for example an inhibitory nucleic acid which targets FUS, and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all

five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0242] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of multiple system atrophy, for example an anti-alpha synuclein antibody (e.g., prasinezumab), and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of multiple system atrophy, for example an antisense oligonucleotide targeting human SNCA, and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of multiple system atrophy, for example human glial cell-derived neurotrophic factor (GDNF) or fragment or variant thereof (e.g., a variant thereof having at least 90% or at least 95% sequence identity to human GDNF), and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0243] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of progressive supranuclear palsy (PSP), for example an anti-Tau antibody (e.g., semorinemab), and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of progressive supranuclear palsy (PSP), for example an anti-alpha-synuclein antibody (e.g., prasinezumab), and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0244] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Freidrich's ataxia, for example human frataxin (FRXN) or fragment or variant thereof (e.g., a variant thereof having at least 90% or at least 95% sequence identity to human FRXN), and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0245] In certain aspects, the disclosure provides a nucleotide sequence which encodes a molecule for the treatment of Angelman syndrome. In embodiments, the molecule for the treatment of Angelman syndrome comprises an inhibitory nucleic acid molecule (e.g., an antisense oligonucleotide or inhibitory RNA (e.g., siRNA, miRNA or shRNA molecule). In embodiments, the molecule for the treatment of Angelman syndrome comprises an inhibitory nucleic acid molecule (e.g., an antisense oligonucleotide or inhibitory RNA (e.g., siRNA, miRNA or shRNA molecule) targeting UBE3A.

[0246] In embodiments, the molecule for the treatment of Angelman syndrome comprises a genome editing system (for example a zinc finger nuclease, a meganuclease, a TALEN, or an RNA-guided genome editing system (e.g. a Cas polypeptide and a guide RNA molecule). In embodiments the genome editing system targets UBE3A.

[0247] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Angelman syndrome, for example an inhibitor of a UBE3A antisense nucleic acid (e.g., rugonersen) or a human UBE3A or fragment or variant thereof (e.g., a variant thereof having at least 90% or at least 95% sequence identity to human UBE3A), and (ii) a promoter operably linked to said nucleotide sequence. An exemplary accession number for human UBE3A is set forth in Table 2. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0248] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Fragile X syndrome, for example human fragile X mental retardation protein (FMRP) or fragment or variant thereof (e.g., a nucleotide sequence comprising an FMR1 gene or fragment or variant thereof), and (ii) a promoter operably linked to said nucleotide sequence. An exemplary accession number for human FMRP is set forth in Table 2. In embodiments, described herein is a virus particle comprising (a) a capsid

polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Fragile X syndrome, for example an inhibitor of transcriptional silencing of FMRP, and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Fragile X syndrome, for example human diacylglycerol kinase (DGKk) or fragment or variant thereof (e.g., a variant thereof having at least 90% or at least 95% sequence identity to human DGKk), and (ii) a promoter operably linked to said nucleotide sequence. An exemplary accession number for human DGKk is set forth in Table 2. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0249] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Rett syndrome, for example a human MECP2 or fragment or variant thereof, e.g., a variant thereof having at least 90% or at least 95% sequence identity to human MECP2 , and (ii) a promoter operably linked to said nucleotide sequence. An exemplary accession number for human MECP2 is set forth in Table 2. The viral genome can further comprise one or more (e.g., two, three, four or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0250] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Dravet syndrome, for example human sodium channel, voltage gated, type 1-alpha (SCN1A or Nav1.1) or fragment or variant thereof, and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Dravet syndrome, for example an inhibitory nucleic acid targeting a mutant SCN1A transcript, and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Dravet syndrome, for example an anti-tau antibody (e.g., semorinemab), or fragment or variant thereof,

and (ii) a promoter operably linked to said nucleotide sequence. In embodiments, described herein is a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Dravet syndrome, for example human Syntaxin-binding protein 1 (STXBP1) or fragment or variant thereof, and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0251] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Friedreich's ataxia, for example a human FXN gene or fragment or variant thereof, and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0252] The disclosure is further directed, in part, to a method of delivering a payload to a subject, e.g., an animal or human subject. In some embodiments, a method of delivering a payload to a subject comprises administering to the subject a dependoparvovirus particle comprising a variant polypeptide (e.g., described herein) comprising the payload, e.g., in a quantity and for a time sufficient to deliver the payload. In some embodiments, the dependoparvovirus particle is a dependoparvovirus particle described herein and comprises a payload described herein. In some embodiments, the particle delivers the payload to the CNS. In some embodiments, the delivery to the CNS is increased as compared to a particle without the variant capsid polypeptide or as compared to a wild-type capsid polypeptide, e.g., a particle with capsid polypeptides of SEQ ID NO:1. In some embodiments, the particle delivers the payload to muscle (e.g., skeletal and/or cardiac) tissue. In some embodiments, the delivery to the muscle tissue is increased as compared to a particle without the variant capsid polypeptide or as compared to a wild-type capsid polypeptide, e.g., a particle with capsid polypeptides of SEQ ID NO:1. In some embodiments, the particle delivers the payload to skeletal muscle tissue. In some embodiments, the delivery to the skeletal muscle tissue is increased as compared to a particle without the variant capsid polypeptide or as compared to a wild-type capsid polypeptide, e.g., a particle with capsid polypeptides of SEQ ID NO:1. In some embodiments, the particle delivers the payload to cardiac muscle tissue. In some embodiments, the delivery to the cardiac muscle tissue is increased as compared to a particle without the variant capsid polypeptide or as compared to a wild-type capsid polypeptide, e.g., a particle with capsid polypeptides of SEQ ID NO:1.

[0253] In some embodiments, virus particles comprising a genome are provided, wherein the genome includes a nucleic acid expression construct including a heterologous transgene and one or more regulatory elements, where the one or more regulatory elements include a muscle (e.g., skeletal muscle and/or cardiac muscle) specific promoter. Examples of muscle specific promoters that can be used to drive expression of a transgene in skeletal muscle include but are not limited to Desmin (DES), CAMK, Mb, myosin (e.g., myo-3), dystrophin, muscle creatine kinase (MCK), MHCK7, CK6, CK7, CK8, CK8e, dMCK, tMCK, MH, SPc-5-12 (also known as C5-12), alpha skeletal actin (ASKA), SP-301, E-syn, myosin light chain (MLC), myosin heavy chain (MHC), four and a half LIM domains protein 1 (FHL1), alpha 2 actinin (ACTN2), filamin-C (FLNC), sarcoplasmic/endoplasmic reticulum calcium ATPase 1 (ATP2A1), troponin I type 1 (TNNI1), myosin-1 (MYH1), phosphorylatable, fast skeletal muscle myosin light chain (MYLPF), alpha-3 chain tropomyosin (TPM3), Pitx3, and ankyrin repeat domain-containing protein 2 (ANKRD2) promoters. Promoters capable of driving expression in skeletal muscle are further described in Skopenkova *et al.*, 2021, Acta Naturae 13(1):47-58, Piekarowicz *et al.*, 2019, Mol Ther Methods Clin Dev. 15:157-169, Wang, 2008 Gene Ther. 15:1489-1499, Coulon *et al.*, 2007, JBC 282(45):33192-33200, WO 2021/127655, and WO 2023/006890, the contents of each of which are incorporated herein by reference in their entireties. Examples of muscle specific promoters that can be used to drive expression of a transgene in cardiac muscle include but are not limited to cardiac troponin T (TNNT2), cardiac troponin C (TNNC1 or cTnC), Desmin (DES), alpha-myosin heavy chain (α-MHC), and myosin light chain 2 (MLC-2). Promoters capable of driving expression in heart muscle are further described in WO 2021/163357 and WO 2023/122804, the contents of each of which are incorporated herein by reference in their entireties.

[0254] In some aspects, the payload comprises a molecule that is effective in treating a muscle disease, such as, for example, a protein or an RNA interference nucleotide (e.g., shRNA, siRNA or miRNA).

[0255] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Duchenne muscular dystrophy (DMD), for example human Dystrophin (DMD) or a fragment or variant thereof (e.g., a variant thereof having at least 90% or at least 95% sequence identity to human DMD), and (ii) a promoter operably linked to said nucleotide sequence. An exemplary accession number for human DMD is set forth in Table 4. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0256] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of X-linked myotubular myopathy, for example human myotubularin (MTM1) or a fragment or variant thereof (e.g., a variant thereof having at least 90% or at least 95% sequence identity to human MTM1), and (ii) a promoter operably linked to said nucleotide sequence. An exemplary accession number for human

MTM1 is set forth in Table 4. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0257] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Myotonic Dystrophy Type 1 (DM1), for example human myotonin-protein kinase (DMPK) or a fragment or variant thereof (e.g., a variant thereof having at least 90% or at least 95% sequence identity to human DMPK, and (ii) a promoter operably linked to said nucleotide sequence. An exemplary accession number for human DMPK is set forth in Table 4. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0258] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Limb-girdle muscular dystrophy (LGMD), for example human Gamma-sarcoglycan, Alpha-sarcoglycan, Beta-sarcoglycan, or Delta-sarcoglycan or a fragment or variant thereof (e.g., a variant thereof having at least 90% or at least 95% sequence identity to human Gamma-sarcoglycan, Alpha-sarcoglycan, Beta-sarcoglycan, or Delta-sarcoglycan), and (ii) a promoter operably linked to said nucleotide sequence. Exemplary accession numbers for human Gamma-sarcoglycan, Alpha-sarcoglycan, Beta-sarcoglycan, and Delta-sarcoglycan are set forth in Table 4. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0259] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Pompe disease, for example human acid alpha-glucosidase (GAA) or a fragment (e.g., exon 2) or variant thereof (e.g., a variant thereof having at least 90% or at least 95% sequence identity to human GAA or a portion thereof), and (ii) a promoter operably linked to said nucleotide sequence. An exemplary accession number for human GAA is set forth in Table 4. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises

ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0260] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Facioscapulohumeral muscular dystrophy (FSHD), for example an antisense oligonucleotide targeting human DUX4, and (ii) a promoter operably linked to said nucleotide sequence. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0261] In certain aspects, the disclosure provides a virus particle comprising (a) a capsid polypeptide described herein, for example, a capsid polypeptide described in Section 6.2 and (b) an engineered viral genome comprising (i) a nucleotide sequence encoding a molecule for the treatment of Facioscapulohumeral muscular dystrophy (FSHD), for example human SMCHD1 or a fragment or variant thereof (e.g., a variant thereof having at least 90% or at least 95% sequence identity to human SMCHD1 or a portion thereof), and (ii) a promoter operably linked to said nucleotide sequence. An exemplary accession number for human SMCHD1 is set forth in Table 4. The viral genome can further comprise one or more (e.g., two, three, four, or all five) of (a) a pair of dependoparvovirus ITRs, (b) an intron, (c) an enhancer or repressor sequence, (d) a stuffer sequence, and (e) a polyA sequence. Preferably, the viral genome comprises ITRs flanking the nucleotide sequence and a polyA sequence operably linked to the nucleotide sequence. Typically, the viral genome lacks rep and cap sequences, which are in trans by the host cell in which the virus particle is produced. In some embodiments, the viral genome is self-complementary.

[0262] Exemplary muscle tissue related diseases that can be treated include but are not limited to Acid Maltase Deficiency (AMD), Amyotrophic Lateral Sclerosis (ALS), Andersen-Tawil Syndrome, Barth syndrome (TAZ), Becker Muscular Dystrophy (BMD), Becker Myotonia Congenita, Bethlem Myopathy, Bulbospinal Muscular Atrophy (Spinal- Bulbar Muscular Atrophy), Carnitine Deficiency, Carnitine Palmityl Transferase Deficiency (CPT Deficiency), Central Core Disease (CCD), Centronuclear Myopathy, Charcot-Marie-Tooth Disease (CMT), Congenital Muscular Dystrophy (CMD), Congenital Myasthenic Syndromes (CMS), Congenital Myotonic Dystrophy, Cori Disease (Debrancher Enzyme Deficiency), Danon disease, Debrancher Enzyme Deficiency, Dejerine-Sottas Disease (DSD), Dermatomyositis (DM), Distal Muscular Dystrophy (DD), Distal myopathy with anterior tibial onset, Duchenne Muscular Dystrophy (DMD), Dystrophia Myotonica (Myotonic Muscular Dystrophy), Emery-Dreifuss Muscular Dystrophy (EDMD), Endocrine Myopathies, Eulenberg Disease (Paramyotonia Congenita), Facioscapulohumeral Muscular Dystrophy (FSH or FSHD), Finnish (Tibial) Distal Myopathy, Forbes Disease (Debrancher Enzyme Deficiency), Friedreich's Ataxia (FA), Fukuyama Congenital Muscular Dystrophy, Glycogenosis Type 10, Glycogenosis Type 11, Glycogenosis Type 2, Glycogenosis Type 3,

Glycogenosis Type 5, Glycogenosis Type 7, Glycogenosis Type 9, Gowers-Laing Distal Myopathy, Hauptmann-Thanheuser MD (Emery- Dreifuss Muscular Dystrophy), Hereditary Inclusion-Body Myositis, Hereditary Motor and Sensory Neuropathy (Charcot-Marie-Tooth Disease), Hyperthyroid Myopathy, Hypothyroid Myopathy, Inclusion-Body Myositis (IBM), Inherited Myopathies, Integrin-Deficient Congenital Muscular Dystrophy, Kennedy Disease (Spinal-Bulbar Muscular Atrophy), Kugelberg-Welander Disease (Spinal Muscular Atrophy), Lactate Dehydrogenase Deficiency, Lambert-Eaton Myasthenic Syndrome (LEMS), Limb-Girdle Muscular Dystrophy (LGMD), Lou Gehrig's Disease (Amyotrophic Lateral Sclerosis), McArdle Disease (Phosphorylase Deficiency), Merosin-Deficient Congenital Muscular Dystrophy, Metabolic Diseases of Muscle, Mitochondrial Myopathy, Miyoshi myopathy, Miyoshi Distal Myopathy, Motor Neurone Disease, Muscle-Eye-Brain Disease, Myasthenia Gravis (MG), Myoadenylate Deaminase Deficiency, Myofibrillar Myopathy, Myophosphorylase Deficiency, Myotonia Congenita (MC), Myotonic Muscular Dystrophy (MMD), Myotubular Myopathy (MTM or MM), Nemaline Myopathy, Nonaka Distal Myopathy, Oculopharyngeal Muscular Dystrophy (OPMD), Paramyotonia Congenita, Pearson Syndrome, Periodic Paralysis, Peroneal Muscular Atrophy (Charcot-Marie-Tooth Disease), Phosphofructokinase Deficiency, Phosphogly cerate Kinase Deficiency, Phosphogly cerate Mutase Deficiency, Phosphorylase Deficiency, Phosphorylase Deficiency, Polymyositis (PM), Pompe Disease (Acid Maltase Deficiency), Primary merosin deficiency (LAMA2), Progressive External Ophthalmoplegia (PEO), Rod Body Disease (Nemaline Myopathy), Spinal Muscular Atrophy (SMA), Spinal-Bulbar Muscular Atrophy (SBMA), Steinert Disease (Myotonic Muscular Dystrophy), Tarui Disease (Phosphofructokinase Deficiency), Thomsen Disease (Myotonia Congenita), Ullrich Congenital Muscular Dystrophy, Walker-Warburg Syndrome (Congenital Muscular Dystrophy), Welander Distal Myopathy, Werdnig-Hoffmann Disease (Spinal Muscular Atrophy), and ZASP-Related Myopathy.

[0263] Payloads suitable for treating muscle-related disease are known in the art and include the following disease (suitable payload) combinations: Barth syndrome (TAZ), Primary merosin deficiency (LAMA2), Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), Danon disease (LAMP2), Limb girdle muscular dystrophy (Subtypes and affected genes: LGMD1A (TTID), LGMD1B (LMNA), LGMD1C (CAV3), LGMD1D (DNAJB6), LGMD1E (DES), LGMD1F (TNP03), LGMD1G (HNRPDL), LGMD1H, LGMD2A (CAPN3), LGMD2B (DYSF), LGMD2C (SGCG), LGMD2D (SGCA), LGMD2E (SGCB), LGMD2F (SGCD), LGMD2G (TCAP), LGMD2H (TRIM32), LGMD2I (FKRP), LGMD2J (TTN), LGMD2K (POMT1), LGMD2L (AN05), LGMD2M (FKTN), LGMD2N (POMT2), LGMD20 (POMGNT1), LGMD2Q (PLEC1)), Miyoshi myopathy (DYSF), Distal myopathy with anterior tibial onset (DYSF), Welander distal myopathy (TIA1), Gowers-Laing distal myopathy (MYH7), Facioscapulohumeral muscular dystrophy (Subtypes and affected genes: Type 1 (DUX4), Type 2 (SMCHD1)), Oculopharyngeal muscular dystrophy (PABPN1), myotonic dystrophy (Subtypes and affected genes: DM1 (DMPK) and DM2 (ZNF9)), congenital myotonia (CLCN1), paramyotonia congenital (SCN4A), myotubular myopathy (MTM1), glycogen storage disease type II (Pompe disease) (GAA).

[0264] In some embodiments, the payload is selected from: TAZ, LAMA2, DMD, LAMP2, CAPN3, DYSF, SGCA, SGCB, FKRP, PABPN1, MTM1, and GAA.

[0265] In some embodiments, the payload is human dystrophin.

[0266] Further exemplary diseases that can be treated and further exemplary heterologous transgenes that can be delivered via the viral particles of the disclosure are provided in Table 2, Table 2-1, Table 3, Table 4, Table 4-1, and Table 5.

TABLE 2
Exemplary CNS indications and transgenes

Indication	Transgene	UniProt Accession # (Human)
Achromatopsia – color blindness	Cyclic nucleotide-gated cation channel alpha-3 (CNGA3)	Q16281
	Cyclic nucleotide-gated cation channel beta-3 (CNGB3)	Q9NQW8
	Guanine nucleotide-binding protein G(t) subunit alpha-2 (GNAT2)	P19087
	Cone cGMP-specific 3',5'-cyclic phosphodiesterase subunit alpha (PDE6C)	P51160
Acute Intermittent Porphyria	Porphobilinogen deaminase (PBGD), HMBS	P08397
Adie syndrome – Adie's pupil	MPZ	P25189
Age-Related Macular Degeneration	Vascular endothelial growth factor receptor 1 (FLT1)	P17948
	Vascular endothelial growth factor A (VEGFA)	P15692
Agenesis of the Corpus Callosum (ACCPN)	SLC12A6	Q9UHW9
Aicardi-Goutieres syndrome	TREX1	Q9NSU2
Alexander disease	GFAP	P14136
Alpers syndrome	POLG	P54098
Alternating hemiplegia	ATP1A2	P50993
	ATP1A3	P13637
Alzheimer's disease	NGF	P01138
	ApoE	P02649
	Presenilin (PSEN1)	A0A024R6A3
	Presenilin-2 (PSEN2)	P49810
	Amyloid-beta precursor protein (APP)	P05067
	ADAM10	O14672
	MAPT, Tau	P10636
Amyotrophic lateral sclerosis (ALS) – Lou Gehrig's disease	Superoxide dismutase-1 (SOD1)	P00441
Amyotrophy, hereditary neuralgic	SEPT9	Q9UHD8
Angelman syndrome	Ubiquitin-protein ligase E3A (UBE3A)	Q05086
Aromatic L-amino acid decarboxylase deficiency (AADCD)	DDC	P20711
Ataxia	APTX	Q7Z2E3
	KCNA1	Q09470
	CACNA1A	O00555
Ataxia Telangiectasia - Louis-Bar syndrome	Serine-protein kinase ATM (ATM)	Q13315
Attention deficit hyperactivity disorder (ADHD)	DRD4	P21917
	CDH2	P19022
Becker muscular dystrophy	Follistatin (FST)	P19883
	DMD	P11532
Benign essential blepharospasm	DRD5	P21918
Bradbury-Eggleston syndrome – pure autonomic failure	COQ2	Q96H96
Bulbar palsy (BVVLS1)	SLC52A3	Q9NQ40
Canavan disease – aminoacylase 2 deficiency	ASPA	P45381

TABLE 2
Exemplary CNS indications and transgenes

Indication	Transgene	UniProt Accession # (Human)
Carpal tunnel syndrome	TTR	P02766
Cavernoma - Cavernous angioma - Cavernous malformations	KRIT1	O00522
Cerebellar Hypoplasia (CHEGDD)	OXR1	Q8N573
Cerebellar ataxia (CAMRQ2)	WDR81	Q562E7
Cerebral Arteriopathy with SCI and Leukoencephalopathy (CADASIL)	NOTCH3	Q9UM47
Cerebral gigantism – Sotos syndrome 1	NSD1	Q96L73
Cerebro-oculo-facio-skeletal syndrome (COFS)	ERCC6	Q03468
Ceroid lipofuscinosis – Batten disease	CLN1 (PPT1)	P50897
	CLN2 (TPP1)	O14773
	CLN3 (battenin)	Q13286
	CLN4	Q9H3Z4
	CLN5	O75503
	CLN6	Q9NWW5
	CLN7 (MFSD8)	Q8NHS3
	CLN8	Q9UBY8
	CLN10 (cathepsin D)	P07339
	CLN11 (progranulin)	P28799
	CLN12 (ATP13A2)	Q9NQ11
	CLN13 (cathepsin F)	Q9UBX1
	CLN14 (KCTD7)	Q96MP8
Charcot-Marie-Tooth disease	PMP22	Q01453
	MPZ	P25189
	DNM2	P50570
	MFN2	O95140
	KIF1B	O60333
	SBF2	Q86WG5
	PNKP	Q96T60
	GDAP1	Q8TB36
	LMNA	P02545
	FGD4	Q96M96
	MTMR2	Q13614
Chorea	NKX2-1	P43699
Choreoacanthocytosis	VPS13A	Q96RL7
Choroideremia	Rab escort protein (Rep1), CHM	P24386
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	PMP22	Q01453
Cockayne syndrome B (CSB)	ERCC6	Q03468
Coffin-Lowry syndrome	RPS6KA3	P51812
Craniosynostosis	MSX2	P35548
	TWIST1	Q15672
	SKI	P12755
	SMAD6	O43541
Creutzfeldt-Jakob disease	PRNP	P04156
	HLA-DQB1	P01920
Crigler-Najjar Syndrome - hyperbilirubinemia	UDP-glucuronosyltransferase 1A1 (UGT1A1)	P22309
Cushing Syndrome	PRKACA	P17612
Dentatorubral atrophy (DRPLA)	ATN1	P54259
Developmental and Epileptic Encephalopathy	ARX	Q96QS3
	FGF12	P61328
	PIGP	P57054

TABLE 2 Exemplary CNS indications and transgenes		
Indication	**Transgene**	**UniProt Accession # (Human)**
	GABRB3	P28472
	NECAP1	Q8NC96
Developmental Dyspraxia – speech-language disorder 1 (SPCH1)	FOXP2	O15409
Dravet syndrome	Sodium channel protein type 1 subunit alpha (SCN1A)	P35498
	SCN1B	Q07699
	SCN2A	Q99250
	GABA receptor subunit gamma-2 (GABRG2)	P18507
Dysautonomia – -Day syndrome	ELP1	O95163
Dystonias	GCH1	P30793
	TOR1A	O14656
	SGCE	O43556
	TUBB4A	P04350
Encephalocele	COL18A1	P39060
Epilepsy disorders	GRIN2A	Q12879
	CSTB	P04080
	STARD7	Q9NQZ5
	DEPDC5	O75140
	PCDH19	Q8TAB3
Essential tremor	DRD3	P35462
	NOTCH2NLC	P0DPK4
	FUS	P35637
Fabry disease	alpha-galactosidase A (GLA)	P06280
Farber disease – ceramidase deficiency	ASAH1	Q13510
Fahr disease	SLC20A2	Q08357
Febrile Seizures	GABRG2	P18507
	ADGRV1	Q8WXG9
	CPA6	P11509
	SCN1A	P35498
Fragile X syndrome	FMR1 (FMRP)	Q06787
	Diacylglycerol kinase (DGKk)	Q5KSL6
Friedreich's ataxia	Frataxin (FXN)	Q16595
Frontotemporal dementia	Progranulin (GRN)	P28799
	MAPT (tau)	P10636
	PSEN1	A0A024R6A3
Fucosidosis	alpha-L-fucosidase (FUCA1)	P04066
Fundus albipunctatus	RLBP1	P12271
Gaucher disease, types I, II and III	Glucocerebrosidase (GBA1)	P04062
Generalized gangliosidoses (GM1, GM2, GM3)	GLB1	P16278
Gerstmann-Straussler-Scheinker disease	PRNP	P04156
Giant axonal neuropathy	Gigaxonin (GAN)	Q9H2C0
Glycogen storage disease II – Pompe disease – Acid Maltase Deficiency	Acid maltase, lysosomal alpha-glucosidase (LYAG, GAA)	P10253
Guillain-Barre syndrome	PMP22	Q01453
Hallervorden-Spatz disease – PKAN – NBIA1	PANK2	Q9BZ23
Hemiplegia Alterans	ATP1A2	P50993
	ATP1A3	P13637
Hereditary Neuropathies	WNK1	Q9H4A3

TABLE 2 Exemplary CNS indications and transgenes		
Indication	**Transgene**	**UniProt Accession # (Human)**
	MFN2	O95140
	HK1	P19367
	TFG	Q92734
	SPTLC1	O15269
Heredopathia Atactica Polyneuritiformis – Refsum disease	PHYH	O14832
Holoprosencephalies	GLI2	P10070
	TGIF1	Q15583
	ZIC2	O95409
	PTCH1	Q13635
	SHH	Q15465
Huntington's disease	HTT	P42858
Hydrocephalus disorders	CCDC88C	Q9P219
	WDR81	Q562E7
	TRIM71	Q2Q1W2
	MPDZ	O75970
Incontinentia Pigmenti	IKBKG	Q9Y6K9
Infantile Hypotonia	NALCN	Q8IZF0
	TBCK	Q8TEA7
	CCDC174	Q6PII3
	UNC80	Q8N2C7
Infantile Neuroaxonal Dystrophy	PLA2G6	O60733
Infantile Phytanic Acid Storage Disease (PBD1B)	PEX1	O43933
Joubert Syndrome	INPP5E	Q9NRR6
Kennedy Disease	Androgen receptor (AR)	P10275
Klippel-Feil Syndrome	GDF6	Q6KF10
Krabbe disease – GALC deficiency	GALC	P54803
Lambert-Eaton Myasthenic Syndrome	CACNA1A	O00555
	CACNB2	Q13936
Landau-Kleffner Syndrome	GRIN2A	Q12879
Late infantile neuronal lipofuscinosis (CLN2)	TPP1	O14773
Lesch-Nyhan Syndrome	HPRT1	P00492
Leber congenital amaurosis – retinal blindness	Retinal guanylyl cyclase 1 (GUCY2D)	Q02846
	Retinoid isomerohydrolase (RPE65)	Q16518
	Centrosomal protein of 290 kDa (CEP290)	O15078
	Protein crumbs homolog 1 (CRB1)	P82279
Leber's hereditary optical neuropathy	NADH-ubiquinone oxidoreductase chain 4 (ND4)	P03905
Leukodystrophy	ARSA	P15289
Levine-Critchley Syndrome - choreoacanthocytosis	VPS13A	Q96RL7
Lewy body dementia	SNCA	P37840
	SNCB	Q16143
Lipoid Proteinosis - Urbach-Wiethe disease	ECM1	Q16610
Lissencephaly	PAFAH1B1	Q9PTR5
	NDE1	Q9NXR1
	TUBA1A	Q71U36
	LAMB1	LAMB1
	KATNB1	Q9BVA0
	RELN	P78509
Macrocephaly/ Megalencephaly	TBC1D7	Q9P0N9

TABLE 2
Exemplary CNS indications and transgenes

Indication	Transgene	UniProt Accession # (Human)
Menkes Disease	ATP7A	Q04656
Metachromatic Leukodystrophy – MLD	Arylsulfatase A (ARSA)	P15289
Microcephaly diseases	KIF11	P52732
	MCPH1	Q8NEM0
	SLC25A19	Q9HC21
Migraine, familial hemiplegic	CACNA1A	O00555
	ATP1A2	P50993
	SCN1A	P35498
Mitochondrial DNA depletion syndromes	RRM2B	Q7LG56
	DGUOK	Q16854
	POLG	P54098
	TYMP	P19971
	TK2	O00142
Morvan disease	WNK1	Q9H4A3
Mucolipidosis	GNPTAB	Q3T906
	MCOLN1	Q9GZU1
Mucopolysaccharidosis Type I (MPS I) – Hurler syndrome	alpha-L-iduronidase (IDUA)	P35475
MPS II – Hunter syndrome	iduronate-2-sulfatase (IDS)	P22304
MPS IIIa - Sanfilippo Type A syndrome	heparan sulfate sulfatase (HSS) or N-sulfoglucosamine sulfohydrolase (SGSH)	P51688
MPS IIIB – Sanfilippo Type B syndrome	N-acetyl-alpha-D-glucosaminidase (NAGLU)	P54802
MPS VI - Maroteaux-Lamy syndrome	arylsulfatase B (ARSB)	P15848
MPS IV A - Morquio syndrome type A	N-acetylgalactosamine-6-sulfatase (GALNS)	P34059
MPS IV B - Morquio syndrome type B	Beta-galactosidase 1 (GLB1)	P16278
MPS VII - Sly syndrome	beta-glucuronidase	P08236
MPS VIII	glucosamine-6-sulfate sulfatase	P15586
MPS IX	Hyaluronidase-1 (HYAL1)	Q12794
Multiple Sclerosis	PDCD1	Q15116
Multiple system atrophy	COQ2	Q96H96
Myasthenic syndrome, congenital presynaptic	CHAT	P28329
Myoclonus	NOL3	O60936
Myoclonic epilepsy (FAME2)	STARD7	Q9NQZ5
Narcolepsy	HCRT, OX	O43612
	MOG	Q16653
Neuroacanthocytosis - McLeod syndrome	XK	P51811
Neurodevelopmental disorder with cerebral atrophy and facial dysmorphism (NEDCAFD)	TTC5	Q8N0Z6
Neurodevelopmental disorder with infantile epileptic spasms	NCDN	Q9UBB6
Neurofibromatosis	NF1	P21359
Neuromyotonia	HINT1	P49773
Neuronal Ceroid Lipofuscinosis	PPT1	P50897
	TPP1	O14773
	CLN5	O75503
	CLN3	Q13286
	CLN6	Q9NWW5
	CLN8	Q9UBY8
	DNAJC5	Q9H3Z4
	MFSD8	Q8NHS3

TABLE 2
Exemplary CNS indications and transgenes

Indication	Transgene	UniProt Accession # (Human)
	CTSD	P07339
Neuropathy, ataxia and retinitis pigmentosa (NARP)	MTATP6	P00846
Neuropathy, hereditary sensory and autonomic, type II	WNK1	Q9H4A3
Neuropathy, hypomyelinating congenital 1	EGR2	P11161
Niemann-Pick disease	Sphingomyelin phosphodiesterase 1 (SMPD1)	P17405
	NPC intracellular cholesterol transporter 1 (NPC1)	O15118
Ohtahara Syndrome – Developmental and epileptic encephalopathy 1	ARX	Q96QS3
Omithine Transcarbamylase deficiency	OTC	P00480
Orthostatic intolerance	SLC6A2	P23975
Parkinson's disease	Glucocerebrosidase (GBA1)	P04062
	Dopamine decarboxylase (DDC)	P20711
	Neurturin	Q99748
	Glial derived growth factor (GDGF)	P39905
	Tyrosine hydroxylase (TH), tyrosine 3-monooxygenase	P07101
	Glutamic acid decarboxylase (GAD)	Q99259
	Fibroblast growth factor 2 (FGF2)	P09038
	Brain-derived neurotrophic factor (BDNF)	P23560
Paroxysmal Choreoathetosis	PNKD	Q8N490
Pelizaeus-Merzbacher Disease	PLP1	P60201
Pena-Shokeir Type II Syndrome	ERCC6	Q03468
Periodic Paralyses	SCN4A	P35499
Phelan-McDermid syndrome	SH3 and multiple ankyrin repeat domains protein 3 (SHANK3)	Q9BYB0
Phytanic Acid Storage Disease – peroxisome biogenesis disorder 1B	PEX1	O43933
Pick disease	PSEN1	A0A024R6A3
	MAPT (tau)	P10636
Porencephaly type 1	COL4A1	P02462
Primary Lateral Sclerosis, juvenile	ALS2	Q96Q42
Primary Progressive Aphasia	GRN	P28799
Progressive external ophtalmoplegia	POLG	P54098
	POLG2	Q9UHN1
	SLC25A4	P12235
	TWNK	Q96RR1
Progressive bulbar palsy	SLC52A3	Q9NQ40
Progressive supranuclear palsy	Microtubule-associated protein tau (MAPT), Tau	P10636
Pseudo-Torch syndrome	OCLN	Q16625
	STAT2	P52630
	USP18	Q9UMW8
Retinitis Pigmentosa 38 – rod-cone dystrophy	Tyrosine-protein kinase Mer (MERTK)	Q12866
Retinitis Pigmentosa 40	PDE6B	P35913
Rett syndrome	Methyl-CpG-binding protein 2 (MECP2)	P51608
Sandhoff disease	Beta-hexosaminidase subunit alpha (HEXA)	P06865
	Beta-hexosaminidase subunit beta (HEXB)	P07686

TABLE 2
Exemplary CNS indications and transgenes

Indication	Transgene	UniProt Accession # (Human)
Schizencephaly	SIX3	O95343
	EMX2	Q04743
	SHH	Q15465
Seitelberger Disease	PLA2G6	O60733
Septo-optic dysplasia – De Morsier syndrome	HESX1	Q9UBX0
Snijders Blok-Fisher syndrome	POU3F3	P20264
Spastic Paraplegias	SPG11	Q96JI7
	SPAST	Q9UBP0
	KIF5A	Q12840
	NIPA1	Q7RTP0
	CYP7B1	O75881
	ATL1	Q8WXF7
Spinal Muscular Atrophy – Kugelberg-Welander Disease	Survival motor neuron protein (SMN), SMN1	Q16637
Spinocerebellar ataxia	Ataxin-1 (ATXN1), SCA1	P54253
	Ataxin-2 (ATXN2), SCA2	Q99700
	Ataxin-3 (ATXN3), SCA3	P54252
	ZFHX3	Q15911
	CACNA1A	O00555
	ATXN7, SCA7	O15265
	TMEM240	Q5SV17
Sporadic Inclusion Body Myositis	Follistatin (FST)	P19883
Steele-Richardson-Olszewski syndrome – Parkinson-dementia syndrome	MAPT(Tau)	P10636
Stiff-Person Syndrome, congenital	GLRA1	P23415
	GLRB	P48167
Striatonigral degeneration	NUP62	P37198
	PDE8B	O95263
	MTATP6	P00846
	VAC14	Q08AM6
Stroke	Tissue-type plasminogen activator (tPA)	P00750
	Neurogenic differentiation factor 1 (NeuroD1)	Q13562
Sturge-Weber Syndrome	GNAQ	P50148
Subcortical Vascular Encephalopathy – Cerebral Arteriopathy	HTRA1	Q92743
Systemic Lupus Erythematosus	DNASE1L3	Q13609
	TLR7	Q9NYK1
Tardive Dyskinesia	CYP2D6	P10635
Tay-Sachs disease	Beta-hexosaminidase subunit alpha (HEXA)	P06865
Tourette Syndrome	HDC	P19113
	SLITRK1	Q96PX8
Tremor, hereditary type 1	DRD3	P35462
Troyer Syndrome	SPART	Q8N0X7
Tuberous Sclerosis	TSC1	Q92574
	TSC2	P49815
	IFNG	P01579
Von Hippel-Lindau Disease	VHL	P40337
	CCND1	P24385
Von Recklinghausen Disease	NF1	P21359
Werdnig-Hoffman Disease	SMN1	Q16637
West Syndrome, X-linked	ARX	Q96QS3

TABLE 2 Exemplary CNS indications and transgenes		
Indication	**Transgene**	**UniProt Accession # (Human)**
Wilson disease	ATP7B	P35670
Wolman's disease – acid lipase disease	LIPA	P38571
X-linked adrenoleukodystrophy	ATP-binding cassette sub-family D member 1 (ABCD1)	P33897
X-linked Retinoschisis	Retinoschisin (RS1)	O15537
X-Linked Retinitis Pigmentosa	X-linked retinitis pigmentosa GTPase regulator (RPGR)	Q92834
X-Linked Spinal and Bulbar Muscular Atrophy	UBA1	P22314

[0267] In some embodiments, the payload is an antisense oligonucleotide effective in treating a CNS disease, for example by modulating expression of a target gene. Exemplary CNS diseases which may be treated using an antisense oligonucleotide include amyotrophic lateral sclerosis, Huntington's disease, and Alzheimer's disease. Exemplary target genes of such antisense oligonucleotides for treatment of CNS disease include SOD1, C9orf72, Ataxin 2, huntingtin (HTT), Sortilin-related receptor, Microtubule-Associated Protein Tau (MAPT), and neutral sphingomyelinase (N-SMase). Various antisense oligonucleotides effective in treatment of CNS diseases are described in the art and include, for example, those described in Bennett et al., 2019 *Annu Rev Neurosci.* 42:385-406, Rinaldi et al., 2018, Nature Reviews Neurology, 14:9-21, and Rook et al., 2022, *BioDrugs* 36(2):105-119, each incorporated herein by reference.

[0268] Non-limiting, example antisense oligonucleotides that can be delivered via the viral particles of the disclosure (along with associated target genes and CNS tissue related diseases that can be treated) are provided in Table 2-1. Where such antisense oligonucleotides are indicated by reference to a patent or patent application publication, such patent and patent applications are incorporated herein by reference in their entirety for their disclosed antisense oligonucleotide structures and sequences.

TABLE 2-1 Exemplary CNS Indications, Target Genes, and Antisense Oligonucleotide Transgenes			
Indication	**Target Gene**	**Uniprot Accession # (Human)**	**Exemplary transgene(s)**
Amyotrophic lateral sclerosis	Superoxide dismutase 1 (SOD 1)	P00441	Antisense oligonucleotides described in U.S. Patent Application Publication Nos. 2024/0182903 A1, 2022/0073930 A1, 2017/0152517 A1, 2020/0354723 A1, 2022/0315930 A1, and 2023/0193281 A1.
	C9orf72	Q96LT7	Antisense oligonucleotides described in U.S. Patent Application Publication Nos. 2018/0023077 A1, 2015/0267197 A1, 2020/0385723 A1, 2016/0237432 A1, 2023/0098111 A1, and 20190231808 A1.
Huntington's disease	Huntingtin (HTT)	P42858	Antisense oligonucleotides described in: U.S. Patent Application Publication Nos. 20140303238 A1, 2017/0253877 A1, and 2022/0098585 A1; and PCT Patent Application Publication No. WO/2024/035946 A1.

TABLE 2-1
Exemplary CNS Indications, Target Genes, and Antisense Oligonucleotide Transgenes

Indication	Target Gene	Uniprot Accession # (Human)	Exemplary transgene(s)
Alzheimer's disease	Sortilin-related receptor (SORL1)	Q92673	Antisense oligonucleotides described in PCT Patent Application Publication No. WO/2023/275376 A1.
	Neutral sphingomyelinase (N-SMase), also known as Sphingomyelin phosphodiesterase 2 (SMPD2)	O60906	Antisense oligonucleotides described in U.S. Patent Application Publication No. 2014/0275210 A1.
Spinocerebellar ataxia type 2 (SCA2)	Ataxin-2 (ATXN2)	Q99700	Antisense oligonucleotides described in U.S. Patent Application Publication No. 2020/0024600 A1
Parkinson's Disease	SNCA	P37840	Antisense oligonucleotides described in U.S. Patent Application Publication Nos. 20050137155 A1, 20050186591 A1, 20200362347 A1, 20040219671 A1, 20220119811 A1, 20210180065 A1, and 20200392494 A1

TABLE 3
Exemplary muscle indications and transgenes

Indication	Transgene	UniProt Accession # (Human)
Acid maltase deficiency – Glycogen storage disease II	GAA	P10253
Advanced heart failure	SERCA2a, ATP2A2	P16615
Amyotrophic lateral sclerosis (ALS) – Lou Gehrig's disease	Superoxide dismutase-1 (SOD1)	P00441
Andersen-Tawil Syndrome	KCNJ2	P63252
Barth syndrome	TAFAZZIN	Q16635
Becker Muscular Dystrophy (BMD)	DMD	P11532
Becker Myotonia Congenita	CLCN1	P35523
Bethlem Myopathy	COL6A3	P12111
	COL6A2	P12110
	COL6A1	P12109
Bulbospinal Muscular Atrophy	AR	P10275
Carnitine Deficiency, systemic primary	SLC22A5	O76082
Carnitine Palmityl Transferase Deficiency, type 1	CPT1A	P50416
Carnitine Palmityl Transferase Deficiency, type 2	CPT2	P23786
Catecholaminergic polymorphic ventricular tachycardia 2 (CPVT2)	Calsequestrin-2 (CASQ2)	O14958
Central Core Disease – congenital myopathy, type 1A	RYR1	P21817
Centronuclear Myopathy type 1	MTMR14	Q8NCE2
	DNM2	O14717
Charcot-Marie-Tooth disease	PMP22	Q01453
	MPZ	P25189
	DNM2	P50570
	MFN2	O95140
	KIF1B	O60333
	SBF2	Q86WG5

TABLE 3 Exemplary muscle indications and transgenes		
Indication	**Transgene**	**UniProt Accession # (Human)**
	PNKP	Q96T60
	GDAP1	Q8TB36
	LMNA	P02545
	FGD4	Q96M96
	MTMR2	Q13614
Congenital Muscular Dystrophy – Ullrich disease	COL6A3	P12111
	COL6A2	P12110
	COL6A1	P12109
Congenital Myasthenic Syndromes	COLQ	Q9Y215
	AGRN	O00468
	RAPSN	Q13702
	GFPT1	Q06210
	SCN4A	P35499
	ALG2	Q9H553
	ALG14	Q96F25
	DPAGT1	Q9H3H5
	CHRNE	Q04844
	CHRNA1	P02708
	DOK7	Q18PE1
	CHAT	P28329
Congenital Myopathy	ACTA1	P68133
	STAC3	Q96MF2
	TPM3	P06753
Congenital Myotonic Dystrophy	DMPK	Q09013
Cori Disease - Debrancher Enzyme Deficiency – Forbes Disease	AGL	P35573
Danon disease	LAMP2	P13473
Dejerine-Sottas Disease	MPZ	P25189
	EGR2	P11161
	PMP22	Q01453
	PRX	Q9BXM0
Distal Muscular Dystrophy, Welander	TIA1	P31483
Distal Muscular Dystrophy, Miyoshi	DYSF	O75923
Distal myopathy with anterior tibial onset	DYSF	O75923
Duchenne Muscular Dystrophy	Dystrophin (DMD)	P11532
	GALGT2, B4GALNT2	Q8NHY0
Dysferlinopathies	Dysferlin (DYSF)	O75923
Emery-Dreifuss Muscular Dystrophy	EMD	P50402
	SYNE1	Q8NF91
	SYNE2	Q8WXH0
	TMEM43	Q9BTV4
	LMNA	P02545
Eulenberg Disease – Paramyotonia Congenita	SCN4A	P35499
Facioscapulohumeral Muscular Dystrophy	SMCHD1	A6NHR9
	LRIF1	Q5T3J3
Friedreich's ataxia	Frataxin (FXN)	Q16595
Fukuyama Congenital Muscular Dystrophy	FKTN	O75072
Glycogenosis Type 10 – Glycogen storage disease X	PGAM2	P15259
Glycogenosis Type 11 – Glycogen storage disease XI	LDHA	P00338

TABLE 3 Exemplary muscle indications and transgenes		
Indication	**Transgene**	**UniProt Accession # (Human)**
Glycogenosis Type 2 – Glycogen storage disease II – Pompe Disease – Acid maltase deficiency	GAA	P10253
Glycogenosis Type 3 – Glycogen storage disease III	AGL	P35573
Glycogenosis Type 5 – Glycogen storage disease V – McArdle Disease – Myophosphorylase Deficiency	PYGM	P11217
Glycogenosis Type 7 – Glycogen storage disease VII - Phosphofructokinase Deficiency - Tarui Disease	PFKM	P08237
Glycogenosis Type 9 – Glycogen storage disease IX	PHKB	Q93100
	PHKA2	P46019
Hereditary Inclusion-Body Myositis	GNE	Q9Y223
Integrin-Deficient Congenital Muscular Dystrophy	ITGA7	Q13683
Kennedy Disease – Spinal-Bulbar Muscular Atrophy	Androgen receptor (AR)	P10275
Kugelberg-Welander Disease	SMN1	Q16637
Lactate dehydrogenase A deficiency	LDHA	P00338
Lactate Dehydrogenase B Deficiency	LDHB	P07195
Lambert-Eaton Myasthenic Syndrome	CACNB2	Q08289
Laing Distal Myopathy	MYH7	A7E2Y1
Limb Girdle Muscular Dystrophy Type 2C (LGMD-2C)	Gamma-sarcoglycan	Q13326
Limb Girdle Muscular Dystrophy Type 2D (LGMD-2D)	Alpha-sarcoglycan	Q16586
Limb Girdle Muscular Dystrophy Type2E (LGMD-2E)	Beta-sarcoglycan	Q16585
Limb Girdle Muscular Dystrophy Type 2F (LGMD-2F)	Delta-sarcoglycan	Q92629
Merosin-Deficient Congenital Muscular Dystrophy	LAMA2	P24043
Muscle-Eye-Brain Disease	POMGNT1	Q8WZA1
Mitochondrial Myopathy	CHCHD10	Q8WYQ3
Miyoshi myopathy	DYSF	O75923
Myoadenylate Deaminase Deficiency	AMPD1	P23109
Myofibrillar Myopathy 1	DES	P17661
Myofibrillar Myopathy 2	CRYAB	P02511
Myofibrillar Myopathy 3	MYOT	Q9UBF9
Myofibrillar Myopathy 4 – ZASP related myopathy	LDB3, ZASP	O75112
Myofibrillar Myopathy 5	FLNC	Q14315
Myofibrillar Myopathy 6	BAG3	O95817
Myofibrillar Myopathy 7	KY	Q8NBH2
Myofibrillar Myopathy 8	PYROXD1	Q8WU10
Myofibrillar Myopathy 9	TTN	Q8WZ42
Myofibrillar Myopathy 10	SVIL	O95425
Myofibrillar Myopathy 11	UNC45B	Q8IWX7
Myofibrillar Myopathy 12	MYL2	Q99972
Myotonic dystrophy Type 1 - Steinert Disease	Myotonin-protein kinase (DMPK)	Q09013
Myotonic dystrophy Type 2	CNBP	P62633
Myotubular Myopathy	MTM1	Q13496
Nemaline Myopathy 1	TPM3	P06753

TABLE 3 Exemplary muscle indications and transgenes		
Indication	**Transgene**	**UniProt Accession # (Human)**
Nemaline Myopathy 2	NEB	P20929
Nemaline Myopathy 5A, 5B, 5C	TNNT1	P13805
Nemaline Myopathy 3	ACTA1	P68133
Nemaline Myopathy 6	KBTBD13	C9JR72
Nemaline Myopathy 4	TPM2	P07951
Nemaline Myopathy 7	CFL2	Q9Y281
Nemaline Myopathy 8	KLHL40	Q2TBA0
Nemaline Myopathy 9	KLHL41	O60662
Nemaline Myopathy 10	LMOD3	Q0VAK6
Nonaka Distal Myopathy	GNE	Q9Y223
Oculopharynggeal muscular dystrophy	PABPN1	Q86U42
Omithine Transcarbamylase deficiency	OTC	P00480
Paramyotonia Congenita	SCN4A	P35499
Periodic Paralysis, hypokalemic	CACNA1S	Q13698
Periodic Paralysis, hyperkalemic	SCN4A	P35499
Phosphoglycerate Kinase Deficiency	PGK1	P00558
Polymyositis	PMSCL2	Q01780
	PMSCL1	Q06265
Progressive External Ophthalmoplegia	POLG	P54098
	POLG2	Q9UHN1
	SLC25A4	P12235
	TWNK	Q96RR1
Spinal Muscular Atrophy type 3 – Kugelberg-Welander Disease	Survival motor neuron protein (SMN), SMN1	Q16637
Thomsen Disease - Myotonia Congenita (autosomal dominant)	CLCN1	P35523
Walker-Warburg Syndrome	POMT1	Q9Y6A1
X-linked myotubular myopathy	Myotubularin (MTM1)	Q13496
Werdnig-Hoffmann Disease - Spinal Muscular Atrophy type 1	SMN1	Q16637

TABLE 4 Exemplary cardiac indications and transgenes		
Indication	**Transgene**	**UniProt Accession # (Human)**
Acid maltase deficiency (Glycogen storage disease II)	GAA	P10253
Advanced heart failure	SERCA2a, ATP2A2	P16615
Andersen-Tawil Syndrome	KCNJ2	P63252
Arrhythmogenic right ventricular cardiomyopathy 1 (ARVD1)	TGFB3	P10600
Arrhythmogenic right ventricular cardiomyopathy 5 (ARVD5)	TMEM43	Q9BTV4
Arrhythmogenic right ventricular cardiomyopathy 8 (ARVD8)	DSP	P15924
Arrhythmogenic right ventricular cardiomyopathy 9 (ARVD9)	PKP2	Q99959
Arrhythmogenic right ventricular cardiomyopathy 10 (ARVD10)	DSG2	Q14126
Arrhythmogenic right ventricular cardiomyopathy 11 (ARVD11)	DSC2	Q02487

TABLE 4
Exemplary cardiac indications and transgenes

Indication	Transgene	UniProt Accession # (Human)
Arrhythmogenic right ventricular cardiomyopathy 12 (ARVD12)	JUP	P14923
Arrhythmogenic right ventricular cardiomyopathy 13 (ARVD13)	CTNNA3	Q9UI47
Arrhythmogenic right ventricular cardiomyopathy 14 (ARVD14)	CDH2	P19022
Arrhythmogenic right ventricular cardiomyopathy 15 (ARVD15)	FLNC	Q14315
Atrial fibrillation 3 (ATFB3)	KCNQ1	P51787
Atrial fibrillation 4 (ATFB4)	KCNE2	Q9Y6J6
Atrial fibrillation 6 (ATFB6)	NPPA	P01160
Atrial fibrillation 7 (ATFB7)	KCNA5	P22460
Atrial fibrillation 9 (ATFB9)	KCNJ2	P63252
Atrial fibrillation 10 (ATFB10)	SCN5A	Q14524
Atrial fibrillation 11 (ATFB11)	GJA5	P36382
Atrial fibrillation 12 (ATFB612)	ABCC9	O60706
Atrial fibrillation 13 (ATFB6)	SCN1B	Q07699
Atrial fibrillation 14 (ATFB14)	SCN2B	O60939
Atrial fibrillation 15 (ATFB15)	NUP155	O75694
Atrial fibrillation 16 (ATFB16)	SCN3B	Q9NY72
Atrial fibrillation 17 (ATFB17)	SCN4B	Q8IWT1
Atrial fibrillation 18 (ATFB18)	MYL4	P12829
Atrial septal defect 2 (ASD2)	GATA4	P43694
Atrial septal defect 3 (ASD3)	MYH6	P13533
Atrial septal defect 4 (ASD4)	TBX20	Q9UMR3
Atrial septal defect 5 (ASD5)	ACTC1	P68032
Atrial septal defect 6 (ASD6)	TLL1	O43897
Atrial septal defect 7 (ASD7)	NKX2-5	P52952
Atrial septal defect 8 (ASD8)	CITED2	Q99967
Atrial septal defect 9 (ASD9)	GATA6	Q92908
Atrial standstill 1	GJA5	P36382
Atrial standstill 2	NPPA	P01160
Barth syndrome	TAFAZZIN, TAZ	Q16635
Becker Muscular Dystrophy (BMD)	DMD	P11532
Brugada syndrome 1	SCN5A	Q14524
Brugada syndrome 2	GPD1L	Q8N335
Brugada syndrome 3	CACNA1C	Q13936
Brugada syndrome 4	CACNB2	Q08289
Brugada syndrome 5	SCN1B	Q07699
Brugada syndrome 6	KCNE3	Q9Y6H6
Brugada syndrome 7	SCN3B	Q9NY72
Brugada syndrome 8	HCN4	Q9Y3Q4
Brugada syndrome 9	KCND3	Q9UK17
Cardiac arrhythmia syndrome	TRDN	Q13061
Cardiac conduct defect	AKAP10	O43572
Cardiac conduction disease	TNNI3K	Q59H18
Cardiac, facial, and digital anomalies with developmental delay (CAFDADD)	TRAF7	Q6Q0C0
Cardiofaciocutaneous syndrome 1	BRAF	P15056
Cardiofaciocutaneous syndrome 2	KRAS	P01116
Cardiofaciocutaneous syndrome 3	MAP2K1	Q02750
Cardiofaciocutaneous syndrome 4	MAP2K2	P36507
Cardiac-urogenital syndrome	MYRF	Q9Y2G1
Cardiac valvular dysplasia, X-linked	FLNA	P21333
Cardiac valvular dysplasia 2	ADAMTS19	Q8TE59

TABLE 4 Exemplary cardiac indications and transgenes		
Indication	**Transgene**	**UniProt Accession # (Human)**
Cardiomyopathy, dilated, 1A	LMNA	P02545
Cardiomyopathy, dilated, 1AA	ACTN2	P35609
Cardiomyopathy, dilated, 1C	LDB3	O75112
Cardiomyopathy, dilated, 1D	TNNT2	P45379
Cardiomyopathy, dilated, 1E	SCN5A	Q14524
Cardiomyopathy, dilated, 1FF	TNNI3	P19429
Cardiomyopathy, dilated, 1FF	MYPN	Q86TC9
Cardiomyopathy, dilated, 1MM	MYBPC3	Q14896
Cardiomyopathy, dilated, 1P	PLN	P26678
Cardiomyopathy, dilated, 1R	ACTC1	P68032
Cardiomyopathy, dilated, 1S	MYH7	P12883
Cardiomyopathy, dilated, 1Y	TPM1	P09493
Cardiomyopathy, dilated, 2A	TNNI3	P19429
Cardiomyopathy, dilated, 2E	JPH2	Q9BR39
Cardiomyopathy, familial restrictive, 1	TNNI3	P19429
Cardiomyopathy, familial restrictive, 3	TNNT2	P45379
Cardiomyopathy, hypertrophic, 1 (CMH1)	MYH7	P12883
	CAV3	P56539
	MYLK2	
Cardiomyopathy, hypertrophic, 2 (CMH2)	TNNT2	P45379
Cardiomyopathy, hypertrophic, 3 (CMH3)	TPM1	P09493
Cardiomyopathy, hypertrophic 4 (CMH4)	MYBPC3	Q14896
Cardiomyopathy, hypertrophic 6 (CMH6)	PRKAG2	Q9UGJ0
Cardiomyopathy, hypertrophic, 7 (CMH7)	TNNI3	P19429
Cardiomyopathy, hypertrophic, 8 (CMH8)	MYL3	P08590
Cardiomyopathy, hypertrophic, 9 (CMH9)	TTN	Q8WZ42
Cardiomyopathy, hypertrophic, 10 (CMH10)	MYL2	P10916
Cardiomyopathy, hypertrophic, 11 (CMH11)	ACTC1	P68032
Cardiomyopathy, hypertrophic, 12 (CMH12)	CSRP3	P50461
Cardiomyopathy, hypertrophic, 13 (CMH13)	TNNC1	P63316
Cardiomyopathy, hypertrophic, 14 (CMH14)	MYH6	P13533
Cardiomyopathy, hypertrophic, 15 (CMH15)	VCL	P18206
Cardiomyopathy, hypertrophic, 16 (CMH16)	MYOZ2	Q9NPC6
Cardiomyopathy, hypertrophic, 17 (CMH17)	JPH2	Q9BR39
Cardiomyopathy, hypertrophic, 18 (CMH18)	PLN	P26678
Cardiomyopathy, hypertrophic, 20 (CMH20)	NEXN	Q0ZGT2
Cardiomyopathy, hypertrophic, 23 (CMH23)	ACTN2	P35609

TABLE 4
Exemplary cardiac indications and transgenes

Indication	Transgene	UniProt Accession # (Human)
Cardiomyopathy, hypertrophic, 25 (CMH25)	TCAP	O15273
Cardiomyopathy, hypertrophic, 26 (CMH26)	FLNC	Q14315
Cardiomyopathy, hypertrophic, 27 (CMH27)	ALPK3	Q96L96
Cardiomyopathy, hypertrophic, 28 (CMH28)	FHOD3	Q2V2M9
Cardiomyopathy, hypertrophic, 29 (CMH29)	KLHL24	Q6TFL4
Cardiomyopathy, restrictive 1 (RCM1)	TNNI3	P19429
Cardiomyopathy, restrictive 3 (RCM3)	TNNT2	P45379
Cardiomyopathy, restrictive 4 (RCM4)	MYPN	Q86TC9
Cardiomyopathy, restrictive 5 (RCM5)	FLNC	Q14315
Cardiomyopathy, restrictive 6 (RCM6)	KIF20A	O95235
Carnitine Deficiency, systemic primary	SLC22A5	O76082
Catecholaminergic polymorphic ventricular tachycardia 2 (CPVT2)	Calsequestrin-2 (CASQ2)	O14958
Combined oxidative phosphorylation deficiency 8	AARS2	Q5JTZ9
Combined oxidative phosphorylation deficiency 10	MTO1	Q9Y2Z2
Congenital Myopathy	ACTA1	P68133
	STAC3	Q96MF2
	TPM3	P06753
Congenital Myotonic Dystrophy	DMPK	Q09013
Conotruncal heart malformations	NKX2-5	P52952
	NKX2-6	A6NCS4
	TBX1	O43435
	GATA6	Q92908
Coronary artery disease 1	MEF2A	Q02078
Coronary artery disease 2	LRP6	O75581
Cori Disease - Debrancher Enzyme Deficiency – Forbes Disease	AGL	P35573
Costello syndrome	HRAS	P01112
Danon disease	LAMP2	P13473
Dextrocardia with other cardiac malformations, x-linked (visceral heterotaxy (HTX1))	ZIC3	O60481
Dilated Cardiomyopathy	BAG3	O95817
Duchenne Muscular Dystrophy	Dystrophin (DMD)	P11532
	GALGT2, B4GALNT2	Q8NHY0
Ehlers-Danlos syndrome, cardiac valvular type	COL1A2	P08123
Emery-Dreifuss Muscular Dystrophy	EMD	P50402
	SYNE1	Q8NF91
	SYNE2	Q8WXH0
	TMEM43	Q9BTV4
	LMNA	P02545
Fabry disease, cardiac variant	GLA	P06280
Frank-ter Haar syndrome	SH3PXD2B	A1X283
Friedreich's ataxia	Frataxin (FXN)	Q16595
Fukuyama Congenital Muscular Dystrophy	FKTN	O75072
Glycogen storage disease III	AGL	P35573

TABLE 4 Exemplary cardiac indications and transgenes		
Indication	**Transgene**	**UniProt Accession # (Human)**
GM1-gangliosidosis, type I with cardiac involvement	GLB1	P16278
Heart failure	SOD3	P08294
Hirschsprung disease (HCAD)	ECE1	P42892
Infantile hypertrophic cardiomyopathy	MTATP6	P00846
	MTATP8	P03928
Ischemia-reperfusion injury	SOD3	P08294
	YY1	P25490
	BMP7	P18075
Jervell and Lange-Nielsen syndrome (JLNS1)	KCNQ1	P51787
Jervell and Lange-Nielsen syndrome 2 (JLNS2)	KCNE1	P15382
Laing Distal Myopathy	MYH7	P12883
Left ventricular noncompaction 1 (LVNC1)	DTNA	
Left ventricular noncompaction 3 (LVNC3)	LDB3	O75112
Left ventricular noncompaction 4 (LVNC4)	ACTC1	P68032
Left ventricular noncompaction 5 (LVNC5)	MYH7	P12883
Left ventricular noncompaction 6 (LVNC6)	TNNT2	P45379
Left ventricular noncompaction 7 (LVNC7)	MIB1	Q86YT6
Left ventricular noncompaction 8 (LVNC8)	PRDM16	Q9HAZ2
Left ventricular noncompaction 9 (LVNC9)	TPM1	P09493
Left ventricular noncompaction 10 (LVNC10)	MYBPC3	Q14896
LEOPARD syndrome 1	PTPN11	Q06124
LEOPARD syndrome 2	RAF1	P04049
LEOPARD syndrome 3	BRAF	P15056
Limb-girdle muscular dystrophy, type 25 (LGMDR25)	BVES	Q8NE79
Lodder-Merla syndrome, type 1	GNB5	O14775
Long QT syndrome 1	KCNQ1	P51787
Long QT syndrome 2	KCNH2, ERG	Q12809
Long QT syndrome 3	SCN5A	Q14524
Long QT syndrome 4	ANK2	Q01484
Long QT syndrome 5	KCNE1	P15382
Long QT syndrome 6	KCNE2	Q9Y6J6
Long QT syndrome 7 (Andersen syndrome)	KCNJ2	P63252
Long QT syndrome 8	CACNA1C	Q13936
Long QT syndrome 9	CAV3	P56539
Long QT syndrome 10	SCN4B	Q8IWT1
Long QT syndrome 11	AKAP9	Q99996
Long QT syndrome 12	SNTA1	Q13424
Long QT syndrome 13	KCNJ5	P48544
Long QT syndrome 14	CALM1	P0DP23
Long QT syndrome 15	CALM2	P0DP24
Long QT syndrome 16	CALM3	P0DP25

TABLE 4 Exemplary cardiac indications and transgenes		
Indication	**Transgene**	**UniProt Accession # (Human)**
Metabolic encephalomyopathic crises (MECRCN)	TANGO2	Q6ICL3
Microphthalmia, syndromic, type 9	STRA6	Q9BX79
Mitochondrial phosphate carrier deficiency (MPCD)	SLC25A3	Q00325
Mitral valve prolapse 3 (MVP3)	DZIP1	Q86YF9
Mungan syndrome (MGS)	RAD21	O60216
Myocardial infarction	SOD3	P08294
	CDK9	P50750
Myofibrillar Myopathy 1	DES	P17661
Myofibrillar Myopathy 2	CRYAB	P02511
Myofibrillar Myopathy 6	BAG3	O95817
Myofibrillar Myopathy 10	SVIL	O95425
Myofibrillar Myopathy 11	UNC45B	Q8IWX7
Myofibrillar Myopathy 12	MYL2	P10916
Myotonic dystrophy Type 1 - Steinert Disease	Myotonin-protein kinase (DMPK)	Q09013
Myotonic dystrophy Type 2	CNBP	P62633
Naxos disease (NXD)	JUP	P14923
Nemaline Myopathy 1	TPM3	P06753
Nemaline Myopathy 3	ACTA1	P68133
Nonprogressive hear block	SCN5A	Q14524
Orthostatic intolerance (soldiers heart)	SLC6A2	P23975
Progeria syndrome	LMNA	P02545
Progressive familial heart block type IA	SCN5A	Q14524
Progressive familial heart block type IB	TRPM4	Q8TD43
RYR2 calcium release deficiency syndrome	RYR2	Q92736
Sengers syndrome	AGK	Q53H12
Sick sinus syndrome 1 (SSS1)	SCN5A	Q14524
Sick sinus syndrome 2 (SSS2)	HCN4	Q9Y3Q4
Sick sinus syndrome 3 (SSS3)	MYH6	P13533
Sick sinus syndrome 4 (SSS4)	GNB2	P62879
Sudden cardiac failure, infantile (SCFI)	PPA2	Q9H2U2
TARP syndrome	RBM10	P98175
Timothy syndrome	CACNA1C	Q13936
Valvular heart disease, congenital	FLNA	P21333
Ventricular fibrillation 1 (VF1)	SCN5A	Q14524
Ventricular tachycardia	CASQ2	O14958
Vertebral, cardiac, renal, and limb defects syndrome 1 (VCRL1)	HAAO	P46952
Vertebral, cardiac, renal, and limb defects syndrome 2 (VCRL2)	KYNU	Q16719
Vertebral, cardiac, renal, and limb defects syndrome 3 (VCRL3)	NADSYN1	Q6IA69

[0269] In some embodiments, the payload is an antisense oligonucleotide effective in treating a muscle disease, for example by modulating expression of a target gene. Exemplary target genes of such antisense oligonucleotides for treatment of muscle disease include, for example, MSTN, INHBA, ACVR1B, MLCK1, ACVR1, FBXO32, TRIM63, MEF2D, KLF15, MED1, MED13, DUX4, LMNA, SMN, GAA, GYS2, DMD, DMPK, MSTN, and PPP1R3A.

[0270] Non-limiting, example antisense oligonucleotides that can be delivered via the viral particles of the disclosure (along with associated target genes and muscle tissue related diseases that can be treated) are provided in Table 4-1. Where such antisense oligonucleotides are indicated by reference to a patent or patent application publication, such patent and patent applications are incorporated herein by reference in their entirety for their disclosed antisense oligonucleotide structures and sequences.

TABLE 4-1
Exemplary Muscle Indications, Target Genes, and Antisense Oligonucleotide Transgenes

Indication	Target Gene	Uniprot Accession # (Human)	Exemplary transgene(s)
Hutchinson-Gilford progeria syndrome (HGPS)	lamin A (LMNA)	P02545	Antisense oligonucleotides described in: U.S. Patent No. 10,076,536 and in U.S. Patent Application Publication Nos. 2017/0051278 A1, 2018/0271893 A1
Spinal Muscular Atrophy (SMA)	Survival Motor Neuron (SMN)	Q16637	Antisense oligonucleotides described in U.S. Patent Application Publication No. 2019/0015440 A1
Glycogen storage disease type II (GSD-II), or Pompe disease	acid alpha-glucosidase (GAA)	P10253	Antisense oligonucleotides described in U.S. Patent Application Publication No. 2018/0216111 A1
	Glycogen synthase (GYS2)	P54840	Antisense oligonucleotides described in U.S. Patent Application Publication No. 2017/0182189 A1
Duchenne muscular dystrophy	Dystrophin (DMD)	P11532	Antisense oligonucleotides described in: U.S. Patent Application Publication Nos. 2019/0177723 A1 and 20210261963 A1; and PCT Patent Application Publication Nos. WO 2017/062835 A2 and 2019/059973 A1
Myotonic dystrophy Type 1 - Steinert Disease	Dystrophia Myotonica-Protein Kinase (DMPK)	Q09013	Antisense oligonucleotides described in U.S. Patent Application Publication Nos. 2024/0117356 A1, 2010/0016215 A1, 2013/0237585 A1, 2015/0064181 A1, 2015/0238627 A1, and 2016/0304877 A1
Muscle atrophy	Myostatin (MSTN)	O14793	Antisense oligonucleotides described in U.S. Patent Application Publication No. 2018/0327749 A1
Facioscapulohumeral Muscular Dystrophy	Double homeobox 4 (DUX4)	Q9UBX2	Antisense oligonucleotides described in U.S. Patent Application Publication No. 2023/0272065 A1

TABLE 5
Additional exemplary indications and transgenes

Indication	Transgene	UniProt Accession # (Human)
Osteogenesis imperfecta (brittle bone disease)Type I, II, III, or IV	COL1A1	P02452
	COL1A2	P08123
Hereditary angioedema	Plasma protease C1 inhibitor (SERPING1, C1NH)	P05155
Osteogenesis imperfecta Type V	Interferon-induced transmembrane protein 5 (IFITM5, IFM5)	A6NNB3
Osteogenesis Imperfecta Type VI	Pigment epithelium-derived factor (SERPINF1, PEDF)	P36955
Osteogenesis Imperfecta Type VII	Cartilage-associated protein (CRTAP)	O75718
Osteogenesis Imperfecta Type VIII	Prolyl 3-hydroxylase 1 (P3H1, LEPRE1)	Q32P28

TABLE 5 Additional exemplary indications and transgenes		
Indication	**Transgene**	**UniProt Accession # (Human)**
Osteogenesis Imperfecta Type IX	PPIB	P23284
Maple syrup urine disease	BCKDHA	P12694
	BCKDHB	P21953
	DBT	P11182
Alpha-mannosidosis	Lysosomal alpha-mannosidase (MAN2B1)	O00754
Beta-mannosidosis	Beta-mannosidase (MANBA)	O00462
Glycogen storage disease Ia – Von Gierke disease	Glucose-6-phosphatase catalytic subunit 1 (G6PC1)	P35575
Bloch-Sulzberger Syndrome	IKBKG	Q9Y6K9
Cholesterol Ester Storage Disease	LIPA	P38571
Danon Disease	Lysosome-associated membrane glycoprotein 2 (LAMP2)	P13473
Cystic Fibrosis	CTFR	A4L9V0
Rheumatoid Arthritis	TNF	P01375
Alpha-1 Antitrypsin Deficiency	Alpha-1-antitrypsin (Alpha1-AT), AAT, SERPINA1	P01009
Hemophilia A	Coagulation factor VIII	P00451
Hemophilia B	Coagulation factor IX	P00740
Homozygous Familial Hypercholesterolemia -FHCL1	Low-density lipoprotein receptor (LDLR)	P01130
Mucopolysaccharidosis Type VI	Arylsulfatase B (ARSB)	P15848
Familial Lipoprotein Lipase Deficiency	LPL	P06858
Fragile X syndrome	FMR1	Q06787

6.6.2. Methods of treatment

[0271] The disclosure is directed, in part, to a method of treating a disease or condition in a subject, e.g., an animal or human subject. In some embodiments, a method of treating a disease or condition in a subject comprises administering to the subject a dependoparvovirus particle comprising a variant polypeptide described herein, e.g., comprising a payload described herein. In some embodiments, the dependoparvovirus particle, which comprises a variant polypeptide, comprising a payload described herein is administered in an amount and/or time effective to treat the disease or condition. In some embodiments, the payload is a therapeutic product. In some embodiments, the payload is a nucleic acid, e.g., encoding an exogenous polypeptide.

[0272] The dependoparvovirus particles comprising a variant polypeptide described herein or produced by the methods described herein can be used to express one or more therapeutic proteins to treat various diseases or disorders. In some embodiments, the disease or disorder is a cancer, e.g., a cancer such as carcinoma, sarcoma, leukemia, lymphoma; or an autoimmune disease, e.g., multiple sclerosis. Non-limiting examples of carcinomas include esophageal carcinoma; bronchogenic carcinoma; colon carcinoma; colorectal carcinoma; gastric carcinoma; hepatocellular carcinoma; basal cell carcinoma, squamous cell carcinoma (various tissues); bladder carcinoma, including transitional cell carcinoma; lung carcinoma, including small cell carcinoma and non-small cell carcinoma of the lung; adrenocortical carcinoma; sweat gland carcinoma; sebaceous gland carcinoma; thyroid carcinoma; pancreatic carcinoma; breast carcinoma; ovarian carcinoma; prostate carcinoma; adenocarcinoma; papillary

carcinoma; papillary adenocarcinoma; cystadenocarcinoma; medullary carcinoma; renal cell carcinoma; uterine carcinoma; testicular carcinoma; osteogenic carcinoma; ductal carcinoma in situ or bile duct carcinoma; choriocarcinoma; seminoma; embryonal carcinoma; Wilm's tumor; cervical carcinoma; epithelial carcinoma; and nasopharyngeal carcinoma. Non-limiting examples of sarcomas include fibrosarcoma, myxosarcoma, liposarcoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, chondrosarcoma, chordoma, osteogenic sarcoma, osteosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's sarcoma, leiomyosarcoma, rhabdomyosarcoma, and other soft tissue sarcomas. Non-limiting examples of solid tumors include ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, menangioma, melanoma, neuroblastoma, and retinoblastoma. Non-limiting examples of leukemias include chronic myeloproliferative syndromes; T-cell CLL prolymphocytic leukemia, acute myelogenous leukemias; chronic lymphocytic leukemias, including B-cell CLL, hairy cell leukemia; and acute lymphoblastic leukemias. Examples of lymphomas include, but are not limited to, B-cell lymphomas, such as Burkitt's lymphoma; and Hodgkin's lymphoma. In some embodiments, the disease or disorder is a genetic disorder. In some embodiments, the genetic disorder is sickle cell anemia, Glycogen storage diseases (GSD, e.g., GSD types I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, and XIV), cystic fibrosis, lysosomal acid lipase (LAL) deficiency 1, Tay-Sachs disease, Phenylketonuria, Mucopolysaccharidoses, Galactosemia, muscular dystrophy (e.g., Duchenne muscular dystrophy), hemophilia such as hemophilia A (classic hemophilia) or hemophilia B (Christmas Disease), Wilson's disease, Fabry Disease, Gaucher Disease hereditary angioedema (HAE), and alpha 1 antitrypsin deficiency. Examples of other diseases or disorders are provided above in Section 6.6.1.

[0273] In some aspects, the disease or condition is a disease of the CNS. Exemplary diseases of the CNS include, 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, Angleman syndrome, 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 (CIDP), 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 ophtalmoplegia, 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 Paralyses, Familial Spastic Paralysis, Farber's Disease, Febrile Seizures, Fibromuscular Dysplasia, Fisher Syndrome, Floppy Infant Syndrome, Foot Drop, Fragile X syndrome, 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, Hemicrania Continua, Hemifacial Spasm, Hemiplegia Alterans, Hereditary Neuropathies, Hereditary Spastic Paraplegia, Heredopathia Atactica Polyneuritiformis, Herpes Zoster, Herpes Zoster Oticus, Hirayama Syndrome, Holmes-Adie syndrome, Holoprosencephaly, HTLV-1 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, Lichtheim'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, Mucolipidoses, 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 Cavernosus, Niemann-Pick Disease, O'Sullivan-McLeod Syndrome, Occipital Neuralgia, Ohtahara 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 Paralyses, 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, Pseudotoxoplasmosis 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. Examples of other diseases or disorders are provided above in Section 6.6.1.

[0274] In some aspects, the disease or condition is a disease of muscle (e.g., skeletal muscle). Exemplary diseases of the muscle include Acid Maltase Deficiency (AMD), Amyotrophic Lateral Sclerosis (ALS), Andersen-Tawil Syndrome, Becker Muscular Dystrophy (BMD), Becker Myotonia Congenita, Bethlem Myopathy, Bulbospinal Muscular Atrophy (Spinal- Bulbar Muscular Atrophy), Carnitine Deficiency, Carnitine Palmityl Transferase Deficiency (CPT Deficiency), Central Core Disease (CCD), Centronuclear Myopathy, Charcot-Marie- Tooth Disease (CMT), Congenital Muscular Dystrophy (CMD), Congenital Myasthenic Syndromes (CMS), Congenital Myotonic Dystrophy, Cori Disease (Debrancher Enzyme Deficiency), Debrancher Enzyme Deficiency, Dejerine-Sottas Disease (DSD), Dermatomyositis (DM), Distal Muscular Dystrophy (DD), Duchenne Muscular Dystrophy (DMD), Dystrophia Myotonica (Myotonic Muscular Dystrophy), Emery-Dreifuss Muscular Dystrophy (EDMD), Endocrine Myopathies, Eulenberg Disease (Paramyotonia Congenita), Facioscapulohumeral Muscular Dystrophy (FSH or FSHD), Finnish (Tibial) Distal Myopathy, Forbes Disease (Debrancher Enzyme Deficiency), Friedreich's Ataxia (FA), Fukuyama Congenital Muscular Dystrophy, Glycogenosis Type 10, Glycogenosis Type 11, Glycogenosis Type 2, Glycogenosis Type 3, Glycogenosis Type 5, Glycogenosis Type 7, Glycogenosis Type 9, Gowers-Laing Distal Myopathy, Hauptmann-Thanheuser MD (Emery- Dreifuss Muscular Dystrophy), Hereditary Inclusion-Body Myositis, Hereditary Motor and Sensory Neuropathy (Charcot-Marie-Tooth Disease), Hyperthyroid Myopathy, Hypothyroid Myopathy, Inclusion-Body Myositis (IBM), Inherited Myopathies, Integrin-Deficient Congenital Muscular Dystrophy, Kennedy Disease (Spinal-Bulbar Muscular Atrophy), Kugelberg-Welander Disease (Spinal Muscular Atrophy), Lactate Dehydrogenase Deficiency, Lambert-Eaton Myasthenic Syndrome (LEMS), Limb-Girdle Muscular Dystrophy (LGMD), Lou Gehrig's Disease (Amyotrophic Lateral Sclerosis), McArdle Disease (Phosphorylase Deficiency), Merosin-Deficient Congenital Muscular Dystrophy, Metabolic Diseases of Muscle, Mitochondrial Myopathy, Miyoshi Distal Myopathy, Motor Neurone Disease, Muscle-Eye-Brain Disease, Myasthenia Gravis (MG), Myoadenylate Deaminase Deficiency, Myofibrillar Myopathy, Myophosphorylase Deficiency, Myotonia Congenita (MC), Myotonic Muscular Dystrophy (MMD), Myotubular Myopathy (MTM or MM), Nemaline Myopathy, Nonaka Distal Myopathy, Oculopharyngeal Muscular Dystrophy (OPMD), Paramyotonia Congenita, Pearson Syndrome, Periodic Paralysis, Peroneal Muscular Atrophy (Charcot-

Marie-Tooth Disease), Phosphofructokinase Deficiency, Phosphogly cerate Kinase Deficiency, Phosphogly cerate Mutase Deficiency, Phosphorylase Deficiency, Phosphorylase Deficiency, Polymyositis (PM), Pompe Disease (Acid Maltase Deficiency), Progressive External Ophthalmoplegia (PEO), Rod Body Disease (Nemaline Myopathy), Spinal Muscular Atrophy (SMA), Spinal-Bulbar Muscular Atrophy (SBMA), Steinert Disease (Myotonic Muscular Dystrophy), Tarui Disease (Phosphofructokinase Deficiency), Thomsen Disease (Myotonia Congenita), Ullrich Congenital Muscular Dystrophy, Walker-Warburg Syndrome (Congenital Muscular Dystrophy), Welander Distal Myopathy, Werdnig-Hoffmann Disease (Spinal Muscular Atrophy), and ZASP-Related Myopathy.

[0275] In some aspects, the disease or condition is a disease of cardiac muscle. Exemplary diseases of cardiac muscle include Acid maltase deficiency (Glycogen storage disease II), Advanced heart failure, Andersen-Tawil Syndrome, Arrhythmogenic right ventricular cardiomyopathy 1 (ARVD1), Arrhythmogenic right ventricular cardiomyopathy 5 (ARVD5), Arrhythmogenic right ventricular cardiomyopathy 8 (ARVD8), Arrhythmogenic right ventricular cardiomyopathy 9 (ARVD9), Arrhythmogenic right ventricular cardiomyopathy 10 (ARVD10), Arrhythmogenic right ventricular cardiomyopathy 11 (ARVD11), Arrhythmogenic right ventricular cardiomyopathy 12 (ARVD12), Arrhythmogenic right ventricular cardiomyopathy 13 (ARVD13), Arrhythmogenic right ventricular cardiomyopathy 14 (ARVD14), Arrhythmogenic right ventricular cardiomyopathy 15 (ARVD15), Atrial fibrillation 3 (ATFB3), Atrial fibrillation 4 (ATFB4), Atrial fibrillation 6 (ATFB6), Atrial fibrillation 7 (ATFB7), Atrial fibrillation 9 (ATFB9), Atrial fibrillation 10 (ATFB10), Atrial fibrillation 11 (ATFB11), Atrial fibrillation 12 (ATFB612), Atrial fibrillation 13 (ATFB6), Atrial fibrillation 14 (ATFB14), Atrial fibrillation 15 (ATFB15), Atrial fibrillation 16 (ATFB16), Atrial fibrillation 17 (ATFB17), Atrial fibrillation 18 (ATFB18), Atrial septal defect 2 (ASD2), Atrial septal defect 3 (ASD3), Atrial septal defect 4 (ASD4), Atrial septal defect 5 (ASD5), Atrial septal defect 6 (ASD6), Atrial septal defect 7 (ASD7), Atrial septal defect 8 (ASD8), Atrial septal defect 9 (ASD9), Atrial standstill 1, Atrial standstill 2, Barth syndrome , Becker Muscular Dystrophy (BMD), Brugada syndrome 1, Brugada syndrome 2, Brugada syndrome 3, Brugada syndrome 4, Brugada syndrome 5, Brugada syndrome 6, Brugada syndrome 7, Brugada syndrome 8, Brugada syndrome 9, Cardiac arrhythmia syndrome, Cardiac conduct defect, Cardiac conduction disease, Cardiac, facial, and digital anomalies with developmental delay (CAFDADD), Cardiofaciocutaneous syndrome 1, Cardiofaciocutaneous syndrome 2, Cardiofaciocutaneous syndrome 3, Cardiofaciocutaneous syndrome 4, Cardiac-urogenital syndrome, Cardiac valvular dysplasia, X-linked, Cardiac valvular dysplasia 2, Cardiomyopathy, dilated, 1A, Cardiomyopathy, dilated, 1AA, Cardiomyopathy, dilated, 1C, Cardiomyopathy, dilated, 1D, Cardiomyopathy, dilated, 1E, Cardiomyopathy, dilated, 1FF, Cardiomyopathy, dilated, 1MM, Cardiomyopathy, dilated, 1P, Cardiomyopathy, dilated, 1R, Cardiomyopathy, dilated, 1S, Cardiomyopathy, dilated, 1Y, Cardiomyopathy, dilated, 2A, Cardiomyopathy, dilated, 2E, Cardiomyopathy, familial restrictive, 1, Cardiomyopathy, familial restrictive, 3, Cardiomyopathy, hypertrophic, 1 (CMH1), Cardiomyopathy, hypertrophic, 2 (CMH2), Cardiomyopathy, hypertrophic, 3 (CMH3), Cardiomyopathy, hypertrophic 4 (CMH4), Cardiomyopathy, hypertrophic 6 (CMH6), Cardiomyopathy, hypertrophic, 7 (CMH7), Cardiomyopathy, hypertrophic, 8 (CMH8), Cardiomyopathy, hypertrophic, 9 (CMH9), Cardiomyopathy, hypertrophic, 10 (CMH10), Cardiomyopathy, hypertrophic, 11 (CMH11), Cardiomyopathy, hypertrophic, 12 (CMH12), Cardiomyopathy, hypertrophic, 13 (CMH13), Cardiomyopathy, hypertrophic, 14 (CMH14), Cardiomyopathy, hypertrophic, 15 (CMH15), Cardiomyopathy, hypertrophic, 16 (CMH16), Cardiomyopathy, hypertrophic, 17 (CMH17),

Cardiomyopathy, hypertrophic, 18 (CMH18), Cardiomyopathy, hypertrophic, 20 (CMH20), Cardiomyopathy, hypertrophic, 23 (CMH23), Cardiomyopathy, hypertrophic, 25 (CMH25), Cardiomyopathy, hypertrophic, 26 (CMH26), Cardiomyopathy, hypertrophic, 27 (CMH27), Cardiomyopathy, hypertrophic, 28 (CMH28), Cardiomyopathy, hypertrophic, 29 (CMH29), Cardiomyopathy, restrictive 1 (RCM1), Cardiomyopathy, restrictive 3 (RCM3), Cardiomyopathy, restrictive 4 (RCM4), Cardiomyopathy, restrictive 5 (RCM5), Cardiomyopathy, restrictive 6 (RCM6), Carnitine Deficiency, systemic primary, Catecholaminergic polymorphic ventricular tachycardia 2 (CPVT2), Combined oxidative phosphorylation deficiency 8, Combined oxidative phosphorylation deficiency 10, Congenital Myopathy, Congenital Myotonic Dystrophy, Conotruncal heart malformations, Coronary artery disease 1, Coronary artery disease 2, Cori Disease - Debrancher Enzyme Deficiency – Forbes Disease, Costello syndrome, Danon disease, Dextrocardia with other cardiac malformations, x-linked (visceral heterotaxy (HTX1)), Dilated Cardiomyopathy, Duchenne Muscular Dystrophy, Ehlers-Danlos syndrome, cardiac valvular type, Emery-Dreifuss Muscular Dystrophy, Fabry disease, cardiac variant, Frank-ter Haar syndrome, Friedreich's ataxia, Fukuyama Congenital Muscular Dystrophy, Glycogen storage disease III, GM1-gangliosidosis, type I with cardiac involvement, Heart failure, Hirschsprung disease (HCAD), Infantile hypertrophic cardiomyopathy, Ischemia-reperfusion injury, Jervell and Lange-Nielsen syndrome (JLNS1), Jervell and Lange-Nielsen syndrome 2 (JLNS2), Laing Distal Myopathy, Left ventricular noncompaction 1 (LVNC1), Left ventricular noncompaction 3 (LVNC3), Left ventricular noncompaction 4 (LVNC4), Left ventricular noncompaction 5 (LVNC5), Left ventricular noncompaction 6 (LVNC6), Left ventricular noncompaction 7 (LVNC7), Left ventricular noncompaction 8 (LVNC8), Left ventricular noncompaction 9 (LVNC9), Left ventricular noncompaction 10 (LVNC10), LEOPARD syndrome 1, LEOPARD syndrome 2, LEOPARD syndrome 3, Limb-girdle muscular dystrophy, type 25 (LGMDR25), Lodder-Merla syndrome, type 1, Long QT syndrome 1, Long QT syndrome 2, Long QT syndrome 3, Long QT syndrome 4, Long QT syndrome 5, Long QT syndrome 6, Long QT syndrome 7 (Andersen syndrome), Long QT syndrome 8, Long QT syndrome 9, Long QT syndrome 10, Long QT syndrome 11, Long QT syndrome 12, Long QT syndrome 13, Long QT syndrome 14, Long QT syndrome 15, Long QT syndrome 16, Metabolic encephalomyopathic crises (MECRCN), Microphthalmia, syndromic, type 9, Mitochondrial phosphate carrier deficiency (MPCD), Mitral valve prolapse 3 (MVP3), Mungan syndrome (MGS), Myocardial infarction, Myofibrillar Myopathy 1, Myofibrillar Myopathy 2, Myofibrillar Myopathy 6, Myofibrillar Myopathy 10, Myofibrillar Myopathy 11, Myofibrillar Myopathy 12, Myotonic dystrophy Type 1 - Steinert Disease, Myotonic dystrophy Type 2, Naxos disease (NXD), Nemaline Myopathy 1, Nemaline Myopathy 3, Nonprogressive hear block, Orthostatic intolerance (soldiers heart), Progeria syndrome, Progressive familial heart block type IA, Progressive familial heart block type IB, RYR2 calcium release deficiency syndrome, Sengers syndrome, Sick sinus syndrome 1 (SSS1), Sick sinus syndrome 2 (SSS2), Sick sinus syndrome 3 (SSS3), Sick sinus syndrome 4 (SSS4), Sudden cardiac failure, infantile (SCFI), TARP syndrome, Timothy syndrome, Valvular heart disease, congenital, Ventricular fibrillation 1 (VF1), Ventricular tachycardia, Vertebral, cardiac, renal, and limb defects syndrome 1 (VCRL1), and Vertebral, cardiac, renal, and limb defects syndrome 2 (VCRL2), Vertebral, cardiac, renal, and limb defects syndrome 3 (VCRL3).

[0276] In some aspects, the disease or condition is a disease affecting the CNS and muscle, for example SMA, multiple sclerosis, Amyotrophic lateral sclerosis (ALS), Ataxia, Becker muscular dystrophy, Charcot-Marie-Tooth disease, Dystonias, Friedreich's ataxia, Glycogen storage disease II,

Kennedy Disease, Lambert-Eaton Myasthenic Syndrome, Mitochondrial DNA depletion syndromes, Muscle-Eye-Brain Disease, Neuromyotonia, Periodic Paralyses, juvenile Primary Lateral Sclerosis, Progressive external ophtalmoplegia, Spastic Paraplegias, congenital Stiff-Person Syndrome, Tardive Dyskinesia, Werdnig-Hoffman Disease, or X-Linked Spinal and Bulbar Muscular Atrophy.

[0277] In some embodiments, administration of a dependoparvovirus particle comprising a variant polypeptide and comprising a payload (e.g., a transgene as described in Section 6.6.1 or its subparts) to a subject induces expression of the payload (e.g., transgene) in a subject. In some embodiments, the expression is induced in the CNS. In some embodiments, the production is similar in the CNS as compared to a similar particle with the wild-type capsid protein. In some embodiments, the production is increased in the CNS as compared to a similar particle with the wild-type capsid protein, for example, a particle with capsid proteins of SEQ ID NO:1. In some embodiments, the expression is induced in muscle. In some embodiments, the production is similar in muscle as compared to a similar particle with the wild-type capsid protein, for example, a particle with capsid proteins of SEQ ID NO:1. In some embodiments, the production is increased in muscle as compared to a similar particle with the wild-type capsid protein (for example, a particle with capsid proteins of SEQ ID NO:1). In some embodiments, the expression is induced in skeletal muscle. In some embodiments, the production is similar in skeletal muscle as compared to a similar particle with the wild-type capsid protein, for example, a particle with capsid proteins of SEQ ID NO:1. In some embodiments, the production is increased in skeletal muscle as compared to a similar particle with the wild-type capsid protein (for example, a particle with capsid proteins of SEQ ID NO:1). In some embodiments, the expression is induced in cardiac muscle. In some embodiments, the production is similar in cardiac muscle as compared to a similar particle with the wild-type capsid protein, for example, a particle with capsid proteins of SEQ ID NO:1. In some embodiments, the production is increased in cardiac muscle as compared to a similar particle with the wild-type capsid protein (for example, a particle with capsid proteins of SEQ ID NO:1). The amount of a payload, e.g., transgene, e.g., heterologous protein, e.g., therapeutic polypeptide, expressed in a subject (e.g., the serum of the subject) can vary. For example, in some embodiments the payload, e.g., protein or RNA product of a transgene, can be expressed in the serum of the subject in the amount of at least about 9 µg/ml, at least about 10 µg/ml, at least about 50 µg/ml, at least about 100 µg/ml, at least about 200 µg/ml, at least about 300 µg/ml, at least about 400 µg/ml, at least about 500 µg/ml, at least about 600 µg/ml, at least about 700 µg/ml, at least about 800 µg/ml, at least about 900 µg/ml, or at least about 1000 µg/ml. In some embodiments, the payload, e.g., protein or RNA product of a transgene, is expressed in the serum of the subject in the amount of about 9 µg/ml, about 10 µg/ml, about 50 µg/ml, about 100 µg/ml, about 200 µg/ml, about 300 µg/ml, about 400 µg/ml, about 500 µg/ml, about 600 µg/ml, about 700 µg/ml, about 800 µg/ml, about 900 µg/ml, about 1000 µg/ml, about 1500 µg/ml, about 2000 µg/ml, about 2500 µg/ml, or a range between any two of these values.

[0278] In some embodiments, for therapeutic applications, a viral particle comprising a capsid polypeptide as described herein is prepared as a pharmaceutical composition. As used herein the term "pharmaceutical composition" refers to a composition comprising at least one active ingredient (e.g., the viral particle) and optionally, one or more pharmaceutically acceptable carriers or excipients.

[0279] Relative amounts of the active ingredient, pharmaceutically acceptable carrier or excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the present

disclosure may vary. Differences in the constitution of a pharmaceutical composition may depend upon the identity, size, and/or condition of the subject being treated, the route by which the composition is to be administered, and/or any other factor. The composition may comprise between 0.0001% and 99% (w/w) of the active ingredient. By way of example, the composition may comprise between 0.0001% and 100%, e.g., between 0.5 and 50%, between 1-30%, between 5-80%, or at least 80% (w/w) active ingredient. Non limiting examples of carriers and/or excipients include solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, or combination thereof.

7. NUMBERED EMBODIMENTS

[0280] While various specific embodiments have been illustrated and described, it will be appreciated that various changes can be made without departing from the spirit and scope of the disclosure(s). The present disclosure is exemplified by the numbered embodiments set forth below. Unless otherwise specified, features of any of the concepts, aspects and/or embodiments described in the detailed description above are applicable mutatis mutandis to any of the following numbered embodiments.

[0281] Various numbered embodiments below refer to virus particles, and it will be understood that such viral particles are engineered particles comprising a capsid polypeptide and a nucleic acid that do not naturally occur together in nature. Further, the nucleic acid can include components that do not naturally occur together in nature. For example, a nucleic acid can comprise a payload (e.g., a nucleotide sequence of a transgene, which may encode a non-naturally occurring, e.g., variant, polypeptide), one or more regulatory elements (which may comprise a non-naturally occurring, e.g., variant, regulatory sequence such as a promoter), and AAV ITRs, where two or more of such components do not naturally occur together in nature. In some embodiments, (a) a viral particle comprises a variant capsid polypeptide of a first serotype (e.g., a variant AAV9 capsid polypeptide) and ITRs from the genome of an AAV of a different serotype (e.g., AAV2 ITRs) and/or (b) the payload is a transgene encoding a human polypeptide or a variant thereof.

1. A capsid polypeptide comprising:
   - (a) a threonine at a position corresponding to Q579 of the VP1 capsid polypeptide of SEQ ID NO:1;
   - (b) a valine at a position corresponding to Q592 of the VP1 capsid polypeptide of SEQ ID NO:1;
   - (c) an alanine at a position corresponding to T593 of the VP1 capsid polypeptide of SEQ ID NO:1;
   - (d) an alanine at a position corresponding to W595 of the VP1 capsid polypeptide of SEQ ID NO:1;
   - (e) a leucine at a position corresponding to V596 of the VP1 capsid polypeptide of SEQ ID NO:1;
   - (f) a serine at a position corresponding to N598 of the VP1 capsid polypeptide of SEQ ID NO:1; and
   - (g) an alanine at a position corresponding to I601 of the VP1 capsid polypeptide of SEQ ID NO:1.

2. In a capsid polypeptide, the improvement comprising:

(a) a threonine at a position corresponding to Q579 of the VP1 capsid polypeptide of SEQ ID NO:1;

(b) a valine at a position corresponding to Q592 of the VP1 capsid polypeptide of SEQ ID NO:1;

(c) an alanine at a position corresponding to T593 of the VP1 capsid polypeptide of SEQ ID NO:1;

(d) an alanine at a position corresponding to W595 of the VP1 capsid polypeptide of SEQ ID NO:1;

(e) a leucine at a position corresponding to V596 of the VP1 capsid polypeptide of SEQ ID NO:1;

(f) a serine at a position corresponding to N598 of the VP1 capsid polypeptide of SEQ ID NO:1; and

(g) an alanine at a position corresponding to I601 of the VP1 capsid polypeptide of SEQ ID NO:1.

3. A capsid polypeptide comprising the peptide TVATNHQSAQAQAVAGALQSQGA (SEQ ID NO:37) or a peptide whose amino acid sequence has one to five amino acid substitutions as compared to the amino acid sequence of SEQ ID NO:37, provided that the amino acids at positions 1, 14, 15, 17, 18, 20, and 23 of the peptide are threonine, valine, alanine, alanine, leucine, serine, and alanine, respectively.

4. In a capsid polypeptide, the improvement comprising including within the capsid polypeptide the peptide TVATNHQSAQAQAVAGALQSQGA (SEQ ID NO:37) or a peptide whose amino acid sequence has one to five amino acid substitutions as compared to the amino acid sequence of SEQ ID NO:37, provided that the amino acids at positions 1, 14, 15, 17, 18, 20, and 23 of the peptide are threonine, valine, alanine, alanine, leucine, serine, and alanine, respectively.

5. The capsid polypeptide of embodiment 3 or embodiment 4, wherein the peptide has up to four amino acid substitutions as compared to the amino acid sequence of SEQ ID NO:37.

6. The capsid polypeptide of embodiment 3 or embodiment 4, wherein the peptide has up to three amino acid substitutions as compared to the amino acid sequence of SEQ ID NO:37.

7. The capsid polypeptide of embodiment 3 or embodiment 4, wherein the peptide has up to two amino acid substitutions as compared to the amino acid sequence of SEQ ID NO:37.

8. The capsid polypeptide of embodiment 3 or embodiment 4, wherein the peptide has up to one amino acid substitution as compared to the amino acid sequence of SEQ ID NO:37.

9. The capsid polypeptide of embodiment 3 or embodiment 4, wherein the peptide has the amino acid sequence of SEQ ID NO:37.

10. The capsid polypeptide of any one of embodiments 3 to 9, wherein the peptide is in a surface loop of the capsid polypeptide.

11. The capsid polypeptide of embodiment 10, wherein the surface loop comprises a VR-VIII variable region.

12. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 70% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

13. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 75% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

14. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 80% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

15. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 85% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

16. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 90% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

17. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 91% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

18. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 92% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

19. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 93% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

20. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 94% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

21. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 95% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

22. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 96% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

23. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 97% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

24. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 98% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

25. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 99% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

26. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 70% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

27. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 75% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

28. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 80% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

29. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 85% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

30. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 90% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

31. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 91% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

32. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 92% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

33. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 93% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

34. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 94% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

35. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 95% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

36. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 96% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

37. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 97% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

38. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 98% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

39. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 99% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:3 or the VP2 or VP3 portion thereof.

40. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 70% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

41. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 75% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

42. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 80% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

43. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 85% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

44. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 90% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

45. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 91% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

46. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 92% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

47. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 93% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

48. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 94% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

49. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 95% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

50. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 96% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

51. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 97% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

52. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 98% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

53. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 99% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:5 or the VP2 or VP3 portion thereof.

54. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 70% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

55. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 75% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

56. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 80% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

57. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 85% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

58. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 90% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

59. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 91% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

60. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 92% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

61. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 93% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

62. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 94% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

63. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 95% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

64. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 96% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

65. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 97% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

66. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 98% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

67. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 99% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:7 or the VP2 or VP3 portion thereof.

68. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 70% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

69. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 75% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

70. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 80% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

71. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 85% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

72. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 90% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

73. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 91% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

74. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 92% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

75. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 93% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

76. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 94% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

77. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 95% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

78. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 96% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

79. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 97% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

80. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 98% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

81. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 99% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:9 or the VP2 or VP3 portion thereof.

82. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 70% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

83. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 75% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

84. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 80% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

85. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 85% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

86. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 90% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

87. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 91% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

88. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 92% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

89. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 93% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

90. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 94% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

91. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 95% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

92. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 96% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

93. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 97% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

94. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 98% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

95. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 99% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:11 or the VP2 or VP3 portion thereof.

96. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 70% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

97. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 75% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

98. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 80% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

99. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 85% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

100. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 90% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

101. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 91% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

102. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 92% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

103. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 93% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

104. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 94% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

105. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 95% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

106. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 96% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

107. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 97% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

108. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 98% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

109. The capsid polypeptide of any one of embodiments 1 to 11, which comprises an amino acid sequence having at least 99% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

110. A capsid polypeptide, which is optionally a capsid polypeptide according to any one of embodiments 1 to 109, which comprises the amino acid sequence of a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

111. A capsid polypeptide which:

(a) comprises the mutations in the mutation set present in the amino acid sequence of SEQ ID NO:12 as compared to the amino acid sequence of SEQ ID NO:1; and

(b) comprises an amino acid sequence with an edit distance of 15 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

112. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 14 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

113. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 13 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

114. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 12 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

115. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 11 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

116. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 10 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

117. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 9 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

118. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 8 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

119. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 7 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

120. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 6 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

121. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 5 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

122. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 4 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

123. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 3 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

124. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 2 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

125. The capsid polypeptide of embodiment 111, comprising an amino acid sequence with an edit distance of 1 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

126. The capsid polypeptide of any one of embodiments 1 to 125, whose sequence has an edit distance of (a) 12 or lower, (b) 11 or lower, or (c) 10 or lower to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

127. The capsid polypeptide of any one of embodiments 1 to 126, whose sequence has an edit distance of (a) 12 or lower, (b) 11 or lower, or (c) 10 or lower to:

(a) a VP1 capsid polypeptide of SEQ ID NO:12;

(b) a VP2 capsid polypeptide corresponding to the VP2 portion of SEQ ID NO:12; or

(c) a VP3 capsid polypeptide corresponding to the VP3 portion of SEQ ID NO:12.

128. The capsid polypeptide of any one of embodiments 1 to 127, which is a VP1 capsid polypeptide.

129. The capsid polypeptide of any one of embodiments 1 to 127, which is a VP2 capsid polypeptide.

130. The capsid polypeptide of any one of embodiments 1 to 127, which is a VP3 capsid polypeptide.

131. A nucleic acid molecule encoding a capsid polypeptide of any one of embodiments 1 to 130.

132. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 70% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

133. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 80% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

134. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 80% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

135. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 85% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

136. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 90% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

137. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 91% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

138. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 92% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

139. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 93% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

140. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 94% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

141. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 95% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

142. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 96% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

143. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 97% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

144. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 98% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

145. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 99% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

146. The nucleic acid molecule of embodiment 131, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

147. The nucleic acid molecule of any one of embodiments 131 to 146, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:13.

148. The nucleic acid molecule of any one of embodiments 131 to 146, wherein the nucleic acid molecule comprises a fragment of the nucleotide sequence of SEQ ID NO:13 that encodes a VP2 capsid polypeptide.

149. The nucleic acid molecule of any one of embodiments 131 to 146, wherein the nucleic acid molecule comprises a fragment of the nucleotide sequence of SEQ ID NO:13 that encodes a VP3 capsid polypeptide.

150. The nucleic acid molecule of any one of embodiments 131 to 149, wherein the nucleic acid molecule is double-stranded or single-stranded, and wherein the nucleic acid molecule is linear or circular, *e.g.*, wherein the nucleic acid molecule is a plasmid.

151. A virus particle (*e.g.*, adeno-associated virus ("AAV") particle) comprising a capsid polypeptide of any one of embodiments 1 to 130 or comprising a capsid polypeptide encoded by the nucleic acid molecule of any one of embodiments 131 to 150.

152. In a virus particle (*e.g.*, adeno-associated virus ("AAV") particle) comprising a capsid polypeptide, the improvement comprising including in the capsid polypeptide:

(a) a threonine at a position corresponding to Q579 of the VP1 capsid polypeptide of SEQ ID NO:1;

(b) a valine at a position corresponding to Q592 of the VP1 capsid polypeptide of SEQ ID NO:1;

(c) an alanine at a position corresponding to T593 of the VP1 capsid polypeptide of SEQ ID NO:1;

(d) an alanine at a position corresponding to W595 of the VP1 capsid polypeptide of SEQ ID NO:1;

(e) a leucine at a position corresponding to V596 of the VP1 capsid polypeptide of SEQ ID NO:1;

(f) a serine at a position corresponding to N598 of the VP1 capsid polypeptide of SEQ ID NO:1; and

(g) an alanine at a position corresponding to I601 of the VP1 capsid polypeptide of SEQ ID NO:1.

153. In a virus particle (*e.g.*, adeno-associated virus ("AAV") particle) comprising a capsid polypeptide and an encapsulated nucleic acid, the improvement comprising including in the capsid polypeptide:

(a) a threonine at a position corresponding to Q579 of the VP1 capsid polypeptide of SEQ ID NO:1;

(b) a valine at a position corresponding to Q592 of the VP1 capsid polypeptide of SEQ ID NO:1;

(c) an alanine at a position corresponding to T593 of the VP1 capsid polypeptide of SEQ ID NO:1;

(d) an alanine at a position corresponding to W595 of the VP1 capsid polypeptide of SEQ ID NO:1;

(e) a leucine at a position corresponding to V596 of the VP1 capsid polypeptide of SEQ ID NO:1;

(f) a serine at a position corresponding to N598 of the VP1 capsid polypeptide of SEQ ID NO:1; and

(g) an alanine at a position corresponding to I601 of the VP1 capsid polypeptide of SEQ ID NO:1.

154. The virus particle of embodiment 153, wherein the encapsulated nucleic acid comprises a payload (*e.g.*, a heterologous transgene) and one or more regulatory elements.

155. The virus particle of any one of embodiments 151 or embodiment 152, comprising a nucleic acid comprising a payload (*e.g.*, a heterologous transgene) and one or more regulatory elements.

156. The virus particle of embodiment 154 or embodiment 155, wherein the payload comprises a heterologous nucleic acid sequence as defined in any one of embodiments 194 to 512, 860 to 997, 1044 to 1069, and 1072 to 1289.

157. The virus particle of any one of embodiments 154 to 156, wherein the one or more regulatory elements comprise a promoter.

158. The virus particle of embodiment 157, wherein the promoter is a constitutive promoter.

159. The virus particle of embodiment 157 or embodiment 158, wherein the promoter is a CBh promoter.

160. The virus particle of embodiment 159, wherein the CBh promoter comprises a nucleotide sequence having at least 90%, at least 95%, at least 96%, at least 97%, or at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO:14.

161. The virus particle of embodiment 157, wherein the promoter is a CNS-specific promoter.

162. The virus particle of embodiment 157 or embodiment 161, wherein the promoter is a hSYN promoter.

163. The virus particle of embodiment 162, wherein the hSYN promoter comprises a nucleotide sequence having at least 90%, at least 95%, at least 96%, at least 97%, or at least 98%, at least 99%, or 100% sequence identity to SEQ ID NO:15.

164. The virus particle of embodiment 157, wherein the promoter is a muscle-specific promoter.

165. The virus particle of embodiment 164, wherein the muscle-specific promoter is a skeletal muscle-specific promoter.

166. The virus particle of embodiment 164, wherein the muscle-specific promoter is a cardiac muscle-specific promoter.

167. The virus particle of any one of embodiments 151 to 166, wherein said virus particle exhibits increased CNS biodistribution, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein, relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the increased CNS biodistribution is measured using a method described in Section 8.1.

168. The virus particle of any one of embodiments 151 to 167, wherein said virus particle exhibits increased brain biodistribution, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein, relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the increased brain biodistribution is measured using a method described in Section 8.1.

169. The virus particle of any one of embodiments 151 to 168, wherein said virus particle exhibits increased muscle biodistribution, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein, relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the increased muscle biodistribution is measured using a method described in Section 8.1.

170. The virus particle of any one of embodiments 151 to 169, wherein said virus particle exhibits increased skeletal muscle biodistribution, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein, relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the increased skeletal muscle biodistribution is measured using a method described in Section 8.1.

171. The virus particle of any one of embodiments 151 to 170, wherein said virus particle exhibits increased cardiac muscle biodistribution, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein, relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the increased cardiac muscle biodistribution is measured using a method described in Section 8.1.

172. The virus particle of any one of embodiments 151 to 171, wherein said virus particle exhibits increased CNS transduction, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein, relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the increased CNS transduction is measured using a method described in Section 8.1.

173. The virus particle of any one of embodiments 151 to 172, wherein said virus particle exhibits increased brain transduction, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein,

relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the increased brain transduction is measured using a method described in Section 8.1.

174. The virus particle of any one of embodiments 151 to 173, wherein said virus particle exhibits increased brain transduction, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein, relative to a virus particle comprising capsid polypeptides of SEQ ID NO:38 or encoded by SEQ ID NO:39, optionally wherein the increased brain transduction is measured using a method described in Section 8.1.

175. The virus particle of any one of embodiments 151 to 174, wherein said virus particle exhibits increased muscle transduction, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein, relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the increased muscle transduction is measured using a method described in Section 8.1.

176. The virus particle of any one of embodiments 151 to 175, wherein said virus particle exhibits increased skeletal muscle transduction, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein, relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the increased skeletal muscle transduction is measured using a method described in Section 8.1.

177. The virus particle of any one of embodiments 151 to 176, wherein said virus particle exhibits increased cardiac muscle transduction, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein, relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the increased cardiac muscle transduction is measured using a method described in Section 8.1.

178. The virus particle of any one of embodiments 151 to 177, wherein said virus particle exhibits reduced liver biodistribution, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein, relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the decreased liver biodistribution is measured using a method described in Section 8.1.

179. The virus particle of any one of embodiments 151 to 178, wherein said virus particle exhibits reduced spleen biodistribution, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein, relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the decreased spleen biodistribution is measured using a method described in Section 8.1.

180. The virus particle of any one of embodiments 151 to 179, wherein said virus particle exhibits reduced liver transduction, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein, relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the decreased liver transduction is measured using a method described in Section 8.1.

181. The virus particle of any one of embodiments 151 to 180, wherein said virus particle exhibits reduced spleen transduction, e.g., as measured in a mammal, e.g., in NHP, e.g., as described herein,

relative to wild-type AAV9 (e.g., a virus particle comprising capsid polypeptides of SEQ ID NO:1 or encoded by SEQ ID NO:2), optionally wherein the decreased spleen transduction is measured using a method described in Section 8.1.

182. An adeno-associated virus particle comprising (a) a capsid polypeptide of any one of embodiments 1 to 130 or comprising a capsid polypeptide encoded by the nucleic acid molecule of any one of embodiments 131 to 150 and (b) a nucleic acid comprising a payload (*e.g.*, a heterologous transgene) and one or more regulatory elements.

183. The virus particle of embodiment 182, wherein the virus particle comprises a capsid polypeptide comprising the amino acid sequence of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

184. The virus particle of embodiment 182 or embodiment 183, wherein the payload comprises a heterologous nucleic acid sequence as defined in any one of embodiments 194 to 512, 860 to 997, 1044 to 1069, and 1072 to 1289.

185. The virus particle of any one of embodiments 182 to 184, wherein the one or more regulatory elements comprise a promoter.

186. The virus particle of embodiment 185, wherein the promoter is as defined in any one of embodiments 158 to 166.

187. The virus particle of any one of embodiments 153 to 186, wherein the nucleic acid comprises AAV inverted terminal repeat sequences, optionally wherein the AAV inverted repeat sequences are AAV2 inverted terminal repeat sequences.

188. The virus particle of any one of embodiments 151 to 187 (suitable) for use in gene therapy.

189. In a method of delivering a nucleic acid to a subject via an adeno-associated virus ("AAV") particle comprising a capsid polypeptide and the nucleic acid, the improvement comprising a capsid polypeptide comprising:

(a) a threonine at a position corresponding to Q579 of the VP1 capsid polypeptide of SEQ ID NO:1;

(b) a valine at a position corresponding to Q592 of the VP1 capsid polypeptide of SEQ ID NO:1;

(c) an alanine at a position corresponding to T593 of the VP1 capsid polypeptide of SEQ ID NO:1;

(d) an alanine at a position corresponding to W595 of the VP1 capsid polypeptide of SEQ ID NO:1;

(e) a leucine at a position corresponding to V596 of the VP1 capsid polypeptide of SEQ ID NO:1;

(f) a serine at a position corresponding to N598 of the VP1 capsid polypeptide of SEQ ID NO:1; and

(g) an alanine at a position corresponding to I601 of the VP1 capsid polypeptide of SEQ ID NO:1.

190. A method of treating a disease or condition in a subject, comprising administering to the subject in an amount effective to treat the disease or condition:

(a) a virus particle:

(i) comprising the capsid polypeptide of any one of embodiments 1 to 127 and a heterologous nucleic acid sequence encoding a therapeutic product suitable for treating the disease or condition;

(ii) comprising a capsid polypeptide encoded by the nucleic acid molecule of any one of embodiments 131 to 150 and a heterologous nucleic acid sequence encoding a therapeutic product suitable for treating the disease or condition, or

(iii) of any one of embodiments 151 to 188 comprising a heterologous nucleic acid sequence encoding a therapeutic product suitable for treating the disease or condition; or

(b) a composition, *e.g.*, a pharmaceutical composition, comprising the virus particle of (a) and, optionally, a pharmaceutically acceptable carrier.

191. In a method of treating a disease or condition in a subject with an adeno-associated virus ("AAV") particle comprising a capsid polypeptide and a heterologous nucleic acid sequence encoding a therapeutic product suitable for treating the disease or condition, the improvement comprising a capsid polypeptide comprising

(a) a threonine at a position corresponding to Q579 of the VP1 capsid polypeptide of SEQ ID NO:1;

(b) a valine at a position corresponding to Q592 of the VP1 capsid polypeptide of SEQ ID NO:1;

(c) an alanine at a position corresponding to T593 of the VP1 capsid polypeptide of SEQ ID NO:1;

(d) an alanine at a position corresponding to W595 of the VP1 capsid polypeptide of SEQ ID NO:1;

(e) a leucine at a position corresponding to V596 of the VP1 capsid polypeptide of SEQ ID NO:1;

(f) a serine at a position corresponding to N598 of the VP1 capsid polypeptide of SEQ ID NO:1; and

(g) an alanine at a position corresponding to I601 of the VP1 capsid polypeptide of SEQ ID NO:1.

192. The method of embodiment 190 or embodiment 191, wherein the disease or condition is a disease or condition of the CNS.

193. The method of any one of embodiments 190 to 192, wherein the disease or condition is selected from Achromatopsia (color blindness), Acute Intermittent Porphyria, Adie syndrome (Adie's pupil), Age-Related Macular Degeneration, Agenesis of the Corpus Callosum (ACCPN), Aicardi-Goutieres syndrome, Alexander disease, Alpers syndrome, Alternating hemiplegia, Alzheimer's disease, Amyotrophic lateral sclerosis (ALS) (Lou Gehrig's disease), Amyotrophy, hereditary neuralgic, Angleman syndrome, Aromatic L-amino acid decarboxylase deficiency (AADCD), Ataxia, Ataxia Telangiectasia (Louis-Bar syndrome), Attention deficit hyperactivity disorder (ADHD), Becker muscular dystrophy, Benign essential blepharospasm, Bradbury-Eggleston syndrome (pure autonomic failure), Bulbar palsy

(BVVLS1), Canavan disease (aminoacylase 2 deficiency), Carpal tunnel syndrome, Cavernoma (Cavernous angioma, Cavernous malformations), Cerebellar Hypoplasia (CHEGDD), Cerebellar ataxia (CAMRQ2), Cerebral Arteriopathy with SCI and Leukoencephalopathy (CADASIL), Cerebral gigantism (Sotos syndrome 1), Cerebro-oculo-facio-skeletal syndrome (COFS), Ceroid lipofuscinosis (Batten disease), Charcot-Marie-Tooth disease, Chorea, Choreoacanthocytosis, Choroideremia, Cockayne syndrome B (CSB), Coffin-Lowry syndrome, Craniosynostosis, Creutzfeldt-Jakob disease, Crigler-Najjar Syndrome (hyperbilirubinemia), Cushing Syndrome, Dentatorubral atrophy (DRPLA), Developmental and Epileptic Encephalopathy, Developmental Dyspraxia (speech-language disorder 1 (SPCH1)), Dravet syndrome, Dysautonomia (Day syndrome), Dystonia, Encephalocele, Epilepsy disorder, Essential tremor, Fabry disease, Farber disease (ceramidase deficiency), Fahr disease, Febrile Seizure, Friedreich's ataxia, Frontotemporal dementia, Fucosidosis , Fundus albipunctatus, Gaucher disease (e.g., types I, II or III), Generalized gangliosidose (e.g., GM1, GM2 or GM3), Gerstmann-Straussler-Scheinker disease, Giant axonal neuropathy, Glycogen storage disease II (Pompe disease or Acid Maltase Deficiency), Guillain-Barre syndrome, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Hallervorden-Spatz disease (PKAN or NBIA1), Hemiplegia Alterans, Hereditary Neuropathy, Heredopathia Atactica Polyneuritiformis (Refsum disease), Holoprosencephaly, Huntington's disease, Hydrocephalus disorder, Incontinentia Pigmenti, Infantile Hypotonia, Infantile Neuroaxonal Dystrophy, Infantile Phytanic Acid Storage Disease (PBD1B), Joubert Syndrome, Kennedy Disease, Klippel-Feil Syndrome, Krabbe disease (GALC deficiency), Lambert-Eaton Myasthenic Syndrome, Landau-Kleffner Syndrome, Late infantile neuronal lipofuscinosis (CLN2), Lesch-Nyhan Syndrome, Leber congenital amaurosis (retinal blindness), Leber's hereditary optical neuropathy, Leukodystrophy, Levine-Critchley Syndrome (choreoacanthocytosis), Lewy body dementia, Lipoid Proteinosis (Urbach-Wiethe disease), Lissencephaly, Macrocephaly/ Megalencephaly, Menkes Disease, Metachromatic Leukodystrophy (MLD), Microcephaly, Migraine, familial hemiplegic, Mitochondrial DNA depletion syndrome, Morvan disease, Mucolipidosis, Mucopolysaccharidosis Type I (MPS I) (Hurler syndrome), MPS II (Hunter syndrome), MPS IIIa (Sanfilippo Type A syndrome), MPS IIIB (Sanfilippo Type B syndrome), MPS VI (Maroteaux-Lamy syndrome), MPS IV A (Morquio syndrome type A), MPS IV B (Morquio syndrome type B), MPS VII (Sly syndrome), MPS VIII, MPS IX, Multiple Sclerosis, Multiple system atrophy, Myasthenic syndrome, congenital presynaptic, Myoclonus, Myoclonic epilepsy (FAME2), Narcolepsy, Neuroacanthocytosis (McLeod syndrome), Neurodevelopmental disorder with cerebral atrophy and facial dysmorphism (NEDCAFD), Neurodevelopmental disorder with infantile epileptic spasms, Neurofibromatosis, Neuromyotonia, Neuronal Ceroid Lipofuscinosis, Neuropathy, ataxia and retinitis pigmentosa (NARP), Neuropathy, hereditary sensory and autonomic, type II, Neuropathy, hypomyelinating congenital 1, Niemann-Pick disease, Ohtahara Syndrome (Developmental and epileptic encephalopathy 1), Omithine Transcarbamylase deficiency, Orthostatic intolerance, Parkinson's disease, Paroxysmal Choreoathetosis, Pelizaeus-Merzbacher Disease, Pena-Shokeir Type II Syndrome, Periodic Paralyses, Phelan-McDermid syndrome, Phytanic Acid Storage Disease (peroxisome biogenesis disorder 1B), Pick disease, Porencephaly type 1, Primary Lateral Sclerosis, juvenile, Primary Progressive Aphasia, Progressive external ophtalmoplegia, Progressive bulbar palsy, Progressive supranuclear palsy, Pseudo-Torch syndrome, Refsum Disease, Retinitis Pigmentosa 38 (rod-cone dystrophy), Retinitis Pigmentosa 40, Rett syndrome, Sandhoff disease, Schizencephaly, Seitelberger Disease, Septo-optic dysplasia (De Morsier syndrome), Snijders Blok-Fisher syndrome, Spastic Paraplegias, Spinal Muscular

Atrophy (Kugelberg-Welander Disease), Spinocerebellar ataxia, Sporadic Inclusion Body Myositis, Steele-Richardson-Olszewski syndrome (Parkinson-dementia syndrome), Stiff-Person Syndrome, congenital, Striatonigral degeneration, Sturge-Weber Syndrome, Subcortical Vascular Encephalopathy (Cerebral Arteriopathy), Systemic Lupus Erythematosus, Tardive Dyskinesia, Tay-Sachs disease, Tourette Syndrome, Tremor, hereditary type 1, Troyer Syndrome, Tuberous Sclerosis, Von Hippel-Lindau Disease, Von Recklinghausen Disease, Werdnig-Hoffman Disease, West Syndrome, X-linked, Wilson disease, Wolman's disease (acid lipase disease), X-linked adrenoleukodystrophy, X-linked Retinoschisis, X-Linked Retinitis Pigmentosa, X-Linked Spinal and Bulbar Muscular Atrophy, Absence of the Septum Pellucidum, Acid Maltase Deficiency, Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, Adrenoleukodystrophy, Agnosia, Aicardi Syndrome, AIDS - Neurological Complications, Anencephaly, Aneurysm, Angelman Syndrome, Angiomatosis, Anoxia, Antiphospholipid Syndrome, Aphasia, Apraxia, Arachnoid Cysts, Arachnoiditis, Arnold-Chiari Malformation, Arteriovenous Malformation, Asperger Syndrome, Ataxias and Cerebellar or Spinocerebellar Degeneration, Atrial Fibrillation and Stroke, Autism Spectrum Disorder, Autonomic Dysfunction, Back Pain, Barth Syndrome, Bechet's Disease, Becker's Myotonia, Bell's Palsy, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bernhardt-Roth Syndrome, Binswanger's Disease, Blepharospasm, Bloch-Sulzberger Syndrome, Brachial Plexus Birth Injuries, Brachial Plexus Injuries, Brain and Spinal Tumors (including, but not limited to those that have metastasized to the brain, for example, metastatic breast cancer), Brain Aneurysm, Brain Injury, Brown-Sequard Syndrome, Bulbospinal Muscular Atrophy, but not limited to those that have metastasized to the brain, Causalgia, 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 Hypoxia, Cerebral Palsy, Chiari Malformation, Cholesterol Ester Storage Disease, Chronic Orthostatic Intolerance, Chronic Pain, Chronic progressive external ophtalmoplegia, 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, Cree encephalitis, Cumulative Trauma Disorders, 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 - Semantic, Dementia -Multi-Infarct, Dementia -Subcortical, Dementia With Lewy Bodies, Demyelination diseases, Dentate Cerebellar Ataxia, Dermatomyositis, Devic's Syndrome, Diabetic Neuropathy, Diffuse Sclerosis, Distal hereditary motor neuronopathies, Dysgraphia, Dyslexia, Dysphagia, Dyspraxia, Dyssynergia Cerebellaris Myoclonica, Dyssynergia Cerebellaris Progressiva, Early Infantile Epileptic Encephalopathy, Empty Sella Syndrome, Encephalitis, Encephalitis Lethargica, Encephalomyelitis, Encephalopathy, Encephalopathy (familial infantile), Encephalotrigeminal Angiomatosis, Epileptic Hemiplegia, Episodic ataxia, Erb-Duchenne and Dejerine-Klumpke Palsies, Erb's Palsy, Extrapontine Myelinolysis, Faber's disease, Fainting, Familial Dysautonomia, Familial Hemangioma, Familial Idiopathic Basal Ganglia Calcification, Familial Periodic Paralyses, Familial Spastic Paralysis, Fibromuscular Dysplasia, Fisher Syndrome, Floppy Infant Syndrome, Foot Drop, for example, Fragile X disease, Gerstmann's Syndrome, Giant Cell Arteritis, Giant Cell Inclusion Disease, Globoid Cell Leukodystrophy, Glossopharyngeal Neuralgia, Head Injury, Headache, Hemicrania Continua, Hemifacial Spasm,

Hereditary Spastic Paraplegia, Herpes Zoster, Herpes Zoster Oticus, Hirayama Syndrome, Holmes-Adie syndrome, HTLV-1 Associated Myelopathy, Hughes Syndrome, Hurler syndrome, Hydranencephaly, Hydrocephalus, Hydrocephalus - Normal Pressure, Hydromyelia, Hypercortisolism, Hypersomnia, Hypertonia, Hypotonia, Hypoxia, Immune-Mediated Encephalomyelitis, Inclusion Body Myositis, Infantile Refsum Disease, Infantile Spasms, Inflammatory Myopathies, Iniencephaly, Intestinal Lipodystrophy, Intracranial Cysts, Intracranial Hypertension, Isaacs' Syndrome, Kearns-Sayre Syndrome, Kinsbourne syndrome, Kleine-Levin Syndrome, Klippel-Trenaunay Syndrome (KTS), Klüver-Bucy Syndrome, Korsakoff's Amnesic Syndrome, Kugelberg-Welander Disease, Kuru, Lateral Femoral Cutaneous Nerve Entrapment, Lateral Medullary Syndrome, Learning Disabilities, Leigh's Disease, Lennox-Gastaut Syndrome, Lichtheim's disease, Lipid Storage Diseases, Locked-In Syndrome, Lupus - Neurological Sequelae, Lyme Disease - Neurological Complications, Lysosomal storage disorders, Machado-Joseph Disease, Megalencephaly, Melkersson-Rosenthal Syndrome, Meningitis, Meningitis and Encephalitis, Meralgia Paresthetica, Migraine, Miller Fisher Syndrome, Mitochondrial Myopathy, Moebius Syndrome, Monomelic Amyotrophy, Motor Neuron Diseases, Moyamoya Disease, Mucolipidoses, Mucopolysaccharidoses, Multifocal Motor Neuropathy, Multi-Infarct Dementia, Multiple System Atrophy with Orthostatic Hypotension, Muscular Dystrophy, Myasthenia - Congenital, Myasthenia Gravis, Myelinoclastic Diffuse Sclerosis, Myelitis, Myoclonic Encephalopathy of Infants, Myoclonus epilepsy, Myopathy, Myopathy- Congenital, Myopathy -Thyrotoxic, Myotonia, Myotonia Congenita, Neuralgiform (SUNCT) Headache, Neurodegeneration with Brain Iron Accumulation, Neurodegenerative disease, 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, Neuronal Migration Disorders, Neuropathic pain, Neuropathy, Neuropathy- Hereditary, Neurosarcoidosis, Neurosyphilis, Neurotoxicity, Nevus Cavernosus, Occipital Neuralgia, Olivopontocerebellar Atrophy, Opsoclonus Myoclonus, Orthostatic Hypotension, O'Sullivan-McLeod Syndrome, Overuse Syndrome, Pain -Chronic, Pantothenate Kinase-Associated Neurodegeneration, Paraneoplastic Syndromes, Paresthesia, Paroxysmal Hemicrania, Parry-Romberg, Perineural Cysts, Peripheral Neuropathy, Periventricular Leukomalacia, Peroneal muscular atrophy, Persistent Vegetative State, Pervasive Developmental Disorders, Pinched Nerve, Piriformis Syndrome, Pituitary Tumors, Polymyositis, Pompe Disease, Porencephaly, Postherpetic Neuralgia, Postinfectious Encephalomyelitis, Post-Polio Syndrome, Postural Hypotension, Postural Orthostatic Tachycardia Syndrome, Postural Tachycardia Syndrome, Primary Dentatum Atrophy, Primary Lateral Sclerosis, Prion Diseases, Progressive Hemifacial Atrophy, Progressive Locomotor Ataxia, Progressive Multifocal Leukoencephalopathy, Progressive Muscular Atrophy, Progressive Sclerosing Poliodystrophy, Prosopagnosia, Pseudobulbar palsy, Pseudotoxoplasmosis syndrome, Pseudotumor Cerebri, Psychogenic Movement, Ramsay Hunt Syndrome I, Ramsay Hunt Syndrome II, Rasmussen's Encephalitis, Reflex Sympathetic Dystrophy Syndrome, Repetitive Motion Disorders, Repetitive Stress Injuries, Restless Legs Syndrome, Retrovirus-Associated Myelopathy, Reye's Syndrome, Rheumatic Encephalitis, Riley-Day Syndrome, Sacral Nerve Root Cysts, Saint Vitus Dance, Salivary Gland Disease, Schilder's Disease, Seizure Disorder, Semantic Dementia, Septo-Optic Dysplasia, Shaken Baby Syndrome, Shingles, Short-lasting, Shy-Drager Syndrome, Sjögren's Syndrome, Sleep Apnea, Sleeping Sickness, Sotos Syndrome, Spasticity, Spina Bifida, Spinal Cord Infarction, Spinal Cord Injury, Spinal Cord Tumors, Spinocerebellar Atrophy,

Spinocerebellar Degeneration, Sporadic ataxia, Stiff-Person Syndrome, Stroke, Subacute Sclerosing Panencephalitis, Subcortical Arteriosclerotic Encephalopathy, Swallowing Disorders, Sydenham Chorea, Syncope, Syphilitic Spinal Sclerosis, Syringohydromyelia, Syringomyelia, Tabes Dorsalis, Tarlov Cysts, Temporal Arteritis, Tethered Spinal Cord Syndrome, Thomsen's Myotonia, Thoracic Outlet Syndrome, Thyrotoxic Myopathy, Tic Douloureux, Todd's Paralysis, Transient Ischemic Attack, Transmissible Spongiform Encephalopathies, Transverse Myelitis, Traumatic Brain Injury, Tremor, Trigeminal Neuralgia, Tropical Spastic Paraparesis, Unilateral, Vascular Erectile Tumor, Vasculitis Syndromes of the Central and Peripheral Nervous Systems, Vitamin B12 deficiency, Von Economo's Disease, Wallenberg's Syndrome, Wernicke-Korsakoff Syndrome, West Syndrome, Whiplash, Whipple's Disease, and Williams Syndrome.

194. The method of any one of embodiments 190 to 192, wherein the disease or condition is Achromatopsia (color blindness) and/or wherein the heterologous nucleic acid sequence encodes Cyclic nucleotide-gated cation channel alpha-3 (CNGA3) (e.g., a polypeptide represented by UniProt Accession number Q16281 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

195. The method of any one of embodiments 190 to 192, wherein the disease or condition is Achromatopsia (color blindness) and/or wherein the heterologous nucleic acid sequence encodes Cyclic nucleotide-gated cation channel beta-3 (CNGB3) (e.g., a polypeptide represented by UniProt Accession number Q9NQW8 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

196. The method of any one of embodiments 190 to 192, wherein the disease or condition is Achromatopsia (color blindness) and/or wherein the heterologous nucleic acid sequence encodes Guanine nucleotide-binding protein G(t) subunit alpha-2 (GNAT2) (e.g., a polypeptide represented by UniProt Accession number P19087 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

197. The method of any one of embodiments 190 to 192, wherein the disease or condition is Achromatopsia (color blindness) and/or wherein the heterologous nucleic acid sequence encodes Cone cGMP-specific 3',5'-cyclic phosphodiesterase subunit alpha (PDE6C) (e.g., a polypeptide represented by UniProt Accession number P51160 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

198. The method of any one of embodiments 190 to 192, wherein the disease or condition is Acute Intermittent Porphyria and/or wherein the heterologous nucleic acid sequence encodes Porphobilinogen deaminase (PBGD), HMBS (e.g., a polypeptide represented by UniProt Accession number P08397 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

199. The method of any one of embodiments 190 to 192, wherein the disease or condition is Adie syndrome (Adie's pupil) and/or wherein the heterologous nucleic acid sequence encodes MPZ (e.g., a polypeptide represented by UniProt Accession number P25189 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

200. The method of any one of embodiments 190 to 192, wherein the disease or condition is Age-Related Macular Degeneration and/or wherein the heterologous nucleic acid sequence encodes Vascular endothelial growth factor receptor 1 (FLT1) (e.g., a polypeptide represented by UniProt Accession

number P17948 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

201. The method of any one of embodiments 190 to 192, wherein the disease or condition is Age-Related Macular Degeneration and/or wherein the heterologous nucleic acid sequence encodes Vascular endothelial growth factor A (VEGFA) (e.g., a polypeptide represented by UniProt Accession number P15692 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

202. The method of any one of embodiments 190 to 192, wherein the disease or condition is Agenesis of the Corpus Callosum (ACCPN) and/or wherein the heterologous nucleic acid sequence encodes SLC12A6 (e.g., a polypeptide represented by UniProt Accession number Q9UHW9 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

203. The method of any one of embodiments 190 to 192, wherein the disease or condition is Aicardi-Goutieres syndrome and/or wherein the heterologous nucleic acid sequence encodes TREX1 (e.g., a polypeptide represented by UniProt Accession number Q9NSU2 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

204. The method of any one of embodiments 190 to 192, wherein the disease or condition is Alexander disease and/or wherein the heterologous nucleic acid sequence encodes GFAP (e.g., a polypeptide represented by UniProt Accession number P14136 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

205. The method of any one of embodiments 190 to 192, wherein the disease or condition is Alpers syndrome and/or wherein the heterologous nucleic acid sequence encodes POLG (e.g., a polypeptide represented by UniProt Accession number P54098 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

206. The method of any one of embodiments 190 to 192, wherein the disease or condition is Alternating hemiplegia and/or wherein the heterologous nucleic acid sequence encodes ATP1A2 (e.g., a polypeptide represented by UniProt Accession number P50993 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

207. The method of any one of embodiments 190 to 192, wherein the disease or condition is Alternating hemiplegia and/or wherein the heterologous nucleic acid sequence encodes ATP1A3 (e.g., a polypeptide represented by UniProt Accession number P13637 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

208. The method of any one of embodiments 190 to 192, wherein the disease or condition is Alzheimer's disease and/or wherein the heterologous nucleic acid sequence encodes NGF (e.g., a polypeptide represented by UniProt Accession number P01138 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

209. The method of any one of embodiments 190 to 192, wherein the disease or condition is Alzheimer's disease and/or wherein the heterologous nucleic acid sequence encodes ApoE (e.g., a polypeptide represented by UniProt Accession number P02649 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

210. The method of any one of embodiments 190 to 192, wherein the disease or condition is Alzheimer's disease and/or wherein the heterologous nucleic acid sequence encodes Presenilin (PSEN1) (e.g., a polypeptide represented by UniProt Accession number A0A024R6A3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

211. The method of any one of embodiments 190 to 192, wherein the disease or condition is Alzheimer's disease and/or wherein the heterologous nucleic acid sequence encodes Presenilin-2 (PSEN2) (e.g., a polypeptide represented by UniProt Accession number P49810 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

212. The method of any one of embodiments 190 to 192, wherein the disease or condition is Alzheimer's disease and/or wherein the heterologous nucleic acid sequence encodes Amyloid-beta precursor protein (APP) (e.g., a polypeptide represented by UniProt Accession number P05067 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

213. The method of any one of embodiments 190 to 192, wherein the disease or condition is Alzheimer's disease and/or wherein the heterologous nucleic acid sequence encodes ADAM10 (e.g., a polypeptide represented by UniProt Accession number O14672 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

214. The method of any one of embodiments 190 to 192, wherein the disease or condition is Alzheimer's disease and/or wherein the heterologous nucleic acid sequence encodes MAPT, Tau (e.g., a polypeptide represented by UniProt Accession number P10636 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

215. The method of any one of embodiments 190 to 192, wherein the disease or condition is Amyotrophic lateral sclerosis (ALS) (Lou Gehrig's disease) and/or wherein the heterologous nucleic acid sequence encodes Superoxide dismutase-1 (SOD1) (e.g., a polypeptide represented by UniProt Accession number P00441 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

216. The method of any one of embodiments 190 to 192, wherein the disease or condition is Amyotrophy, hereditary neuralgic and/or wherein the heterologous nucleic acid sequence encodes 45544 (e.g., a polypeptide represented by UniProt Accession number Q9UHD8 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

217. The method of any one of embodiments 190 to 192, wherein the disease or condition is Angleman syndrome and/or wherein the heterologous nucleic acid sequence encodes Ubiquitin-protein ligase E3A (UBE3A) (e.g., a polypeptide represented by UniProt Accession number Q05086 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

218. The method of any one of embodiments 190 to 192, wherein the disease or condition is Aromatic L-amino acid decarboxylase deficiency (AADCD) and/or wherein the heterologous nucleic acid sequence encodes DDC (e.g., a polypeptide represented by UniProt Accession number P20711 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

219. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ataxia and/or wherein the heterologous nucleic acid sequence encodes APTX (e.g., a polypeptide represented

by UniProt Accession number Q7Z2E3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

220. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ataxia and/or wherein the heterologous nucleic acid sequence encodes KCNA1 (e.g., a polypeptide represented by UniProt Accession number Q09470 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

221. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ataxia and/or wherein the heterologous nucleic acid sequence encodes CACNA1A (e.g., a polypeptide represented by UniProt Accession number O00555 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

222. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ataxia Telangiectasia (Louis-Bar syndrome) and/or wherein the heterologous nucleic acid sequence encodes Serine-protein kinase ATM (ATM) (e.g., a polypeptide represented by UniProt Accession number Q13315 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

223. The method of any one of embodiments 190 to 192, wherein the disease or condition is Attention deficit hyperactivity disorder (ADHD) and/or wherein the heterologous nucleic acid sequence encodes DRD4 (e.g., a polypeptide represented by UniProt Accession number P21917 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

224. The method of any one of embodiments 190 to 192, wherein the disease or condition is Attention deficit hyperactivity disorder (ADHD) and/or wherein the heterologous nucleic acid sequence encodes CDH2 (e.g., a polypeptide represented by UniProt Accession number P19022 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

225. The method of any one of embodiments 190 to 192, wherein the disease or condition is Becker muscular dystrophy and/or wherein the heterologous nucleic acid sequence encodes Follistatin (FST) (e.g., a polypeptide represented by UniProt Accession number P19883 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

226. The method of any one of embodiments 190 to 192, wherein the disease or condition is Becker muscular dystrophy and/or wherein the heterologous nucleic acid sequence encodes DMD (e.g., a polypeptide represented by UniProt Accession number P11532 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

227. The method of any one of embodiments 190 to 192, wherein the disease or condition is Benign essential blepharospasm and/or wherein the heterologous nucleic acid sequence encodes DRD5 (e.g., a polypeptide represented by UniProt Accession number P21918 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

228. The method of any one of embodiments 190 to 192, wherein the disease or condition is Bradbury-Eggleston syndrome (pure autonomic failure) and/or wherein the heterologous nucleic acid sequence encodes COQ2 (e.g., a polypeptide represented by UniProt Accession number Q96H96 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

229. The method of any one of embodiments 190 to 192, wherein the disease or condition is Bulbar palsy (BVVLS1) and/or wherein the heterologous nucleic acid sequence encodes SLC52A3 (e.g., a

polypeptide represented by UniProt Accession number Q9NQ40 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

230. The method of any one of embodiments 190 to 192, wherein the disease or condition is Canavan disease (aminoacylase 2 deficiency) and/or wherein the heterologous nucleic acid sequence encodes ASPA (e.g., a polypeptide represented by UniProt Accession number P45381 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

231. The method of any one of embodiments 190 to 192, wherein the disease or condition is Carpal tunnel syndrome and/or wherein the heterologous nucleic acid sequence encodes TTR (e.g., a polypeptide represented by UniProt Accession number P02766 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

232. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cavernoma (Cavernous angioma, Cavernous malformations) and/or wherein the heterologous nucleic acid sequence encodes KRIT1 (e.g., a polypeptide represented by UniProt Accession number O00522 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

233. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebellar Hypoplasia (CHEGDD) and/or wherein the heterologous nucleic acid sequence encodes OXR1 (e.g., a polypeptide represented by UniProt Accession number Q8N573 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

234. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebellar ataxia (CAMRQ2) and/or wherein the heterologous nucleic acid sequence encodes WDR81 (e.g., a polypeptide represented by UniProt Accession number Q562E7 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

235. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebral Arteriopathy with SCI and Leukoencephalopathy (CADASIL) and/or wherein the heterologous nucleic acid sequence encodes NOTCH3 (e.g., a polypeptide represented by UniProt Accession number Q9UM47 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

236. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebral gigantism (Sotos syndrome 1) and/or wherein the heterologous nucleic acid sequence encodes NSD1 (e.g., a polypeptide represented by UniProt Accession number Q96L73 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

237. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebro-oculo-facio-skeletal syndrome (COFS) and/or wherein the heterologous nucleic acid sequence encodes ERCC6 (e.g., a polypeptide represented by UniProt Accession number Q03468 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

238. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceroid lipofuscinosis (Batten disease) and/or wherein the heterologous nucleic acid sequence encodes CLN1 (PPT1) (e.g., a polypeptide represented by UniProt Accession number P50897 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

239. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceroid lipofuscinosis (Batten disease) and/or wherein the heterologous nucleic acid sequence encodes CLN2 (TPP1) (e.g., a polypeptide represented by UniProt Accession number O14773 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

240. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceroid lipofuscinosis (Batten disease) and/or wherein the heterologous nucleic acid sequence encodes CLN3 (battenin) (e.g., a polypeptide represented by UniProt Accession number Q13286 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

241. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceroid lipofuscinosis (Batten disease) and/or wherein the heterologous nucleic acid sequence encodes CLN4 (e.g., a polypeptide represented by UniProt Accession number Q9H3Z4 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

242. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceroid lipofuscinosis (Batten disease) and/or wherein the heterologous nucleic acid sequence encodes CLN5 (e.g., a polypeptide represented by UniProt Accession number O75503 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

243. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceroid lipofuscinosis (Batten disease) and/or wherein the heterologous nucleic acid sequence encodes CLN6 (e.g., a polypeptide represented by UniProt Accession number Q9NWW5 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

244. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceroid lipofuscinosis (Batten disease) and/or wherein the heterologous nucleic acid sequence encodes CLN7 (MFSD8) (e.g., a polypeptide represented by UniProt Accession number Q8NHS3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

245. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceroid lipofuscinosis (Batten disease) and/or wherein the heterologous nucleic acid sequence encodes CLN8 (e.g., a polypeptide represented by UniProt Accession number Q9UBY8 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

246. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceroid lipofuscinosis (Batten disease) and/or wherein the heterologous nucleic acid sequence encodes CLN10 (cathepsin D) (e.g., a polypeptide represented by UniProt Accession number P07339 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

247. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceroid lipofuscinosis (Batten disease) and/or wherein the heterologous nucleic acid sequence encodes CLN11 (progranulin) (e.g., a polypeptide represented by UniProt Accession number P28799 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

248. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceroid lipofuscinosis (Batten disease) and/or wherein the heterologous nucleic acid sequence encodes CLN12 (ATP13A2) (e.g., a polypeptide represented by UniProt Accession number Q9NQ11 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

249. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceroid lipofuscinosis (Batten disease) and/or wherein the heterologous nucleic acid sequence encodes CLN13 (cathepsin F) (e.g., a polypeptide represented by UniProt Accession number Q9UBX1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

250. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceroid lipofuscinosis (Batten disease) and/or wherein the heterologous nucleic acid sequence encodes CLN14 (KCTD7) (e.g., a polypeptide represented by UniProt Accession number Q96MP8 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

251. The method of any one of embodiments 190 to 192, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes PMP22 (e.g., a polypeptide represented by UniProt Accession number Q01453 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

252. The method of any one of embodiments 190 to 192, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes MPZ (e.g., a polypeptide represented by UniProt Accession number P25189 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

253. The method of any one of embodiments 190 to 192, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes DNM2 (e.g., a polypeptide represented by UniProt Accession number P50570 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

254. The method of any one of embodiments 190 to 192, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes MFN2 (e.g., a polypeptide represented by UniProt Accession number O95140 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

255. The method of any one of embodiments 190 to 192, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes KIF1B (e.g., a polypeptide represented by UniProt Accession number O60333 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

256. The method of any one of embodiments 190 to 192, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes SBF2 (e.g., a polypeptide represented by UniProt Accession number Q86WG5 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

257. The method of any one of embodiments 190 to 192, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes PNKP (e.g., a polypeptide represented by UniProt Accession number Q96T60 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

258. The method of any one of embodiments 190 to 192, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes GDAP1 (e.g., a polypeptide represented by UniProt Accession number Q8TB36 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

259. The method of any one of embodiments 190 to 192, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes LMNA (e.g., a polypeptide represented by UniProt Accession number P02545 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

260. The method of any one of embodiments 190 to 192, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes FGD4 (e.g., a polypeptide represented by UniProt Accession number Q96M96 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

261. The method of any one of embodiments 190 to 192, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes MTMR2 (e.g., a polypeptide represented by UniProt Accession number Q13614 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

262. The method of any one of embodiments 190 to 192, wherein the disease or condition is Chorea and/or wherein the heterologous nucleic acid sequence encodes NKX2-1 (e.g., a polypeptide represented by UniProt Accession number P43699 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

263. The method of any one of embodiments 190 to 192, wherein the disease or condition is Choreoacanthocytosis and/or wherein the heterologous nucleic acid sequence encodes VPS13A (e.g., a polypeptide represented by UniProt Accession number Q96RL7 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

264. The method of any one of embodiments 190 to 192, wherein the disease or condition is Choroideremia and/or wherein the heterologous nucleic acid sequence encodes Rab escort protein (Rep1), CHM (e.g., a polypeptide represented by UniProt Accession number P24386 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

265. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cockayne syndrome B (CSB) and/or wherein the heterologous nucleic acid sequence encodes ERCC6 (e.g., a polypeptide represented by UniProt Accession number Q03468 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

266. The method of any one of embodiments 190 to 192, wherein the disease or condition is Coffin-Lowry syndrome and/or wherein the heterologous nucleic acid sequence encodes RPS6KA3 (e.g., a polypeptide represented by UniProt Accession number P51812 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

267. The method of any one of embodiments 190 to 192, wherein the disease or condition is Craniosynostosis and/or wherein the heterologous nucleic acid sequence encodes MSX2 (e.g., a polypeptide represented by UniProt Accession number P35548 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

268. The method of any one of embodiments 190 to 192, wherein the disease or condition is Craniosynostosis and/or wherein the heterologous nucleic acid sequence encodes TWIST1 (e.g., a polypeptide represented by UniProt Accession number Q15672 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

269. The method of any one of embodiments 190 to 192, wherein the disease or condition is Craniosynostosis and/or wherein the heterologous nucleic acid sequence encodes SKI (e.g., a polypeptide represented by UniProt Accession number P12755 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

270. The method of any one of embodiments 190 to 192, wherein the disease or condition is Craniosynostosis and/or wherein the heterologous nucleic acid sequence encodes SMAD6 (e.g., a polypeptide represented by UniProt Accession number O43541 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

271. The method of any one of embodiments 190 to 192, wherein the disease or condition is Creutzfeldt-Jakob disease and/or wherein the heterologous nucleic acid sequence encodes PRNP (e.g., a polypeptide represented by UniProt Accession number P04156 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

272. The method of any one of embodiments 190 to 192, wherein the disease or condition is Creutzfeldt-Jakob disease and/or wherein the heterologous nucleic acid sequence encodes HLA-DQB1 (e.g., a polypeptide represented by UniProt Accession number P01920 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

273. The method of any one of embodiments 190 to 192, wherein the disease or condition is Crigler-Najjar Syndrome (hyperbilirubinemia) and/or wherein the heterologous nucleic acid sequence encodes UDP-glucuronosyltransferase 1A1 (UGT1A1) (e.g., a polypeptide represented by UniProt Accession number P22309 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

274. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cushing Syndrome and/or wherein the heterologous nucleic acid sequence encodes PRKACA (e.g., a polypeptide represented by UniProt Accession number P17612 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

275. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dentatorubral atrophy (DRPLA) and/or wherein the heterologous nucleic acid sequence encodes ATN1 (e.g., a polypeptide represented by UniProt Accession number P54259 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

276. The method of any one of embodiments 190 to 192, wherein the disease or condition is Developmental and Epileptic Encephalopathy and/or wherein the heterologous nucleic acid sequence encodes ARX (e.g., a polypeptide represented by UniProt Accession number Q96QS3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

277. The method of any one of embodiments 190 to 192, wherein the disease or condition is Developmental and Epileptic Encephalopathy and/or wherein the heterologous nucleic acid sequence encodes FGF12 (e.g., a polypeptide represented by UniProt Accession number P61328 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

278. The method of any one of embodiments 190 to 192, wherein the disease or condition is Developmental and Epileptic Encephalopathy and/or wherein the heterologous nucleic acid sequence

encodes PIGP (e.g., a polypeptide represented by UniProt Accession number P57054 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

279. The method of any one of embodiments 190 to 192, wherein the disease or condition is Developmental and Epileptic Encephalopathy and/or wherein the heterologous nucleic acid sequence encodes GABRB3 (e.g., a polypeptide represented by UniProt Accession number P28472 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

280. The method of any one of embodiments 190 to 192, wherein the disease or condition is Developmental and Epileptic Encephalopathy and/or wherein the heterologous nucleic acid sequence encodes NECAP1 (e.g., a polypeptide represented by UniProt Accession number Q8NC96 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

281. The method of any one of embodiments 190 to 192, wherein the disease or condition is Developmental Dyspraxia (speech-language disorder 1 (SPCH1)) and/or wherein the heterologous nucleic acid sequence encodes FOXP2 (e.g., a polypeptide represented by UniProt Accession number O15409 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

282. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dravet syndrome and/or wherein the heterologous nucleic acid sequence encodes Sodium channel protein type 1 subunit alpha (SCN1A) (e.g., a polypeptide represented by UniProt Accession number P35498 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

283. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dravet syndrome and/or wherein the heterologous nucleic acid sequence encodes SCN1B (e.g., a polypeptide represented by UniProt Accession number Q07699 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

284. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dravet syndrome and/or wherein the heterologous nucleic acid sequence encodes SCN2A (e.g., a polypeptide represented by UniProt Accession number Q99250 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

285. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dravet syndrome and/or wherein the heterologous nucleic acid sequence encodes GABA receptor subunit gamma-2 (GABRG2) (e.g., a polypeptide represented by UniProt Accession number P18507 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

286. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dysautonomia (Day syndrome) and/or wherein the heterologous nucleic acid sequence encodes ELP1 (e.g., a polypeptide represented by UniProt Accession number O95163 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

287. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dystonia and/or wherein the heterologous nucleic acid sequence encodes GCH1 (e.g., a polypeptide represented by UniProt Accession number P30793 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

288. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dystonia and/or wherein the heterologous nucleic acid sequence encodes TOR1A (e.g., a polypeptide represented by UniProt Accession number O14656 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

289. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dystonia and/or wherein the heterologous nucleic acid sequence encodes SGCE (e.g., a polypeptide represented by UniProt Accession number O43556 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

290. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dystonia and/or wherein the heterologous nucleic acid sequence encodes TUBB4A (e.g., a polypeptide represented by UniProt Accession number P04350 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

291. The method of any one of embodiments 190 to 192, wherein the disease or condition is Encephalocele and/or wherein the heterologous nucleic acid sequence encodes COL18A1 (e.g., a polypeptide represented by UniProt Accession number P39060 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

292. The method of any one of embodiments 190 to 192, wherein the disease or condition is Epilepsy disorder and/or wherein the heterologous nucleic acid sequence encodes GRIN2A (e.g., a polypeptide represented by UniProt Accession number Q12879 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

293. The method of any one of embodiments 190 to 192, wherein the disease or condition is Epilepsy disorder and/or wherein the heterologous nucleic acid sequence encodes CSTB (e.g., a polypeptide represented by UniProt Accession number P04080 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

294. The method of any one of embodiments 190 to 192, wherein the disease or condition is Epilepsy disorder and/or wherein the heterologous nucleic acid sequence encodes STARD7 (e.g., a polypeptide represented by UniProt Accession number Q9NQZ5 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

295. The method of any one of embodiments 190 to 192, wherein the disease or condition is Epilepsy disorder and/or wherein the heterologous nucleic acid sequence encodes DEPDC5 (e.g., a polypeptide represented by UniProt Accession number O75140 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

296. The method of any one of embodiments 190 to 192, wherein the disease or condition is Epilepsy disorder and/or wherein the heterologous nucleic acid sequence encodes PCDH19 (e.g., a polypeptide represented by UniProt Accession number Q8TAB3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

297. The method of any one of embodiments 190 to 192, wherein the disease or condition is Essential tremor and/or wherein the heterologous nucleic acid sequence encodes DRD3 (e.g., a polypeptide represented by UniProt Accession number P35462 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

298. The method of any one of embodiments 190 to 192, wherein the disease or condition is Essential tremor and/or wherein the heterologous nucleic acid sequence encodes NOTCH2NLC (e.g., a polypeptide represented by UniProt Accession number P0DPK4 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

299. The method of any one of embodiments 190 to 192, wherein the disease or condition is Essential tremor and/or wherein the heterologous nucleic acid sequence encodes FUS (e.g., a polypeptide represented by UniProt Accession number P35637 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

300. The method of any one of embodiments 190 to 192, wherein the disease or condition is Fabry disease and/or wherein the heterologous nucleic acid sequence encodes alpha-galactosidase A (GLA) (e.g., a polypeptide represented by UniProt Accession number P06280 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

301. The method of any one of embodiments 190 to 192, wherein the disease or condition is Farber disease (ceramidase deficiency) and/or wherein the heterologous nucleic acid sequence encodes ASAH1 (e.g., a polypeptide represented by UniProt Accession number Q13510 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

302. The method of any one of embodiments 190 to 192, wherein the disease or condition is Fahr disease and/or wherein the heterologous nucleic acid sequence encodes SLC20A2 (e.g., a polypeptide represented by UniProt Accession number Q08357 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

303. The method of any one of embodiments 190 to 192, wherein the disease or condition is Febrile Seizure and/or wherein the heterologous nucleic acid sequence encodes GABRG2 (e.g., a polypeptide represented by UniProt Accession number P18507 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

304. The method of any one of embodiments 190 to 192, wherein the disease or condition is Febrile Seizure and/or wherein the heterologous nucleic acid sequence encodes ADGRV1 (e.g., a polypeptide represented by UniProt Accession number Q8WXG9 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

305. The method of any one of embodiments 190 to 192, wherein the disease or condition is Febrile Seizure and/or wherein the heterologous nucleic acid sequence encodes CPA6 (e.g., a polypeptide represented by UniProt Accession number P11509 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

306. The method of any one of embodiments 190 to 192, wherein the disease or condition is Febrile Seizure and/or wherein the heterologous nucleic acid sequence encodes SCN1A (e.g., a polypeptide represented by UniProt Accession number P35498 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

307. The method of any one of embodiments 190 to 192, wherein the disease or condition is Friedreich's ataxia and/or wherein the heterologous nucleic acid sequence encodes Frataxin (FXN) (e.g., a polypeptide represented by UniProt Accession number Q16595 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

308. The method of any one of embodiments 190 to 192, wherein the disease or condition is Frontotemporal dementia and/or wherein the heterologous nucleic acid sequence encodes Progranulin (GRN) (e.g., a polypeptide represented by UniProt Accession number P28799 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

309. The method of any one of embodiments 190 to 192, wherein the disease or condition is Frontotemporal dementia and/or wherein the heterologous nucleic acid sequence encodes MAPT (tau) (e.g., a polypeptide represented by UniProt Accession number P10636 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

310. The method of any one of embodiments 190 to 192, wherein the disease or condition is Frontotemporal dementia and/or wherein the heterologous nucleic acid sequence encodes PSEN1 (e.g., a polypeptide represented by UniProt Accession number A0A024R6A3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

311. The method of any one of embodiments 190 to 192, wherein the disease or condition is Fucosidosis and/or wherein the heterologous nucleic acid sequence encodes alpha-L-fucosidase (FUCA1) (e.g., a polypeptide represented by UniProt Accession number P04066 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

312. The method of any one of embodiments 190 to 192, wherein the disease or condition is Fundus albipunctatus and/or wherein the heterologous nucleic acid sequence encodes RLBP1 (e.g., a polypeptide represented by UniProt Accession number P12271 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

313. The method of any one of embodiments 190 to 192, wherein the disease or condition is Gaucher disease (e.g., types I, II or III) and/or wherein the heterologous nucleic acid sequence encodes Glucocerebrosidase (GBA1) (e.g., a polypeptide represented by UniProt Accession number P04062 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

314. The method of any one of embodiments 190 to 192, wherein the disease or condition is Generalized gangliosidose (e.g., GM1, GM2 or GM3) and/or wherein the heterologous nucleic acid sequence encodes GLB1 (e.g., a polypeptide represented by UniProt Accession number P16278 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

315. The method of any one of embodiments 190 to 192, wherein the disease or condition is Gerstmann-Straussler-Scheinker disease and/or wherein the heterologous nucleic acid sequence encodes PRNP (e.g., a polypeptide represented by UniProt Accession number P04156 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

316. The method of any one of embodiments 190 to 192, wherein the disease or condition is Giant axonal neuropathy and/or wherein the heterologous nucleic acid sequence encodes Gigaxonin (GAN) (e.g., a polypeptide represented by UniProt Accession number Q9H2C0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

317. The method of any one of embodiments 190 to 192, wherein the disease or condition is Glycogen storage disease II (Pompe disease or Acid Maltase Deficiency) and/or wherein the heterologous nucleic acid sequence encodes Acid maltase, lysosomal alpha-glucosidase (LYAG, GAA)

(e.g., a polypeptide represented by UniProt Accession number P10253 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

318. The method of any one of embodiments 190 to 192, wherein the disease or condition is Guillain-Barre syndrome and/or wherein the heterologous nucleic acid sequence encodes PMP22 (e.g., a polypeptide represented by UniProt Accession number Q01453 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

319. The method of any one of embodiments 190 to 192, wherein the disease or condition is Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and/or wherein the heterologous nucleic acid sequence encodes PMP22 (e.g., a polypeptide represented by UniProt Accession number Q01453 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

320. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hallervorden-Spatz disease (PKAN or NBIA1) and/or wherein the heterologous nucleic acid sequence encodes PANK2 (e.g., a polypeptide represented by UniProt Accession number Q9BZ23 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

321. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hemiplegia Alterans and/or wherein the heterologous nucleic acid sequence encodes ATP1A2 (e.g., a polypeptide represented by UniProt Accession number P50993 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

322. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hemiplegia Alterans and/or wherein the heterologous nucleic acid sequence encodes ATP1A3 (e.g., a polypeptide represented by UniProt Accession number P13637 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

323. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hereditary Neuropathy and/or wherein the heterologous nucleic acid sequence encodes WNK1 (e.g., a polypeptide represented by UniProt Accession number Q9H4A3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

324. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hereditary Neuropathy and/or wherein the heterologous nucleic acid sequence encodes MFN2 (e.g., a polypeptide represented by UniProt Accession number O95140 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

325. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hereditary Neuropathy and/or wherein the heterologous nucleic acid sequence encodes HK1 (e.g., a polypeptide represented by UniProt Accession number P19367 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

326. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hereditary Neuropathy and/or wherein the heterologous nucleic acid sequence encodes TFG (e.g., a polypeptide represented by UniProt Accession number Q92734 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

327. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hereditary Neuropathy and/or wherein the heterologous nucleic acid sequence encodes SPTLC1 (e.g., a

polypeptide represented by UniProt Accession number O15269 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

328. The method of any one of embodiments 190 to 192, wherein the disease or condition is Heredopathia Atactica Polyneuritiformis (Refsum disease) and/or wherein the heterologous nucleic acid sequence encodes PHYH (e.g., a polypeptide represented by UniProt Accession number O14832 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

329. The method of any one of embodiments 190 to 192, wherein the disease or condition is Holoprosencephaly and/or wherein the heterologous nucleic acid sequence encodes GLI2 (e.g., a polypeptide represented by UniProt Accession number P10070 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

330. The method of any one of embodiments 190 to 192, wherein the disease or condition is Holoprosencephaly and/or wherein the heterologous nucleic acid sequence encodes TGIF1 (e.g., a polypeptide represented by UniProt Accession number Q15583 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

331. The method of any one of embodiments 190 to 192, wherein the disease or condition is Holoprosencephaly and/or wherein the heterologous nucleic acid sequence encodes ZIC2 (e.g., a polypeptide represented by UniProt Accession number O95409 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

332. The method of any one of embodiments 190 to 192, wherein the disease or condition is Holoprosencephaly and/or wherein the heterologous nucleic acid sequence encodes PTCH1 (e.g., a polypeptide represented by UniProt Accession number Q13635 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

333. The method of any one of embodiments 190 to 192, wherein the disease or condition is Holoprosencephaly and/or wherein the heterologous nucleic acid sequence encodes SHH (e.g., a polypeptide represented by UniProt Accession number Q15465 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

334. The method of any one of embodiments 190 to 192, wherein the disease or condition is Huntington's disease and/or wherein the heterologous nucleic acid sequence encodes HTT (e.g., a polypeptide represented by UniProt Accession number P42858 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

335. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hydrocephalus disorder and/or wherein the heterologous nucleic acid sequence encodes CCDC88C (e.g., a polypeptide represented by UniProt Accession number Q9P219 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

336. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hydrocephalus disorder and/or wherein the heterologous nucleic acid sequence encodes WDR81 (e.g., a polypeptide represented by UniProt Accession number Q562E7 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

337. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hydrocephalus disorder and/or wherein the heterologous nucleic acid sequence encodes TRIM71 (e.g., a

polypeptide represented by UniProt Accession number Q2Q1W2 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

338. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hydrocephalus disorder and/or wherein the heterologous nucleic acid sequence encodes MPDZ (e.g., a polypeptide represented by UniProt Accession number O75970 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

339. The method of any one of embodiments 190 to 192, wherein the disease or condition is Incontinentia Pigmenti and/or wherein the heterologous nucleic acid sequence encodes IKBKG (e.g., a polypeptide represented by UniProt Accession number Q9Y6K9 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

340. The method of any one of embodiments 190 to 192, wherein the disease or condition is Infantile Hypotonia and/or wherein the heterologous nucleic acid sequence encodes NALCN (e.g., a polypeptide represented by UniProt Accession number Q8IZF0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

341. The method of any one of embodiments 190 to 192, wherein the disease or condition is Infantile Hypotonia and/or wherein the heterologous nucleic acid sequence encodes TBCK (e.g., a polypeptide represented by UniProt Accession number Q8TEA7 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

342. The method of any one of embodiments 190 to 192, wherein the disease or condition is Infantile Hypotonia and/or wherein the heterologous nucleic acid sequence encodes CCDC174 (e.g., a polypeptide represented by UniProt Accession number Q6PII3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

343. The method of any one of embodiments 190 to 192, wherein the disease or condition is Infantile Hypotonia and/or wherein the heterologous nucleic acid sequence encodes UNC80 (e.g., a polypeptide represented by UniProt Accession number Q8N2C7 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

344. The method of any one of embodiments 190 to 192, wherein the disease or condition is Infantile Neuroaxonal Dystrophy and/or wherein the heterologous nucleic acid sequence encodes PLA2G6 (e.g., a polypeptide represented by UniProt Accession number O60733 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

345. The method of any one of embodiments 190 to 192, wherein the disease or condition is Infantile Phytanic Acid Storage Disease (PBD1B) and/or wherein the heterologous nucleic acid sequence encodes PEX1 (e.g., a polypeptide represented by UniProt Accession number O43933 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

346. The method of any one of embodiments 190 to 192, wherein the disease or condition is Joubert Syndrome and/or wherein the heterologous nucleic acid sequence encodes INPP5E (e.g., a polypeptide represented by UniProt Accession number Q9NRR6 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

347. The method of any one of embodiments 190 to 192, wherein the disease or condition is Kennedy Disease and/or wherein the heterologous nucleic acid sequence encodes Androgen receptor (AR) (e.g.,

a polypeptide represented by UniProt Accession number P10275 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

348. The method of any one of embodiments 190 to 192, wherein the disease or condition is Klippel-Feil Syndrome and/or wherein the heterologous nucleic acid sequence encodes GDF6 (e.g., a polypeptide represented by UniProt Accession number Q6KF10 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

349. The method of any one of embodiments 190 to 192, wherein the disease or condition is Krabbe disease (GALC deficiency) and/or wherein the heterologous nucleic acid sequence encodes GALC (e.g., a polypeptide represented by UniProt Accession number P54803 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

350. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lambert-Eaton Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes CACNA1A (e.g., a polypeptide represented by UniProt Accession number O00555 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

351. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lambert-Eaton Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes CACNB2 (e.g., a polypeptide represented by UniProt Accession number Q13936 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

352. The method of any one of embodiments 190 to 192, wherein the disease or condition is Landau-Kleffner Syndrome and/or wherein the heterologous nucleic acid sequence encodes GRIN2A (e.g., a polypeptide represented by UniProt Accession number Q12879 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

353. The method of any one of embodiments 190 to 192, wherein the disease or condition is Late infantile neuronal lipofuscinosis (CLN2) and/or wherein the heterologous nucleic acid sequence encodes TPP1 (e.g., a polypeptide represented by UniProt Accession number O14773 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

354. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lesch-Nyhan Syndrome and/or wherein the heterologous nucleic acid sequence encodes HPRT1 (e.g., a polypeptide represented by UniProt Accession number P00492 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

355. The method of any one of embodiments 190 to 192, wherein the disease or condition is Leber congenital amaurosis (retinal blindness) and/or wherein the heterologous nucleic acid sequence encodes Retinal guanylyl cyclase 1 (GUCY2D) (e.g., a polypeptide represented by UniProt Accession number Q02846 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

356. The method of any one of embodiments 190 to 192, wherein the disease or condition is Leber congenital amaurosis (retinal blindness) and/or wherein the heterologous nucleic acid sequence encodes Retinoid isomerohydrolase (RPE65) (e.g., a polypeptide represented by UniProt Accession number Q16518 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

357. The method of any one of embodiments 190 to 192, wherein the disease or condition is Leber congenital amaurosis (retinal blindness) and/or wherein the heterologous nucleic acid sequence encodes Centrosomal protein of 290 kDa (CEP290) (e.g., a polypeptide represented by UniProt Accession number O15078 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

358. The method of any one of embodiments 190 to 192, wherein the disease or condition is Leber congenital amaurosis (retinal blindness) and/or wherein the heterologous nucleic acid sequence encodes Protein crumbs homolog 1 (CRB1) (e.g., a polypeptide represented by UniProt Accession number P82279 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

359. The method of any one of embodiments 190 to 192, wherein the disease or condition is Leber's hereditary optical neuropathy and/or wherein the heterologous nucleic acid sequence encodes NADH-ubiquinone oxidoreductase chain 4 (ND4) (e.g., a polypeptide represented by UniProt Accession number P03905 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

360. The method of any one of embodiments 190 to 192, wherein the disease or condition is Leukodystrophy and/or wherein the heterologous nucleic acid sequence encodes ARSA (e.g., a polypeptide represented by UniProt Accession number P15289 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

361. The method of any one of embodiments 190 to 192, wherein the disease or condition is Levine-Critchley Syndrome (choreoacanthocytosis) and/or wherein the heterologous nucleic acid sequence encodes VPS13A (e.g., a polypeptide represented by UniProt Accession number Q96RL7 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

362. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lewy body dementia and/or wherein the heterologous nucleic acid sequence encodes SNCA (e.g., a polypeptide represented by UniProt Accession number P37840 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

363. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lewy body dementia and/or wherein the heterologous nucleic acid sequence encodes SNCB (e.g., a polypeptide represented by UniProt Accession number Q16143 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

364. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lipoid Proteinosis (Urbach-Wiethe disease) and/or wherein the heterologous nucleic acid sequence encodes ECM1 (e.g., a polypeptide represented by UniProt Accession number Q16610 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

365. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lissencephaly and/or wherein the heterologous nucleic acid sequence encodes PAFAH1B1 (e.g., a polypeptide represented by UniProt Accession number Q9PTR5 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

366. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lissencephaly and/or wherein the heterologous nucleic acid sequence encodes NDE1 (e.g., a polypeptide represented by UniProt Accession number Q9NXR1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

367. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lissencephaly and/or wherein the heterologous nucleic acid sequence encodes TUBA1A (e.g., a polypeptide represented by UniProt Accession number Q71U36 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

368. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lissencephaly and/or wherein the heterologous nucleic acid sequence encodes LAMB1 (e.g., a polypeptide represented by UniProt Accession number LAMB1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

369. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lissencephaly and/or wherein the heterologous nucleic acid sequence encodes KATNB1 (e.g., a polypeptide represented by UniProt Accession number Q9BVA0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

370. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lissencephaly and/or wherein the heterologous nucleic acid sequence encodes RELN (e.g., a polypeptide represented by UniProt Accession number P78509 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

371. The method of any one of embodiments 190 to 192, wherein the disease or condition is Macrocephaly/ Megalencephaly and/or wherein the heterologous nucleic acid sequence encodes TBC1D7 (e.g., a polypeptide represented by UniProt Accession number Q9P0N9 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

372. The method of any one of embodiments 190 to 192, wherein the disease or condition is Menkes Disease and/or wherein the heterologous nucleic acid sequence encodes ATP7A (e.g., a polypeptide represented by UniProt Accession number Q04656 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

373. The method of any one of embodiments 190 to 192, wherein the disease or condition is Metachromatic Leukodystrophy (MLD) and/or wherein the heterologous nucleic acid sequence encodes Arylsulfatase A (ARSA) (e.g., a polypeptide represented by UniProt Accession number P15289 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

374. The method of any one of embodiments 190 to 192, wherein the disease or condition is Microcephaly and/or wherein the heterologous nucleic acid sequence encodes KIF11 (e.g., a polypeptide represented by UniProt Accession number P52732 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

375. The method of any one of embodiments 190 to 192, wherein the disease or condition is Microcephaly and/or wherein the heterologous nucleic acid sequence encodes MCPH1 (e.g., a polypeptide represented by UniProt Accession number Q8NEM0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

376. The method of any one of embodiments 190 to 192, wherein the disease or condition is Microcephaly and/or wherein the heterologous nucleic acid sequence encodes SLC25A19 (e.g., a polypeptide represented by UniProt Accession number Q9HC21 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

377. The method of any one of embodiments 190 to 192, wherein the disease or condition is Migraine, familial hemiplegic and/or wherein the heterologous nucleic acid sequence encodes CACNA1A (e.g., a polypeptide represented by UniProt Accession number O00555 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

378. The method of any one of embodiments 190 to 192, wherein the disease or condition is Migraine, familial hemiplegic and/or wherein the heterologous nucleic acid sequence encodes ATP1A2 (e.g., a polypeptide represented by UniProt Accession number P50993 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

379. The method of any one of embodiments 190 to 192, wherein the disease or condition is Migraine, familial hemiplegic and/or wherein the heterologous nucleic acid sequence encodes SCN1A (e.g., a polypeptide represented by UniProt Accession number P35498 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

380. The method of any one of embodiments 190 to 192, wherein the disease or condition is Mitochondrial DNA depletion syndrome and/or wherein the heterologous nucleic acid sequence encodes RRM2B (e.g., a polypeptide represented by UniProt Accession number Q7LG56 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

381. The method of any one of embodiments 190 to 192, wherein the disease or condition is Mitochondrial DNA depletion syndrome and/or wherein the heterologous nucleic acid sequence encodes DGUOK (e.g., a polypeptide represented by UniProt Accession number Q16854 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

382. The method of any one of embodiments 190 to 192, wherein the disease or condition is Mitochondrial DNA depletion syndrome and/or wherein the heterologous nucleic acid sequence encodes POLG (e.g., a polypeptide represented by UniProt Accession number P54098 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

383. The method of any one of embodiments 190 to 192, wherein the disease or condition is Mitochondrial DNA depletion syndrome and/or wherein the heterologous nucleic acid sequence encodes TYMP (e.g., a polypeptide represented by UniProt Accession number P19971 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

384. The method of any one of embodiments 190 to 192, wherein the disease or condition is Mitochondrial DNA depletion syndrome and/or wherein the heterologous nucleic acid sequence encodes TK2 (e.g., a polypeptide represented by UniProt Accession number O00142 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

385. The method of any one of embodiments 190 to 192, wherein the disease or condition is Morvan disease and/or wherein the heterologous nucleic acid sequence encodes WNK1 (e.g., a polypeptide represented by UniProt Accession number Q9H4A3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

386. The method of any one of embodiments 190 to 192, wherein the disease or condition is Mucolipidosis and/or wherein the heterologous nucleic acid sequence encodes GNPTAB (e.g., a polypeptide represented by UniProt Accession number Q3T906 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

387. The method of any one of embodiments 190 to 192, wherein the disease or condition is Mucolipidosis and/or wherein the heterologous nucleic acid sequence encodes MCOLN1 (e.g., a polypeptide represented by UniProt Accession number Q9GZU1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

388. The method of any one of embodiments 190 to 192, wherein the disease or condition is Mucopolysaccharidosis Type I (MPS I) (Hurler syndrome) and/or wherein the heterologous nucleic acid sequence encodes alpha-L-iduronidase (IDUA) (e.g., a polypeptide represented by UniProt Accession number P35475 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

389. The method of any one of embodiments 190 to 192, wherein the disease or condition is MPS II (Hunter syndrome) and/or wherein the heterologous nucleic acid sequence encodes iduronate-2-sulfatase (IDS) (e.g., a polypeptide represented by UniProt Accession number P22304 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

390. The method of any one of embodiments 190 to 192, wherein the disease or condition is MPS IIIa (Sanfilippo Type A syndrome) and/or wherein the heterologous nucleic acid sequence encodes heparan sulfate sulfatase (HSS) or N-sulfoglucosamine sulfohydrolase (SGSH) (e.g., a polypeptide represented by UniProt Accession number P51688 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

391. The method of any one of embodiments 190 to 192, wherein the disease or condition is MPS IIIB (Sanfilippo Type B syndrome) and/or wherein the heterologous nucleic acid sequence encodes N-acetyl-alpha-D-glucosaminidase (NAGLU) (e.g., a polypeptide represented by UniProt Accession number P54802 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

392. The method of any one of embodiments 190 to 192, wherein the disease or condition is MPS VI (Maroteaux-Lamy syndrome) and/or wherein the heterologous nucleic acid sequence encodes arylsulfatase B (ARSB) (e.g., a polypeptide represented by UniProt Accession number P15848 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

393. The method of any one of embodiments 190 to 192, wherein the disease or condition is MPS IV A (Morquio syndrome type A) and/or wherein the heterologous nucleic acid sequence encodes N-acetylgalactosamine-6-sulfatase (GALNS) (e.g., a polypeptide represented by UniProt Accession number P34059 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

394. The method of any one of embodiments 190 to 192, wherein the disease or condition is MPS IV B (Morquio syndrome type B) and/or wherein the heterologous nucleic acid sequence encodes Beta-galactosidase 1 (GLB1) (e.g., a polypeptide represented by UniProt Accession number P16278 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

395. The method of any one of embodiments 190 to 192, wherein the disease or condition is MPS VII (Sly syndrome) and/or wherein the heterologous nucleic acid sequence encodes beta-glucuronidase (e.g., a polypeptide represented by UniProt Accession number P08236 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

396. The method of any one of embodiments 190 to 192, wherein the disease or condition is MPS VIII and/or wherein the heterologous nucleic acid sequence encodes glucosamine-6-sulfate sulfatase (e.g., a polypeptide represented by UniProt Accession number P15586 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

397. The method of any one of embodiments 190 to 192, wherein the disease or condition is MPS IX and/or wherein the heterologous nucleic acid sequence encodes Hyaluronidase-1 (HYAL1) (e.g., a polypeptide represented by UniProt Accession number Q12794 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

398. The method of any one of embodiments 190 to 192, wherein the disease or condition is Multiple Sclerosis and/or wherein the heterologous nucleic acid sequence encodes PDCD1 (e.g., a polypeptide represented by UniProt Accession number Q15116 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

399. The method of any one of embodiments 190 to 192, wherein the disease or condition is Multiple system atrophy and/or wherein the heterologous nucleic acid sequence encodes COQ2 (e.g., a polypeptide represented by UniProt Accession number Q96H96 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

400. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myasthenic syndrome, congenital presynaptic and/or wherein the heterologous nucleic acid sequence encodes CHAT (e.g., a polypeptide represented by UniProt Accession number P28329 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

401. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myoclonus and/or wherein the heterologous nucleic acid sequence encodes NOL3 (e.g., a polypeptide represented by UniProt Accession number O60936 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

402. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myoclonic epilepsy (FAME2) and/or wherein the heterologous nucleic acid sequence encodes STARD7 (e.g., a polypeptide represented by UniProt Accession number Q9NQZ5 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

403. The method of any one of embodiments 190 to 192, wherein the disease or condition is Narcolepsy and/or wherein the heterologous nucleic acid sequence encodes HCRT, OX (e.g., a polypeptide represented by UniProt Accession number O43612 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

404. The method of any one of embodiments 190 to 192, wherein the disease or condition is Narcolepsy and/or wherein the heterologous nucleic acid sequence encodes MOG (e.g., a polypeptide represented by UniProt Accession number Q16653 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

405. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuroacanthocytosis (McLeod syndrome) and/or wherein the heterologous nucleic acid sequence encodes XK (e.g., a polypeptide represented by UniProt Accession number P51811 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

406. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neurodevelopmental disorder with cerebral atrophy and facial dysmorphism (NEDCAFD) and/or wherein the heterologous nucleic acid sequence encodes TTC5 (e.g., a polypeptide represented by UniProt Accession number Q8N0Z6 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

407. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neurodevelopmental disorder with infantile epileptic spasms and/or wherein the heterologous nucleic acid sequence encodes NCDN (e.g., a polypeptide represented by UniProt Accession number Q9UBB6 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

408. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neurofibromatosis and/or wherein the heterologous nucleic acid sequence encodes NF1 (e.g., a polypeptide represented by UniProt Accession number P21359 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

409. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuromyotonia and/or wherein the heterologous nucleic acid sequence encodes HINT1 (e.g., a polypeptide represented by UniProt Accession number P49773 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

410. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuronal Ceroid Lipofuscinosis and/or wherein the heterologous nucleic acid sequence encodes PPT1 (e.g., a polypeptide represented by UniProt Accession number P50897 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

411. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuronal Ceroid Lipofuscinosis and/or wherein the heterologous nucleic acid sequence encodes TPP1 (e.g., a polypeptide represented by UniProt Accession number O14773 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

412. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuronal Ceroid Lipofuscinosis and/or wherein the heterologous nucleic acid sequence encodes CLN5 (e.g., a polypeptide represented by UniProt Accession number O75503 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

413. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuronal Ceroid Lipofuscinosis and/or wherein the heterologous nucleic acid sequence encodes CLN3 (e.g., a polypeptide represented by UniProt Accession number Q13286 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

414. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuronal Ceroid Lipofuscinosis and/or wherein the heterologous nucleic acid sequence encodes CLN6 (e.g., a

polypeptide represented by UniProt Accession number Q9NWW5 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

415. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuronal Ceroid Lipofuscinosis and/or wherein the heterologous nucleic acid sequence encodes CLN8 (e.g., a polypeptide represented by UniProt Accession number Q9UBY8 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

416. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuronal Ceroid Lipofuscinosis and/or wherein the heterologous nucleic acid sequence encodes DNAJC5 (e.g., a polypeptide represented by UniProt Accession number Q9H3Z4 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

417. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuronal Ceroid Lipofuscinosis and/or wherein the heterologous nucleic acid sequence encodes MFSD8 (e.g., a polypeptide represented by UniProt Accession number Q8NHS3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

418. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuronal Ceroid Lipofuscinosis and/or wherein the heterologous nucleic acid sequence encodes CTSD (e.g., a polypeptide represented by UniProt Accession number P07339 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

419. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuropathy, ataxia and retinitis pigmentosa (NARP) and/or wherein the heterologous nucleic acid sequence encodes MTATP6 (e.g., a polypeptide represented by UniProt Accession number P00846 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

420. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuropathy, hereditary sensory and autonomic, type II and/or wherein the heterologous nucleic acid sequence encodes WNK1 (e.g., a polypeptide represented by UniProt Accession number Q9H4A3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

421. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuropathy, hypomyelinating congenital 1 and/or wherein the heterologous nucleic acid sequence encodes EGR2 (e.g., a polypeptide represented by UniProt Accession number P11161 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

422. The method of any one of embodiments 190 to 192, wherein the disease or condition is Niemann-Pick disease and/or wherein the heterologous nucleic acid sequence encodes Sphingomyelin phosphodiesterase 1 (SMPD1) (e.g., a polypeptide represented by UniProt Accession number P17405 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

423. The method of any one of embodiments 190 to 192, wherein the disease or condition is Niemann-Pick disease and/or wherein the heterologous nucleic acid sequence encodes NPC intracellular cholesterol transporter 1 (NPC1) (e.g., a polypeptide represented by UniProt Accession number O15118 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

424. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ohtahara Syndrome (Developmental and epileptic encephalopathy 1) and/or wherein the heterologous

nucleic acid sequence encodes ARX (e.g., a polypeptide represented by UniProt Accession number Q96QS3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

425. The method of any one of embodiments 190 to 192, wherein the disease or condition is Omithine Transcarbamylase deficiency and/or wherein the heterologous nucleic acid sequence encodes OTC (e.g., a polypeptide represented by UniProt Accession number P00480 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

426. The method of any one of embodiments 190 to 192, wherein the disease or condition is Orthostatic intolerance and/or wherein the heterologous nucleic acid sequence encodes SLC6A2 (e.g., a polypeptide represented by UniProt Accession number P23975 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

427. The method of any one of embodiments 190 to 192, wherein the disease or condition is Parkinson's disease and/or wherein the heterologous nucleic acid sequence encodes Glucocerebrosidase (GBA1) (e.g., a polypeptide represented by UniProt Accession number P04062 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

428. The method of any one of embodiments 190 to 192, wherein the disease or condition is Parkinson's disease and/or wherein the heterologous nucleic acid sequence encodes Dopamine decarboxylase (DDC) (e.g., a polypeptide represented by UniProt Accession number P20711 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

429. The method of any one of embodiments 190 to 192, wherein the disease or condition is Parkinson's disease and/or wherein the heterologous nucleic acid sequence encodes Neurturin (e.g., a polypeptide represented by UniProt Accession number Q99748 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

430. The method of any one of embodiments 190 to 192, wherein the disease or condition is Parkinson's disease and/or wherein the heterologous nucleic acid sequence encodes Glial derived growth factor (GDGF) (e.g., a polypeptide represented by UniProt Accession number P39905 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

431. The method of any one of embodiments 190 to 192, wherein the disease or condition is Parkinson's disease and/or wherein the heterologous nucleic acid sequence encodes Tyrosine hydroxylase (TH), tyrosine 3-monooxygenase (e.g., a polypeptide represented by UniProt Accession number P07101 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

432. The method of any one of embodiments 190 to 192, wherein the disease or condition is Parkinson's disease and/or wherein the heterologous nucleic acid sequence encodes Glutamic acid decarboxylase (GAD) (e.g., a polypeptide represented by UniProt Accession number Q99259 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

433. The method of any one of embodiments 190 to 192, wherein the disease or condition is Parkinson's disease and/or wherein the heterologous nucleic acid sequence encodes Fibroblast growth factor 2 (FGF2) (e.g., a polypeptide represented by UniProt Accession number P09038 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

434. The method of any one of embodiments 190 to 192, wherein the disease or condition is Parkinson's disease and/or wherein the heterologous nucleic acid sequence encodes Brain-derived neurotrophic factor (BDNF) (e.g., a polypeptide represented by UniProt Accession number P23560 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

435. The method of any one of embodiments 190 to 192, wherein the disease or condition is Paroxysmal Choreoathetosis and/or wherein the heterologous nucleic acid sequence encodes PNKD (e.g., a polypeptide represented by UniProt Accession number Q8N490 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

436. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pelizaeus-Merzbacher Disease and/or wherein the heterologous nucleic acid sequence encodes PLP1 (e.g., a polypeptide represented by UniProt Accession number P60201 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

437. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pena-Shokeir Type II Syndrome and/or wherein the heterologous nucleic acid sequence encodes ERCC6 (e.g., a polypeptide represented by UniProt Accession number Q03468 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

438. The method of any one of embodiments 190 to 192, wherein the disease or condition is Periodic Paralyses and/or wherein the heterologous nucleic acid sequence encodes SCN4A (e.g., a polypeptide represented by UniProt Accession number P35499 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

439. The method of any one of embodiments 190 to 192, wherein the disease or condition is Phelan-McDermid syndrome and/or wherein the heterologous nucleic acid sequence encodes SH3 and multiple ankyrin repeat domains protein 3 (SHANK3) (e.g., a polypeptide represented by UniProt Accession number Q9BYB0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

440. The method of any one of embodiments 190 to 192, wherein the disease or condition is Phytanic Acid Storage Disease (peroxisome biogenesis disorder 1B) and/or wherein the heterologous nucleic acid sequence encodes PEX1 (e.g., a polypeptide represented by UniProt Accession number O43933 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

441. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pick disease and/or wherein the heterologous nucleic acid sequence encodes PSEN1 (e.g., a polypeptide represented by UniProt Accession number A0A024R6A3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

442. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pick disease and/or wherein the heterologous nucleic acid sequence encodes MAPT (tau) (e.g., a polypeptide represented by UniProt Accession number P10636 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

443. The method of any one of embodiments 190 to 192, wherein the disease or condition is Porencephaly type 1 and/or wherein the heterologous nucleic acid sequence encodes COL4A1 (e.g., a

polypeptide represented by UniProt Accession number P02462 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

444. The method of any one of embodiments 190 to 192, wherein the disease or condition is Primary Lateral Sclerosis, juvenile and/or wherein the heterologous nucleic acid sequence encodes ALS2 (e.g., a polypeptide represented by UniProt Accession number Q96Q42 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

445. The method of any one of embodiments 190 to 192, wherein the disease or condition is Primary Progressive Aphasia and/or wherein the heterologous nucleic acid sequence encodes GRN (e.g., a polypeptide represented by UniProt Accession number P28799 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

446. The method of any one of embodiments 190 to 192, wherein the disease or condition is Progressive external ophtalmoplegia and/or wherein the heterologous nucleic acid sequence encodes POLG (e.g., a polypeptide represented by UniProt Accession number P54098 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

447. The method of any one of embodiments 190 to 192, wherein the disease or condition is Progressive external ophtalmoplegia and/or wherein the heterologous nucleic acid sequence encodes POLG2 (e.g., a polypeptide represented by UniProt Accession number Q9UHN1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

448. The method of any one of embodiments 190 to 192, wherein the disease or condition is Progressive external ophtalmoplegia and/or wherein the heterologous nucleic acid sequence encodes SLC25A4 (e.g., a polypeptide represented by UniProt Accession number P12235 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

449. The method of any one of embodiments 190 to 192, wherein the disease or condition is Progressive external ophtalmoplegia and/or wherein the heterologous nucleic acid sequence encodes TWNK (e.g., a polypeptide represented by UniProt Accession number Q96RR1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

450. The method of any one of embodiments 190 to 192, wherein the disease or condition is Progressive bulbar palsy and/or wherein the heterologous nucleic acid sequence encodes SLC52A3 (e.g., a polypeptide represented by UniProt Accession number Q9NQ40 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

451. The method of any one of embodiments 190 to 192, wherein the disease or condition is Progressive supranuclear palsy and/or wherein the heterologous nucleic acid sequence encodes Microtubule-associated protein tau (MAPT), Tau (e.g., a polypeptide represented by UniProt Accession number P10636 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

452. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pseudo-Torch syndrome and/or wherein the heterologous nucleic acid sequence encodes OCLN (e.g., a polypeptide represented by UniProt Accession number Q16625 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

453. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pseudo-Torch syndrome and/or wherein the heterologous nucleic acid sequence encodes STAT2 (e.g., a polypeptide represented by UniProt Accession number P52630 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

454. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pseudo-Torch syndrome and/or wherein the heterologous nucleic acid sequence encodes USP18 (e.g., a polypeptide represented by UniProt Accession number Q9UMW8 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

455. The method of any one of embodiments 190 to 192, wherein the disease or condition is Refsum Disease and/or wherein the heterologous nucleic acid sequence encodes PHYH (e.g., a polypeptide represented by UniProt Accession number O14832 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

456. The method of any one of embodiments 190 to 192, wherein the disease or condition is Retinitis Pigmentosa 38 (rod-cone dystrophy) and/or wherein the heterologous nucleic acid sequence encodes Tyrosine-protein kinase Mer (MERTK) (e.g., a polypeptide represented by UniProt Accession number Q12866 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

457. The method of any one of embodiments 190 to 192, wherein the disease or condition is Retinitis Pigmentosa 40 and/or wherein the heterologous nucleic acid sequence encodes PDE6B (e.g., a polypeptide represented by UniProt Accession number P35913 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

458. The method of any one of embodiments 190 to 192, wherein the disease or condition is Rett syndrome and/or wherein the heterologous nucleic acid sequence encodes Methyl-CpG-binding protein 2 (MECP2) (e.g., a polypeptide represented by UniProt Accession number P51608 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

459. The method of any one of embodiments 190 to 192, wherein the disease or condition is Sandhoff disease and/or wherein the heterologous nucleic acid sequence encodes Beta-hexosaminidase subunit alpha (HEXA) (e.g., a polypeptide represented by UniProt Accession number P06865 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

460. The method of any one of embodiments 190 to 192, wherein the disease or condition is Sandhoff disease and/or wherein the heterologous nucleic acid sequence encodes Beta-hexosaminidase subunit beta (HEXB) (e.g., a polypeptide represented by UniProt Accession number P07686 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

461. The method of any one of embodiments 190 to 192, wherein the disease or condition is Schizencephaly and/or wherein the heterologous nucleic acid sequence encodes SIX3 (e.g., a polypeptide represented by UniProt Accession number O95343 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

462. The method of any one of embodiments 190 to 192, wherein the disease or condition is Schizencephaly and/or wherein the heterologous nucleic acid sequence encodes EMX2 (e.g., a

polypeptide represented by UniProt Accession number Q04743 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

463. The method of any one of embodiments 190 to 192, wherein the disease or condition is Schizencephaly and/or wherein the heterologous nucleic acid sequence encodes SHH (e.g., a polypeptide represented by UniProt Accession number Q15465 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

464. The method of any one of embodiments 190 to 192, wherein the disease or condition is Seitelberger Disease and/or wherein the heterologous nucleic acid sequence encodes PLA2G6 (e.g., a polypeptide represented by UniProt Accession number O60733 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

465. The method of any one of embodiments 190 to 192, wherein the disease or condition is Septo-optic dysplasia (De Morsier syndrome) and/or wherein the heterologous nucleic acid sequence encodes HESX1 (e.g., a polypeptide represented by UniProt Accession number Q9UBX0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

466. The method of any one of embodiments 190 to 192, wherein the disease or condition is Snijders Blok-Fisher syndrome and/or wherein the heterologous nucleic acid sequence encodes POU3F3 (e.g., a polypeptide represented by UniProt Accession number P20264 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

467. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spastic Paraplegias and/or wherein the heterologous nucleic acid sequence encodes SPG11 (e.g., a polypeptide represented by UniProt Accession number Q96JI7 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

468. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spastic Paraplegias and/or wherein the heterologous nucleic acid sequence encodes SPAST (e.g., a polypeptide represented by UniProt Accession number Q9UBP0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

469. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spastic Paraplegias and/or wherein the heterologous nucleic acid sequence encodes KIF5A (e.g., a polypeptide represented by UniProt Accession number Q12840 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

470. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spastic Paraplegias and/or wherein the heterologous nucleic acid sequence encodes NIPA1 (e.g., a polypeptide represented by UniProt Accession number Q7RTP0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

471. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spastic Paraplegias and/or wherein the heterologous nucleic acid sequence encodes CYP7B1 (e.g., a polypeptide represented by UniProt Accession number O75881 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

472. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spastic Paraplegias and/or wherein the heterologous nucleic acid sequence encodes ATL1 (e.g., a polypeptide

represented by UniProt Accession number Q8WXF7 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

473. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spinal Muscular Atrophy (Kugelberg-Welander Disease) and/or wherein the heterologous nucleic acid sequence encodes Survival motor neuron protein (SMN), SMN1 (e.g., a polypeptide represented by UniProt Accession number Q16637 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

474. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spinocerebellar ataxia and/or wherein the heterologous nucleic acid sequence encodes Ataxin-1 (ATXN1), SCA1 (e.g., a polypeptide represented by UniProt Accession number P54253 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

475. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spinocerebellar ataxia and/or wherein the heterologous nucleic acid sequence encodes Ataxin-2 (ATXN2), SCA2 (e.g., a polypeptide represented by UniProt Accession number Q99700 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

476. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spinocerebellar ataxia and/or wherein the heterologous nucleic acid sequence encodes Ataxin-3 (ATXN3), SCA3 (e.g., a polypeptide represented by UniProt Accession number P54252 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

477. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spinocerebellar ataxia and/or wherein the heterologous nucleic acid sequence encodes ZFHX3 (e.g., a polypeptide represented by UniProt Accession number Q15911 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

478. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spinocerebellar ataxia and/or wherein the heterologous nucleic acid sequence encodes CACNA1A (e.g., a polypeptide represented by UniProt Accession number O00555 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

479. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spinocerebellar ataxia and/or wherein the heterologous nucleic acid sequence encodes ATXN7, SCA7 (e.g., a polypeptide represented by UniProt Accession number O15265 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

480. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spinocerebellar ataxia and/or wherein the heterologous nucleic acid sequence encodes TMEM240 (e.g., a polypeptide represented by UniProt Accession number Q5SV17 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

481. The method of any one of embodiments 190 to 192, wherein the disease or condition is Sporadic Inclusion Body Myositis and/or wherein the heterologous nucleic acid sequence encodes Follistatin (FST) (e.g., a polypeptide represented by UniProt Accession number P19883 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

482. The method of any one of embodiments 190 to 192, wherein the disease or condition is Steele-Richardson-Olszewski syndrome (Parkinson-dementia syndrome) and/or wherein the heterologous nucleic acid sequence encodes MAPT(Tau) (e.g., a polypeptide represented by UniProt Accession number P10636 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

483. The method of any one of embodiments 190 to 192, wherein the disease or condition is Stiff-Person Syndrome, congenital and/or wherein the heterologous nucleic acid sequence encodes GLRA1 (e.g., a polypeptide represented by UniProt Accession number P23415 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

484. The method of any one of embodiments 190 to 192, wherein the disease or condition is Stiff-Person Syndrome, congenital and/or wherein the heterologous nucleic acid sequence encodes GLRB (e.g., a polypeptide represented by UniProt Accession number P48167 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

485. The method of any one of embodiments 190 to 192, wherein the disease or condition is Striatonigral degeneration and/or wherein the heterologous nucleic acid sequence encodes NUP62 (e.g., a polypeptide represented by UniProt Accession number P37198 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

486. The method of any one of embodiments 190 to 192, wherein the disease or condition is Striatonigral degeneration and/or wherein the heterologous nucleic acid sequence encodes PDE8B (e.g., a polypeptide represented by UniProt Accession number O95263 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

487. The method of any one of embodiments 190 to 192, wherein the disease or condition is Striatonigral degeneration and/or wherein the heterologous nucleic acid sequence encodes MTATP6 (e.g., a polypeptide represented by UniProt Accession number P00846 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

488. The method of any one of embodiments 190 to 192, wherein the disease or condition is Striatonigral degeneration and/or wherein the heterologous nucleic acid sequence encodes VAC14 (e.g., a polypeptide represented by UniProt Accession number Q08AM6 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

489. The method of any one of embodiments 190 to 192, wherein the disease or condition is Sturge-Weber Syndrome and/or wherein the heterologous nucleic acid sequence encodes GNAQ (e.g., a polypeptide represented by UniProt Accession number P50148 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

490. The method of any one of embodiments 190 to 192, wherein the disease or condition is Subcortical Vascular Encephalopathy (Cerebral Arteriopathy) and/or wherein the heterologous nucleic acid sequence encodes HTRA1 (e.g., a polypeptide represented by UniProt Accession number Q92743 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

491. The method of any one of embodiments 190 to 192, wherein the disease or condition is Systemic Lupus Erythematosus and/or wherein the heterologous nucleic acid sequence encodes DNASE1L3 (e.g.,

a polypeptide represented by UniProt Accession number Q13609 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

492. The method of any one of embodiments 190 to 192, wherein the disease or condition is Systemic Lupus Erythematosus and/or wherein the heterologous nucleic acid sequence encodes TLR7 (e.g., a polypeptide represented by UniProt Accession number Q9NYK1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

493. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tardive Dyskinesia and/or wherein the heterologous nucleic acid sequence encodes CYP2D6 (e.g., a polypeptide represented by UniProt Accession number P10635 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

494. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tay-Sachs disease and/or wherein the heterologous nucleic acid sequence encodes Beta-hexosaminidase subunit alpha (HEXA) (e.g., a polypeptide represented by UniProt Accession number P06865 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

495. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tourette Syndrome and/or wherein the heterologous nucleic acid sequence encodes HDC (e.g., a polypeptide represented by UniProt Accession number P19113 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

496. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tourette Syndrome and/or wherein the heterologous nucleic acid sequence encodes SLITRK1 (e.g., a polypeptide represented by UniProt Accession number Q96PX8 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

497. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tremor, hereditary type 1 and/or wherein the heterologous nucleic acid sequence encodes DRD3 (e.g., a polypeptide represented by UniProt Accession number P35462 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

498. The method of any one of embodiments 190 to 192, wherein the disease or condition is Troyer Syndrome and/or wherein the heterologous nucleic acid sequence encodes SPART (e.g., a polypeptide represented by UniProt Accession number Q8N0X7 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

499. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tuberous Sclerosis and/or wherein the heterologous nucleic acid sequence encodes TSC1 (e.g., a polypeptide represented by UniProt Accession number Q92574 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

500. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tuberous Sclerosis and/or wherein the heterologous nucleic acid sequence encodes TSC2 (e.g., a polypeptide represented by UniProt Accession number P49815 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

501. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tuberous Sclerosis and/or wherein the heterologous nucleic acid sequence encodes IFNG (e.g., a

polypeptide represented by UniProt Accession number P01579 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

502. The method of any one of embodiments 190 to 192, wherein the disease or condition is Von Hippel-Lindau Disease and/or wherein the heterologous nucleic acid sequence encodes VHL (e.g., a polypeptide represented by UniProt Accession number P40337 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

503. The method of any one of embodiments 190 to 192, wherein the disease or condition is Von Hippel-Lindau Disease and/or wherein the heterologous nucleic acid sequence encodes CCND1 (e.g., a polypeptide represented by UniProt Accession number P24385 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

504. The method of any one of embodiments 190 to 192, wherein the disease or condition is Von Recklinghausen Disease and/or wherein the heterologous nucleic acid sequence encodes NF1 (e.g., a polypeptide represented by UniProt Accession number P21359 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

505. The method of any one of embodiments 190 to 192, wherein the disease or condition is Werdnig-Hoffman Disease and/or wherein the heterologous nucleic acid sequence encodes SMN1 (e.g., a polypeptide represented by UniProt Accession number Q16637 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

506. The method of any one of embodiments 190 to 192, wherein the disease or condition is West Syndrome, X-linked and/or wherein the heterologous nucleic acid sequence encodes ARX (e.g., a polypeptide represented by UniProt Accession number Q96QS3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

507. The method of any one of embodiments 190 to 192, wherein the disease or condition is Wilson disease and/or wherein the heterologous nucleic acid sequence encodes ATP7B (e.g., a polypeptide represented by UniProt Accession number P35670 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

508. The method of any one of embodiments 190 to 192, wherein the disease or condition is Wolman's disease (acid lipase disease) and/or wherein the heterologous nucleic acid sequence encodes LIPA (e.g., a polypeptide represented by UniProt Accession number P38571 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

509. The method of any one of embodiments 190 to 192, wherein the disease or condition is X-linked adrenoleukodystrophy and/or wherein the heterologous nucleic acid sequence encodes ATP-binding cassette sub-family D member 1 (ABCD1) (e.g., a polypeptide represented by UniProt Accession number P33897 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

510. The method of any one of embodiments 190 to 192, wherein the disease or condition is X-linked Retinoschisis and/or wherein the heterologous nucleic acid sequence encodes Retinoschisin (RS1) (e.g., a polypeptide represented by UniProt Accession number O15537 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

511. The method of any one of embodiments 190 to 192, wherein the disease or condition is X-Linked Retinitis Pigmentosa and/or wherein the heterologous nucleic acid sequence encodes X-linked retinitis pigmentosa GTPase regulator (RPGR) (e.g., a polypeptide represented by UniProt Accession number Q92834 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

512. The method of any one of embodiments 190 to 192, wherein the disease or condition is X-Linked Spinal and Bulbar Muscular Atrophy and/or wherein the heterologous nucleic acid sequence encodes UBA1 (e.g., a polypeptide represented by UniProt Accession number P22314 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

513. The method of any one of embodiments 190 to 192, wherein the disease or condition is Absence of the Septum Pellucidum.

514. The method of any one of embodiments 190 to 192, wherein the disease or condition is Acid Maltase Deficiency.

515. The method of any one of embodiments 190 to 192, wherein the disease or condition is Acquired Epileptiform Aphasia.

516. The method of any one of embodiments 190 to 192, wherein the disease or condition is Acute Disseminated Encephalomyelitis.

517. The method of any one of embodiments 190 to 192, wherein the disease or condition is Adrenoleukodystrophy.

518. The method of any one of embodiments 190 to 192, wherein the disease or condition is Agnosia.

519. The method of any one of embodiments 190 to 192, wherein the disease or condition is Aicardi Syndrome.

520. The method of any one of embodiments 190 to 192, wherein the disease or condition is AIDS - Neurological Complications.

521. The method of any one of embodiments 190 to 192, wherein the disease or condition is Anencephaly.

522. The method of any one of embodiments 190 to 192, wherein the disease or condition is Aneurysm.

523. The method of any one of embodiments 190 to 192, wherein the disease or condition is Angelman Syndrome.

524. The method of any one of embodiments 190 to 192, wherein the disease or condition is Angiomatosis.

525. The method of any one of embodiments 190 to 192, wherein the disease or condition is Anoxia.

526. The method of any one of embodiments 190 to 192, wherein the disease or condition is Antiphospholipid Syndrome.

527. The method of any one of embodiments 190 to 192, wherein the disease or condition is Aphasia.

528. The method of any one of embodiments 190 to 192, wherein the disease or condition is Apraxia.

529. The method of any one of embodiments 190 to 192, wherein the disease or condition is Arachnoid Cysts.

530. The method of any one of embodiments 190 to 192, wherein the disease or condition is Arachnoiditis.

531. The method of any one of embodiments 190 to 192, wherein the disease or condition is Arnold-Chiari Malformation.

532. The method of any one of embodiments 190 to 192, wherein the disease or condition is Arteriovenous Malformation.

533. The method of any one of embodiments 190 to 192, wherein the disease or condition is Asperger Syndrome.

534. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ataxias and Cerebellar or Spinocerebellar Degeneration.

535. The method of any one of embodiments 190 to 192, wherein the disease or condition is Atrial Fibrillation and Stroke.

536. The method of any one of embodiments 190 to 192, wherein the disease or condition is Autism Spectrum Disorder.

537. The method of any one of embodiments 190 to 192, wherein the disease or condition is Autonomic Dysfunction.

538. The method of any one of embodiments 190 to 192, wherein the disease or condition is Back Pain.

539. The method of any one of embodiments 190 to 192, wherein the disease or condition is Barth Syndrome.

540. The method of any one of embodiments 190 to 192, wherein the disease or condition is Bechet's Disease.

541. The method of any one of embodiments 190 to 192, wherein the disease or condition is Becker's Myotonia.

542. The method of any one of embodiments 190 to 192, wherein the disease or condition is Bell's Palsy.

543. The method of any one of embodiments 190 to 192, wherein the disease or condition is Benign Focal Amyotrophy.

544. The method of any one of embodiments 190 to 192, wherein the disease or condition is Benign Intracranial Hypertension.

545. The method of any one of embodiments 190 to 192, wherein the disease or condition is Bernhardt-Roth Syndrome.

546. The method of any one of embodiments 190 to 192, wherein the disease or condition is Binswanger's Disease.

547. The method of any one of embodiments 190 to 192, wherein the disease or condition is Blepharospasm.

548. The method of any one of embodiments 190 to 192, wherein the disease or condition is Bloch-Sulzberger Syndrome.

549. The method of any one of embodiments 190 to 192, wherein the disease or condition is Brachial Plexus Birth Injuries.

550. The method of any one of embodiments 190 to 192, wherein the disease or condition is Brachial Plexus Injuries.

551. The method of any one of embodiments 190 to 192, wherein the disease or condition is Brain and Spinal Tumors (including, but not limited to those that have metastasized to the brain, for example, metastatic breast cancer).

552. The method of any one of embodiments 190 to 192, wherein the disease or condition is Brain Aneurysm.

553. The method of any one of embodiments 190 to 192, wherein the disease or condition is Brain Injury.

554. The method of any one of embodiments 190 to 192, wherein the disease or condition is Brown-Sequard Syndrome.

555. The method of any one of embodiments 190 to 192, wherein the disease or condition is Bulbospinal Muscular Atrophy.

556. The method of any one of embodiments 190 to 192, wherein the disease or condition is but not limited to those that have metastasized to the brain.

557. The method of any one of embodiments 190 to 192, wherein the disease or condition is Causalgia.

558. The method of any one of embodiments 190 to 192, wherein the disease or condition is Central Cervical Cord Syndrome.

559. The method of any one of embodiments 190 to 192, wherein the disease or condition is Central Cord Syndrome.

560. The method of any one of embodiments 190 to 192, wherein the disease or condition is Central Pain Syndrome.

561. The method of any one of embodiments 190 to 192, wherein the disease or condition is Central Pontine Myelinolysis.

562. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cephalic Disorders.

563. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ceramidase Deficiency.

564. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebellar Degeneration.

565. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebellar Hypoplasia.

566. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebral Aneurysms.

567. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebral Arteriosclerosis.

568. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebral Atrophy.

569. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebral Beriberi.

570. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebral Cavernous Malformation.

571. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebral Hypoxia.

572. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cerebral Palsy.

573. The method of any one of embodiments 190 to 192, wherein the disease or condition is Chiari Malformation.

574. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cholesterol Ester Storage Disease.

575. The method of any one of embodiments 190 to 192, wherein the disease or condition is Chronic Orthostatic Intolerance.

576. The method of any one of embodiments 190 to 192, wherein the disease or condition is Chronic Pain.

577. The method of any one of embodiments 190 to 192, wherein the disease or condition is Chronic progressive external ophtalmoplegia.

578. The method of any one of embodiments 190 to 192, wherein the disease or condition is Colpocephaly.

579. The method of any one of embodiments 190 to 192, wherein the disease or condition is Coma.

580. The method of any one of embodiments 190 to 192, wherein the disease or condition is Complex Regional Pain Syndrome.

581. The method of any one of embodiments 190 to 192, wherein the disease or condition is Concentric sclerosis (Baló's sclerosis).

582. The method of any one of embodiments 190 to 192, wherein the disease or condition is Congenital Facial Diplegia.

583. The method of any one of embodiments 190 to 192, wherein the disease or condition is Congenital Myasthenia.

584. The method of any one of embodiments 190 to 192, wherein the disease or condition is Congenital Myopathy.

585. The method of any one of embodiments 190 to 192, wherein the disease or condition is Congenital Vascular Cavernous Malformations.

586. The method of any one of embodiments 190 to 192, wherein the disease or condition is Corticobasal Degeneration.

587. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cranial Arteritis.

588. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cree encephalitis.

589. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cumulative Trauma Disorders.

590. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cytomegalic Inclusion Body Disease.

591. The method of any one of embodiments 190 to 192, wherein the disease or condition is Cytomegalovirus Infection.

592. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dancing Eyes-Dancing Feet Syndrome.

593. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dandy-Walker Syndrome.

594. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dawson Disease.

595. The method of any one of embodiments 190 to 192, wherein the disease or condition is De Morsier's Syndrome.

596. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dejerine-Klumpke Palsy.

597. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dementia.

598. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dementia - Semantic.

599. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dementia -Multi-Infarct.

600. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dementia -Subcortical.

601. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dementia With Lewy Bodies.

602. The method of any one of embodiments 190 to 192, wherein the disease or condition is Demyelination diseases.

603. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dentate Cerebellar Ataxia.

604. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dermatomyositis.

605. The method of any one of embodiments 190 to 192, wherein the disease or condition is Devic's Syndrome.

606. The method of any one of embodiments 190 to 192, wherein the disease or condition is Diabetic Neuropathy.

607. The method of any one of embodiments 190 to 192, wherein the disease or condition is Diffuse Sclerosis.

608. The method of any one of embodiments 190 to 192, wherein the disease or condition is Distal hereditary motor neuronopathies.

609. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dysgraphia.

610. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dyslexia.

611. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dysphagia.

612. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dyspraxia.

613. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dyssynergia Cerebellaris Myoclonica.

614. The method of any one of embodiments 190 to 192, wherein the disease or condition is Dyssynergia Cerebellaris Progressiva.

615. The method of any one of embodiments 190 to 192, wherein the disease or condition is Early Infantile Epileptic Encephalopathy.

616. The method of any one of embodiments 190 to 192, wherein the disease or condition is Empty Sella Syndrome.

617. The method of any one of embodiments 190 to 192, wherein the disease or condition is Encephalitis.

618. The method of any one of embodiments 190 to 192, wherein the disease or condition is Encephalitis Lethargica.

619. The method of any one of embodiments 190 to 192, wherein the disease or condition is Encephalomyelitis.

620. The method of any one of embodiments 190 to 192, wherein the disease or condition is Encephalopathy.

621. The method of any one of embodiments 190 to 192, wherein the disease or condition is Encephalopathy (familial infantile).

622. The method of any one of embodiments 190 to 192, wherein the disease or condition is Encephalotrigeminal Angiomatosis.

623. The method of any one of embodiments 190 to 192, wherein the disease or condition is Epileptic Hemiplegia.

624. The method of any one of embodiments 190 to 192, wherein the disease or condition is Episodic ataxia.

625. The method of any one of embodiments 190 to 192, wherein the disease or condition is Erb-Duchenne and Dejerine-Klumpke Palsies.

626. The method of any one of embodiments 190 to 192, wherein the disease or condition is Erb's Palsy.

627. The method of any one of embodiments 190 to 192, wherein the disease or condition is Extrapontine Myelinolysis.

628. The method of any one of embodiments 190 to 192, wherein the disease or condition is Faber's disease.

629. The method of any one of embodiments 190 to 192, wherein the disease or condition is Fainting.

630. The method of any one of embodiments 190 to 192, wherein the disease or condition is Familial Dysautonomia.

631. The method of any one of embodiments 190 to 192, wherein the disease or condition is Familial Hemangioma.

632. The method of any one of embodiments 190 to 192, wherein the disease or condition is Familial Idiopathic Basal Ganglia Calcification.

633. The method of any one of embodiments 190 to 192, wherein the disease or condition is Familial Periodic Paralyses.

634. The method of any one of embodiments 190 to 192, wherein the disease or condition is Familial Spastic Paralysis.

635. The method of any one of embodiments 190 to 192, wherein the disease or condition is Fibromuscular Dysplasia.

636. The method of any one of embodiments 190 to 192, wherein the disease or condition is Fisher Syndrome.

637. The method of any one of embodiments 190 to 192, wherein the disease or condition is Floppy Infant Syndrome.

638. The method of any one of embodiments 190 to 192, wherein the disease or condition is Foot Drop.

639. The method of any one of embodiments 190 to 192, wherein the disease or condition is for example.

640. The method of any one of embodiments 190 to 192, wherein the disease or condition is Fragile X disease.

641. The method of any one of embodiments 190 to 192, wherein the disease or condition is Gerstmann's Syndrome.

642. The method of any one of embodiments 190 to 192, wherein the disease or condition is Giant Cell Arteritis.

643. The method of any one of embodiments 190 to 192, wherein the disease or condition is Giant Cell Inclusion Disease.

644. The method of any one of embodiments 190 to 192, wherein the disease or condition is Globoid Cell Leukodystrophy.

645. The method of any one of embodiments 190 to 192, wherein the disease or condition is Glossopharyngeal Neuralgia.

646. The method of any one of embodiments 190 to 192, wherein the disease or condition is Head Injury.

647. The method of any one of embodiments 190 to 192, wherein the disease or condition is Headache.

648. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hemicrania Continua.

649. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hemifacial Spasm.

650. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hereditary Spastic Paraplegia.

651. The method of any one of embodiments 190 to 192, wherein the disease or condition is Herpes Zoster.

652. The method of any one of embodiments 190 to 192, wherein the disease or condition is Herpes Zoster Oticus.

653. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hirayama Syndrome.

654. The method of any one of embodiments 190 to 192, wherein the disease or condition is Holmes-Adie syndrome.

655. The method of any one of embodiments 190 to 192, wherein the disease or condition is HTLV-1 Associated Myelopathy.

656. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hughes Syndrome.

657. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hurler syndrome.

658. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hydranencephaly.

659. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hydrocephalus.

660. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hydrocephalus - Normal Pressure.

661. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hydromyelia.

662. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hypercortisolism.

663. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hypersomnia.

664. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hypertonia.

665. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hypotonia.

666. The method of any one of embodiments 190 to 192, wherein the disease or condition is Hypoxia.

667. The method of any one of embodiments 190 to 192, wherein the disease or condition is Immune-Mediated Encephalomyelitis.

668. The method of any one of embodiments 190 to 192, wherein the disease or condition is Inclusion Body Myositis.

669. The method of any one of embodiments 190 to 192, wherein the disease or condition is Infantile Refsum Disease.

670. The method of any one of embodiments 190 to 192, wherein the disease or condition is Infantile Spasms.

671. The method of any one of embodiments 190 to 192, wherein the disease or condition is Inflammatory Myopathies.

672. The method of any one of embodiments 190 to 192, wherein the disease or condition is Iniencephaly.

673. The method of any one of embodiments 190 to 192, wherein the disease or condition is Intestinal Lipodystrophy.

674. The method of any one of embodiments 190 to 192, wherein the disease or condition is Intracranial Cysts.

675. The method of any one of embodiments 190 to 192, wherein the disease or condition is Intracranial Hypertension.

676. The method of any one of embodiments 190 to 192, wherein the disease or condition is Isaacs' Syndrome.

677. The method of any one of embodiments 190 to 192, wherein the disease or condition is Kearns-Sayre Syndrome.

678. The method of any one of embodiments 190 to 192, wherein the disease or condition is Kinsbourne syndrome.

679. The method of any one of embodiments 190 to 192, wherein the disease or condition is Kleine-Levin Syndrome.

680. The method of any one of embodiments 190 to 192, wherein the disease or condition is Klippel-Trenaunay Syndrome (KTS).

681. The method of any one of embodiments 190 to 192, wherein the disease or condition is Klüver-Bucy Syndrome.

682. The method of any one of embodiments 190 to 192, wherein the disease or condition is Korsakoff's Amnesic Syndrome.

683. The method of any one of embodiments 190 to 192, wherein the disease or condition is Kugelberg-Welander Disease.

684. The method of any one of embodiments 190 to 192, wherein the disease or condition is Kuru.

685. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lateral Femoral Cutaneous Nerve Entrapment.

686. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lateral Medullary Syndrome.

687. The method of any one of embodiments 190 to 192, wherein the disease or condition is Learning Disabilities.

688. The method of any one of embodiments 190 to 192, wherein the disease or condition is Leigh's Disease.

689. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lennox-Gastaut Syndrome.

690. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lichtheim's disease.

691. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lipid Storage Diseases.

692. The method of any one of embodiments 190 to 192, wherein the disease or condition is Locked-In Syndrome.

693. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lupus - Neurological Sequelae.

694. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lyme Disease - Neurological Complications.

695. The method of any one of embodiments 190 to 192, wherein the disease or condition is Lysosomal storage disorders.

696. The method of any one of embodiments 190 to 192, wherein the disease or condition is Machado-Joseph Disease.

697. The method of any one of embodiments 190 to 192, wherein the disease or condition is Megalencephaly.

698. The method of any one of embodiments 190 to 192, wherein the disease or condition is Melkersson-Rosenthal Syndrome.

699. The method of any one of embodiments 190 to 192, wherein the disease or condition is Meningitis.

700. The method of any one of embodiments 190 to 192, wherein the disease or condition is Meningitis and Encephalitis.

701. The method of any one of embodiments 190 to 192, wherein the disease or condition is Meralgia Paresthetica.

702. The method of any one of embodiments 190 to 192, wherein the disease or condition is Migraine.

703. The method of any one of embodiments 190 to 192, wherein the disease or condition is Miller Fisher Syndrome.

704. The method of any one of embodiments 190 to 192, wherein the disease or condition is Mitochondrial Myopathy.

705. The method of any one of embodiments 190 to 192, wherein the disease or condition is Moebius Syndrome.

706. The method of any one of embodiments 190 to 192, wherein the disease or condition is Monomelic Amyotrophy.

707. The method of any one of embodiments 190 to 192, wherein the disease or condition is Motor Neuron Diseases.

708. The method of any one of embodiments 190 to 192, wherein the disease or condition is Moyamoya Disease.

709. The method of any one of embodiments 190 to 192, wherein the disease or condition is Mucolipidoses.

710. The method of any one of embodiments 190 to 192, wherein the disease or condition is Mucopolysaccharidoses.

711. The method of any one of embodiments 190 to 192, wherein the disease or condition is Multifocal Motor Neuropathy.

712. The method of any one of embodiments 190 to 192, wherein the disease or condition is Multi-Infarct Dementia.

713. The method of any one of embodiments 190 to 192, wherein the disease or condition is Multiple System Atrophy with Orthostatic Hypotension.

714. The method of any one of embodiments 190 to 192, wherein the disease or condition is Muscular Dystrophy.

715. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myasthenia - Congenital.

716. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myasthenia Gravis.

717. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myelinoclastic Diffuse Sclerosis.

718. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myelitis.

719. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myoclonic Encephalopathy of Infants.

720. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myoclonus epilepsy.

721. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myopathy.

722. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myopathy- Congenital.

723. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myopathy -Thyrotoxic.

724. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myotonia.

725. The method of any one of embodiments 190 to 192, wherein the disease or condition is Myotonia Congenita.

726. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuralgiform (SUNCT) Headache.

727. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neurodegeneration with Brain Iron Accumulation.

728. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neurodegenerative disease.

729. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuroleptic Malignant Syndrome.

730. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neurological Complications of AIDS.

731. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neurological Complications of Lyme Disease.

732. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neurological Consequences of Cytomegalovirus Infection.

733. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neurological Manifestations of Pompe Disease.

734. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neurological Sequelae Of Lupus.

735. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuromyelitis Optica.

736. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuronal Migration Disorders.

737. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuropathic pain.

738. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuropathy.

739. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neuropathy- Hereditary.

740. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neurosarcoidosis.

741. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neurosyphilis.

742. The method of any one of embodiments 190 to 192, wherein the disease or condition is Neurotoxicity.

743. The method of any one of embodiments 190 to 192, wherein the disease or condition is Nevus Cavernosus.

744. The method of any one of embodiments 190 to 192, wherein the disease or condition is Occipital Neuralgia.

745. The method of any one of embodiments 190 to 192, wherein the disease or condition is Olivopontocerebellar Atrophy.

746. The method of any one of embodiments 190 to 192, wherein the disease or condition is Opsoclonus Myoclonus.

747. The method of any one of embodiments 190 to 192, wherein the disease or condition is Orthostatic Hypotension.

748. The method of any one of embodiments 190 to 192, wherein the disease or condition is O'Sullivan-McLeod Syndrome.

749. The method of any one of embodiments 190 to 192, wherein the disease or condition is Overuse Syndrome.

750. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pain - Chronic.

751. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pantothenate Kinase-Associated Neurodegeneration.

752. The method of any one of embodiments 190 to 192, wherein the disease or condition is Paraneoplastic Syndromes.

753. The method of any one of embodiments 190 to 192, wherein the disease or condition is Paresthesia.

754. The method of any one of embodiments 190 to 192, wherein the disease or condition is Paroxysmal Hemicrania.

755. The method of any one of embodiments 190 to 192, wherein the disease or condition is Parry-Romberg.

756. The method of any one of embodiments 190 to 192, wherein the disease or condition is Perineural Cysts.

757. The method of any one of embodiments 190 to 192, wherein the disease or condition is Peripheral Neuropathy.

758. The method of any one of embodiments 190 to 192, wherein the disease or condition is Periventricular Leukomalacia.

759. The method of any one of embodiments 190 to 192, wherein the disease or condition is Peroneal muscular atrophy.

760. The method of any one of embodiments 190 to 192, wherein the disease or condition is Persistent Vegetative State.

761. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pervasive Developmental Disorders.

762. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pinched Nerve.

763. The method of any one of embodiments 190 to 192, wherein the disease or condition is Piriformis Syndrome.

764. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pituitary Tumors.

765. The method of any one of embodiments 190 to 192, wherein the disease or condition is Polymyositis.

766. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pompe Disease.

767. The method of any one of embodiments 190 to 192, wherein the disease or condition is Porencephaly.

768. The method of any one of embodiments 190 to 192, wherein the disease or condition is Postherpetic Neuralgia.

769. The method of any one of embodiments 190 to 192, wherein the disease or condition is Postinfectious Encephalomyelitis.

770. The method of any one of embodiments 190 to 192, wherein the disease or condition is Post-Polio Syndrome.

771. The method of any one of embodiments 190 to 192, wherein the disease or condition is Postural Hypotension.

772. The method of any one of embodiments 190 to 192, wherein the disease or condition is Postural Orthostatic Tachycardia Syndrome.

773. The method of any one of embodiments 190 to 192, wherein the disease or condition is Postural Tachycardia Syndrome.

774. The method of any one of embodiments 190 to 192, wherein the disease or condition is Primary Dentatum Atrophy.

775. The method of any one of embodiments 190 to 192, wherein the disease or condition is Primary Lateral Sclerosis.

776. The method of any one of embodiments 190 to 192, wherein the disease or condition is Prion Diseases.

777. The method of any one of embodiments 190 to 192, wherein the disease or condition is Progressive Hemifacial Atrophy.

778. The method of any one of embodiments 190 to 192, wherein the disease or condition is Progressive Locomotor Ataxia.

779. The method of any one of embodiments 190 to 192, wherein the disease or condition is Progressive Multifocal Leukoencephalopathy.

780. The method of any one of embodiments 190 to 192, wherein the disease or condition is Progressive Muscular Atrophy.

781. The method of any one of embodiments 190 to 192, wherein the disease or condition is Progressive Sclerosing Poliodystrophy.

782. The method of any one of embodiments 190 to 192, wherein the disease or condition is Prosopagnosia.

783. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pseudobulbar palsy.

784. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pseudotoxoplasmosis syndrome.

785. The method of any one of embodiments 190 to 192, wherein the disease or condition is Pseudotumor Cerebri.

786. The method of any one of embodiments 190 to 192, wherein the disease or condition is Psychogenic Movement.

787. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ramsay Hunt Syndrome I.

788. The method of any one of embodiments 190 to 192, wherein the disease or condition is Ramsay Hunt Syndrome II.

789. The method of any one of embodiments 190 to 192, wherein the disease or condition is Rasmussen's Encephalitis.

790. The method of any one of embodiments 190 to 192, wherein the disease or condition is Reflex Sympathetic Dystrophy Syndrome.

791. The method of any one of embodiments 190 to 192, wherein the disease or condition is Repetitive Motion Disorders.

792. The method of any one of embodiments 190 to 192, wherein the disease or condition is Repetitive Stress Injuries.

793. The method of any one of embodiments 190 to 192, wherein the disease or condition is Restless Legs Syndrome.

794. The method of any one of embodiments 190 to 192, wherein the disease or condition is Retrovirus-Associated Myelopathy.

795. The method of any one of embodiments 190 to 192, wherein the disease or condition is Reye's Syndrome.

796. The method of any one of embodiments 190 to 192, wherein the disease or condition is Rheumatic Encephalitis.

797. The method of any one of embodiments 190 to 192, wherein the disease or condition is Riley-Day Syndrome.

798. The method of any one of embodiments 190 to 192, wherein the disease or condition is Sacral Nerve Root Cysts.

799. The method of any one of embodiments 190 to 192, wherein the disease or condition is Saint Vitus Dance.

800. The method of any one of embodiments 190 to 192, wherein the disease or condition is Salivary Gland Disease.

801. The method of any one of embodiments 190 to 192, wherein the disease or condition is Schilder's Disease.

802. The method of any one of embodiments 190 to 192, wherein the disease or condition is Seizure Disorder.

803. The method of any one of embodiments 190 to 192, wherein the disease or condition is Semantic Dementia.

804. The method of any one of embodiments 190 to 192, wherein the disease or condition is Septo-Optic Dysplasia.

805. The method of any one of embodiments 190 to 192, wherein the disease or condition is Shaken Baby Syndrome.

806. The method of any one of embodiments 190 to 192, wherein the disease or condition is Shingles.

807. The method of any one of embodiments 190 to 192, wherein the disease or condition is Short-lasting.

808. The method of any one of embodiments 190 to 192, wherein the disease or condition is Shy-Drager Syndrome.

809. The method of any one of embodiments 190 to 192, wherein the disease or condition is Sjögren's Syndrome.

810. The method of any one of embodiments 190 to 192, wherein the disease or condition is Sleep Apnea.

811. The method of any one of embodiments 190 to 192, wherein the disease or condition is Sleeping Sickness.

812. The method of any one of embodiments 190 to 192, wherein the disease or condition is Sotos Syndrome.

813. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spasticity.

814. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spina Bifida.

815. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spinal Cord Infarction.

816. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spinal Cord Injury.

817. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spinal Cord Tumors.

818. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spinocerebellar Atrophy.

819. The method of any one of embodiments 190 to 192, wherein the disease or condition is Spinocerebellar Degeneration.

820. The method of any one of embodiments 190 to 192, wherein the disease or condition is Sporadic ataxia.

821. The method of any one of embodiments 190 to 192, wherein the disease or condition is Stiff-Person Syndrome.

822. The method of any one of embodiments 190 to 192, wherein the disease or condition is Stroke.

823. The method of any one of embodiments 190 to 192, wherein the disease or condition is Subacute Sclerosing Panencephalitis.

824. The method of any one of embodiments 190 to 192, wherein the disease or condition is Subcortical Arteriosclerotic Encephalopathy.

825. The method of any one of embodiments 190 to 192, wherein the disease or condition is Swallowing Disorders.

826. The method of any one of embodiments 190 to 192, wherein the disease or condition is Sydenham Chorea.

827. The method of any one of embodiments 190 to 192, wherein the disease or condition is Syncope.

828. The method of any one of embodiments 190 to 192, wherein the disease or condition is Syphilitic Spinal Sclerosis.

829. The method of any one of embodiments 190 to 192, wherein the disease or condition is Syringohydromyelia.

830. The method of any one of embodiments 190 to 192, wherein the disease or condition is Syringomyelia.

831. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tabes Dorsalis.

832. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tarlov Cysts.

833. The method of any one of embodiments 190 to 192, wherein the disease or condition is Temporal Arteritis.

834. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tethered Spinal Cord Syndrome.

835. The method of any one of embodiments 190 to 192, wherein the disease or condition is Thomsen's Myotonia.

836. The method of any one of embodiments 190 to 192, wherein the disease or condition is Thoracic Outlet Syndrome.

837. The method of any one of embodiments 190 to 192, wherein the disease or condition is Thyrotoxic Myopathy.

838. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tic Douloureux.

839. The method of any one of embodiments 190 to 192, wherein the disease or condition is Todd's Paralysis.

840. The method of any one of embodiments 190 to 192, wherein the disease or condition is Transient Ischemic Attack.

841. The method of any one of embodiments 190 to 192, wherein the disease or condition is Transmissible Spongiform Encephalopathies.

842. The method of any one of embodiments 190 to 192, wherein the disease or condition is Transverse Myelitis.

843. The method of any one of embodiments 190 to 192, wherein the disease or condition is Traumatic Brain Injury.

844. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tremor.

845. The method of any one of embodiments 190 to 192, wherein the disease or condition is Trigeminal Neuralgia.

846. The method of any one of embodiments 190 to 192, wherein the disease or condition is Tropical Spastic Paraparesis.

847. The method of any one of embodiments 190 to 192, wherein the disease or condition is Unilateral.

848. The method of any one of embodiments 190 to 192, wherein the disease or condition is Vascular Erectile Tumor.

849. The method of any one of embodiments 190 to 192, wherein the disease or condition is Vasculitis Syndromes of the Central and Peripheral Nervous Systems.

850. The method of any one of embodiments 190 to 192, wherein the disease or condition is Vitamin B12 deficiency.

851. The method of any one of embodiments 190 to 192, wherein the disease or condition is Von Economo's Disease.

852. The method of any one of embodiments 190 to 192, wherein the disease or condition is Wallenberg's Syndrome.

853. The method of any one of embodiments 190 to 192, wherein the disease or condition is Wernicke-Korsakoff Syndrome.

854. The method of any one of embodiments 190 to 192, wherein the disease or condition is West Syndrome.

855. The method of any one of embodiments 190 to 192, wherein the disease or condition is Whiplash.

856. The method of any one of embodiments 190 to 192, wherein the disease or condition is Whipple's Disease.

857. The method of any one of embodiments 190 to 192, wherein the disease or condition is Williams Syndrome.

858. The method of embodiment 190 or embodiment 191, wherein the disease or condition is a disease or condition of skeletal muscle.

859. The method of any one of embodiments 190, 191, and 858, wherein the disease or condition is Advanced heart failure, Amyotrophic lateral sclerosis (ALS) (Lou Gehrig's disease), Andersen-Tawil Syndrome, Barth syndrome, Becker Muscular Dystrophy (BMD), Becker Myotonia Congenita, Bethlem Myopathy, Bulbospinal Muscular Atrophy, Carnitine Deficiency, systemic primary, Carnitine Palmityl Transferase Deficiency, type 1 , Carnitine Palmityl Transferase Deficiency, type 2, Catecholaminergic polymorphic ventricular tachycardia 2 (CPVT2), Central Core Disease (congenital myopathy, type 1A),

Centronuclear Myopathy type 1, Centronuclear Myopathy type 2, Charcot-Marie-Tooth disease, Congenital Muscular Dystrophy (Ullrich disease), Congenital Myasthenic Syndrome, Congenital Myopathy, Congenital Myotonic Dystrophy, Cori Disease (Debrancher Enzyme Deficiency or Forbes Disease), Danon disease, Dejerine-Sottas Disease, Distal Muscular Dystrophy, Miyoshi, Distal Muscular Dystrophy, Welander, Distal myopathy with anterior tibial onset, Duchenne Muscular Dystrophy, Dysferlinopathy, Emery-Dreifuss Muscular Dystrophy, Eulenberg Disease (Paramyotonia Congenita), Facioscapulohumeral Muscular Dystrophy, Friedreich's ataxia, Fukuyama Congenital Muscular Dystrophy, Glycogen storage disease II (Pompe disease or Acid Maltase Deficiency), Glycogenosis Type 10 (Glycogen storage disease X), Glycogenosis Type 11 (Glycogen storage disease XI), Glycogenosis Type 2 (Glycogen storage disease II or Pompe Disease or Acid maltase deficiency), Glycogenosis Type 3 (Glycogen storage disease III), Glycogenosis Type 5 (Glycogen storage disease V or McArdle Disease or Myophosphorylase Deficiency), Glycogenosis Type 7 (Glycogen storage disease VII or Phosphofructokinase Deficiency or Tarui Disease), Glycogenosis Type 9 (Glycogen storage disease IX), Hereditary Inclusion-Body Myositis, Integrin-Deficient Congenital Muscular Dystrophy, Kennedy Disease (Spinal-Bulbar Muscular Atrophy), Kugelberg-Welander Disease, Lactate dehydrogenase A deficiency, Lactate Dehydrogenase B Deficiency, Laing Distal Myopathy, Lambert-Eaton Myasthenic Syndrome, Limb Girdle Muscular Dystrophy Type 2C (LGMD-2C), Limb Girdle Muscular Dystrophy Type 2D (LGMD-2D) , Limb Girdle Muscular Dystrophy Type 2F (LGMD-2F) , Limb Girdle Muscular Dystrophy Type2E (LGMD-2E) , Merosin-Deficient Congenital Muscular Dystrophy, Mitochondrial Myopathy, Miyoshi myopathy, Muscle-Eye-Brain Disease, Myoadenylate Deaminase Deficiency, Myofibrillar Myopathy 1, Myofibrillar Myopathy 10, Myofibrillar Myopathy 11, Myofibrillar Myopathy 12, Myofibrillar Myopathy 2, Myofibrillar Myopathy 3, Myofibrillar Myopathy 4 (ZASP related myopathy), Myofibrillar Myopathy 5, Myofibrillar Myopathy 6, Myofibrillar Myopathy 7, Myofibrillar Myopathy 8, Myofibrillar Myopathy 9, Myotonic dystrophy Type 1 (Steinert Disease), Myotonic dystrophy Type 2, Myotubular Myopathy, Nemaline Myopathy 1, Nemaline Myopathy 10, Nemaline Myopathy 2, Nemaline Myopathy 3, Nemaline Myopathy 4, Nemaline Myopathy 5A, 5B, 5C, Nemaline Myopathy 6, Nemaline Myopathy 7, Nemaline Myopathy 8, Nemaline Myopathy 9, Nonaka Distal Myopathy, Oculopharynggeal muscular dystrophy, Omithine Transcarbamylase deficiency, Paramyotonia Congenita, Periodic Paralysis, hyperkalemic, Periodic Paralysis, hypokalemic, Phosphoglycerate Kinase Deficiency, Polymyositis, Progressive External Ophthalmoplegia , Spinal Muscular Atrophy type 3 – Kugelberg-Welander Disease, Thomsen Disease (Myotonia Congenita (autosomal dominant)), Walker-Warburg Syndrome, Werdnig-Hoffmann Disease - Spinal Muscular Atrophy type 1, X-linked myotubular myopathy , Carnitine Deficiency, Carnitine Palmityl Transferase Deficiency (CPT Deficiency), Centronuclear Myopathy, Debrancher Enzyme Deficiency, Dermatomyositis (DM), Distal Muscular Dystrophy (DD), Dystrophia Myotonica (Myotonic Muscular Dystrophy), Endocrine Myopathy, Finnish (Tibial) Distal Myopathy, Forbes Disease (Debrancher Enzyme Deficiency), Gowers-Laing Distal Myopathy, Hauptmann-Thanheuser MD (Emery-Dreifuss Muscular Dystrophy), Hereditary Motor and Sensory Neuropathy (Charcot-Marie-Tooth Disease), Hyperthyroid Myopathy, Hypothyroid Myopathy, Inclusion-Body Myositis (IBM), Inherited Myopathies, Lactate Dehydrogenase Deficiency, Limb-Girdle Muscular Dystrophy (LGMD), McArdle Disease (Phosphorylase Deficiency), Metabolic Diseases of Muscle, Miyoshi Distal Myopathy, Motor Neurone Disease, Myasthenia Gravis (MG), Myofibrillar Myopathy, Myophosphorylase Deficiency, Myotonia Congenita (MC), Myotonic Muscular Dystrophy (MMD), Nemaline Myopathy, Pearson

Syndrome, Periodic Paralysis, Peroneal Muscular Atrophy (Charcot-Marie-Tooth Disease), Phosphofructokinase Deficiency, Phosphogly cerate Kinase Deficiency, Phosphorylase Deficiency, Primary merosin deficiency (LAMA2), Rod Body Disease (Nemaline Myopathy), Spinal Muscular Atrophy (SMA), Spinal-Bulbar Muscular Atrophy (SBMA), Steinert Disease (Myotonic Muscular Dystrophy), Tarui Disease (Phosphofructokinase Deficiency), Thomsen Disease (Myotonia Congenita), Ullrich Congenital Muscular Dystrophy, Welander Distal Myopathy, or ZASP-Related Myopathy.

860. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Advanced heart failure and/or wherein the heterologous nucleic acid sequence encodes SERCA2a, ATP2A2 (e.g., a polypeptide represented by UniProt Accession number P16615 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

861. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Amyotrophic lateral sclerosis (ALS) (Lou Gehrig's disease) and/or wherein the heterologous nucleic acid sequence encodes Superoxide dismutase-1 (SOD1) (e.g., a polypeptide represented by UniProt Accession number P00441 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

862. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Andersen-Tawil Syndrome and/or wherein the heterologous nucleic acid sequence encodes KCNJ2 (e.g., a polypeptide represented by UniProt Accession number P63252 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

863. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Barth syndrome and/or wherein the heterologous nucleic acid sequence encodes TAFAZZIN (e.g., a polypeptide represented by UniProt Accession number Q16635 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

864. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Becker Muscular Dystrophy (BMD) and/or wherein the heterologous nucleic acid sequence encodes DMD (e.g., a polypeptide represented by UniProt Accession number P11532 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

865. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Becker Myotonia Congenita and/or wherein the heterologous nucleic acid sequence encodes CLCN1 (e.g., a polypeptide represented by UniProt Accession number P35523 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

866. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Bethlem Myopathy and/or wherein the heterologous nucleic acid sequence encodes COL6A3 (e.g., a polypeptide represented by UniProt Accession number P12111 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

867. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Bethlem Myopathy and/or wherein the heterologous nucleic acid sequence encodes COL6A2 (e.g., a polypeptide represented by UniProt Accession number P12110 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

868. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Bethlem Myopathy and/or wherein the heterologous nucleic acid sequence encodes COL6A1 (e.g., a polypeptide represented by UniProt Accession number P12109 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

869. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Bulbospinal Muscular Atrophy and/or wherein the heterologous nucleic acid sequence encodes AR (e.g., a polypeptide represented by UniProt Accession number P10275 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

870. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Carnitine Deficiency, systemic primary and/or wherein the heterologous nucleic acid sequence encodes SLC22A5 (e.g., a polypeptide represented by UniProt Accession number O76082 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

871. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Carnitine Palmityl Transferase Deficiency, type 1 and/or wherein the heterologous nucleic acid sequence encodes CPT1A (e.g., a polypeptide represented by UniProt Accession number P50416 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

872. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Carnitine Palmityl Transferase Deficiency, type 2 and/or wherein the heterologous nucleic acid sequence encodes CPT2 (e.g., a polypeptide represented by UniProt Accession number P23786 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

873. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Catecholaminergic polymorphic ventricular tachycardia 2 (CPVT2) and/or wherein the heterologous nucleic acid sequence encodes Calsequestrin-2 (CASQ2) (e.g., a polypeptide represented by UniProt Accession number O14958 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

874. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Central Core Disease (congenital myopathy, type 1A) and/or wherein the heterologous nucleic acid sequence encodes RYR1 (e.g., a polypeptide represented by UniProt Accession number P21817 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

875. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Centronuclear Myopathy type 1 and/or wherein the heterologous nucleic acid sequence encodes MTMR14 (e.g., a polypeptide represented by UniProt Accession number Q8NCE2 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

876. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Centronuclear Myopathy type 2 and/or wherein the heterologous nucleic acid sequence encodes DNM2 (e.g., a polypeptide represented by UniProt Accession number O14717 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

877. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence

encodes PMP22 (e.g., a polypeptide represented by UniProt Accession number Q01453 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

878. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes MPZ (e.g., a polypeptide represented by UniProt Accession number P25189 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

879. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes DNM2 (e.g., a polypeptide represented by UniProt Accession number P50570 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

880. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes MFN2 (e.g., a polypeptide represented by UniProt Accession number O95140 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

881. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes KIF1B (e.g., a polypeptide represented by UniProt Accession number O60333 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

882. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes SBF2 (e.g., a polypeptide represented by UniProt Accession number Q86WG5 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

883. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes PNKP (e.g., a polypeptide represented by UniProt Accession number Q96T60 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

884. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes GDAP1 (e.g., a polypeptide represented by UniProt Accession number Q8TB36 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

885. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes LMNA (e.g., a polypeptide represented by UniProt Accession number P02545 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

886. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence encodes FGD4 (e.g., a polypeptide represented by UniProt Accession number Q96M96 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

887. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Charcot-Marie-Tooth disease and/or wherein the heterologous nucleic acid sequence

encodes MTMR2 (e.g., a polypeptide represented by UniProt Accession number Q13614 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

888. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Muscular Dystrophy (Ullrich disease) and/or wherein the heterologous nucleic acid sequence encodes COL6A3 (e.g., a polypeptide represented by UniProt Accession number P12111 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

889. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Muscular Dystrophy (Ullrich disease) and/or wherein the heterologous nucleic acid sequence encodes COL6A2 (e.g., a polypeptide represented by UniProt Accession number P12110 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

890. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Muscular Dystrophy (Ullrich disease) and/or wherein the heterologous nucleic acid sequence encodes COL6A1 (e.g., a polypeptide represented by UniProt Accession number P12109 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

891. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes COLQ (e.g., a polypeptide represented by UniProt Accession number Q9Y215 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

892. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes AGRN (e.g., a polypeptide represented by UniProt Accession number O00468 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

893. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes RAPSN (e.g., a polypeptide represented by UniProt Accession number Q13702 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

894. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes GFPT1 (e.g., a polypeptide represented by UniProt Accession number Q06210 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

895. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes SCN4A (e.g., a polypeptide represented by UniProt Accession number P35499 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

896. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes ALG2 (e.g., a polypeptide represented by UniProt Accession number Q9H553 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

897. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence

encodes ALG14 (e.g., a polypeptide represented by UniProt Accession number Q96F25 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

898. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes DPAGT1 (e.g., a polypeptide represented by UniProt Accession number Q9H3H5 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

899. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes CHRNE (e.g., a polypeptide represented by UniProt Accession number Q04844 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

900. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes CHRNA1 (e.g., a polypeptide represented by UniProt Accession number P02708 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

901. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes DOK7 (e.g., a polypeptide represented by UniProt Accession number Q18PE1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

902. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes CHAT (e.g., a polypeptide represented by UniProt Accession number P28329 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

903. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myopathy and/or wherein the heterologous nucleic acid sequence encodes ACTA1 (e.g., a polypeptide represented by UniProt Accession number P68133 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

904. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myopathy and/or wherein the heterologous nucleic acid sequence encodes STAC3 (e.g., a polypeptide represented by UniProt Accession number Q96MF2 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

905. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myopathy and/or wherein the heterologous nucleic acid sequence encodes TPM3 (e.g., a polypeptide represented by UniProt Accession number P06753 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

906. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Congenital Myotonic Dystrophy and/or wherein the heterologous nucleic acid sequence encodes DMPK (e.g., a polypeptide represented by UniProt Accession number Q09013 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

907. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Cori Disease (Debrancher Enzyme Deficiency or Forbes Disease) and/or wherein the

heterologous nucleic acid sequence encodes AGL (e.g., a polypeptide represented by UniProt Accession number P35573 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

908. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Danon disease and/or wherein the heterologous nucleic acid sequence encodes LAMP2 (e.g., a polypeptide represented by UniProt Accession number P13473 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

909. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Dejerine-Sottas Disease and/or wherein the heterologous nucleic acid sequence encodes MPZ (e.g., a polypeptide represented by UniProt Accession number P25189 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

910. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Dejerine-Sottas Disease and/or wherein the heterologous nucleic acid sequence encodes EGR2 (e.g., a polypeptide represented by UniProt Accession number P11161 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

911. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Dejerine-Sottas Disease and/or wherein the heterologous nucleic acid sequence encodes PMP22 (e.g., a polypeptide represented by UniProt Accession number Q01453 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

912. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Dejerine-Sottas Disease and/or wherein the heterologous nucleic acid sequence encodes PRX (e.g., a polypeptide represented by UniProt Accession number Q9BXM0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

913. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Distal Muscular Dystrophy, Welander and/or wherein the heterologous nucleic acid sequence encodes TIA1 (e.g., a polypeptide represented by UniProt Accession number P31483 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

914. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Distal Muscular Dystrophy, Miyoshi and/or wherein the heterologous nucleic acid sequence encodes DYSF (e.g., a polypeptide represented by UniProt Accession number O75923 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

915. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Distal myopathy with anterior tibial onset and/or wherein the heterologous nucleic acid sequence encodes DYSF (e.g., a polypeptide represented by UniProt Accession number O75923 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

916. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Duchenne Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes Dystrophin (DMD) (e.g., a polypeptide represented by UniProt Accession number P11532 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

917. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Duchenne Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes GALGT2, B4GALNT2 (e.g., a polypeptide represented by UniProt Accession number Q8NHY0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

918. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Dysferlinopathy and/or wherein the heterologous nucleic acid sequence encodes Dysferlin (DYSF) (e.g., a polypeptide represented by UniProt Accession number O75923 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

919. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Emery-Dreifuss Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes EMD (e.g., a polypeptide represented by UniProt Accession number P50402 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

920. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Emery-Dreifuss Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes SYNE1 (e.g., a polypeptide represented by UniProt Accession number Q8NF91 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

921. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Emery-Dreifuss Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes SYNE2 (e.g., a polypeptide represented by UniProt Accession number Q8WXH0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

922. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Emery-Dreifuss Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes TMEM43 (e.g., a polypeptide represented by UniProt Accession number Q9BTV4 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

923. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Emery-Dreifuss Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes LMNA (e.g., a polypeptide represented by UniProt Accession number P02545 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

924. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Eulenberg Disease (Paramyotonia Congenita) and/or wherein the heterologous nucleic acid sequence encodes SCN4A (e.g., a polypeptide represented by UniProt Accession number P35499 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

925. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Facioscapulohumeral Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes SMCHD1 (e.g., a polypeptide represented by UniProt Accession number A6NHR9 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

926. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Facioscapulohumeral Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes LRIF1 (e.g., a polypeptide represented by UniProt Accession number Q5T3J3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

927. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Friedreich's ataxia and/or wherein the heterologous nucleic acid sequence encodes Frataxin (FXN) (e.g., a polypeptide represented by UniProt Accession number Q16595 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

928. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Fukuyama Congenital Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes FKTN (e.g., a polypeptide represented by UniProt Accession number O75072 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

929. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Glycogen storage disease II (Pompe disease or Acid Maltase Deficiency) and/or wherein the heterologous nucleic acid sequence encodes GAA (e.g., a polypeptide represented by UniProt Accession number P10253 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

930. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Glycogenosis Type 10 (Glycogen storage disease X) and/or wherein the heterologous nucleic acid sequence encodes PGAM2 (e.g., a polypeptide represented by UniProt Accession number P15259 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

931. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Glycogenosis Type 11 (Glycogen storage disease XI) and/or wherein the heterologous nucleic acid sequence encodes LDHA (e.g., a polypeptide represented by UniProt Accession number P00338 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

932. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Glycogenosis Type 2 (Glycogen storage disease II or Pompe Disease or Acid maltase deficiency) and/or wherein the heterologous nucleic acid sequence encodes GAA (e.g., a polypeptide represented by UniProt Accession number P10253 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

933. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Glycogenosis Type 3 (Glycogen storage disease III) and/or wherein the heterologous nucleic acid sequence encodes AGL (e.g., a polypeptide represented by UniProt Accession number P35573 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

934. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Glycogenosis Type 5 (Glycogen storage disease V or McArdle Disease or Myophosphorylase Deficiency) and/or wherein the heterologous nucleic acid sequence encodes PYGM (e.g., a polypeptide represented by UniProt Accession number P11217 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

935. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Glycogenosis Type 7 (Glycogen storage disease VII or Phosphofructokinase Deficiency or Tarui Disease) and/or wherein the heterologous nucleic acid sequence encodes PFKM (e.g., a

polypeptide represented by UniProt Accession number P08237 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

936. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Glycogenosis Type 9 (Glycogen storage disease IX) and/or wherein the heterologous nucleic acid sequence encodes PHKB (e.g., a polypeptide represented by UniProt Accession number Q93100 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

937. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Glycogenosis Type 9 (Glycogen storage disease IX) and/or wherein the heterologous nucleic acid sequence encodes PHKA2 (e.g., a polypeptide represented by UniProt Accession number P46019 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

938. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Hereditary Inclusion-Body Myositis and/or wherein the heterologous nucleic acid sequence encodes GNE (e.g., a polypeptide represented by UniProt Accession number Q9Y223 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

939. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Integrin-Deficient Congenital Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes ITGA7 (e.g., a polypeptide represented by UniProt Accession number Q13683 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

940. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Kennedy Disease (Spinal-Bulbar Muscular Atrophy) and/or wherein the heterologous nucleic acid sequence encodes Androgen receptor (AR) (e.g., a polypeptide represented by UniProt Accession number P10275 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

941. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Kugelberg-Welander Disease and/or wherein the heterologous nucleic acid sequence encodes SMN1 (e.g., a polypeptide represented by UniProt Accession number Q16637 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

942. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Lactate dehydrogenase A deficiency and/or wherein the heterologous nucleic acid sequence encodes LDHA (e.g., a polypeptide represented by UniProt Accession number P00338 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

943. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Lactate Dehydrogenase B Deficiency and/or wherein the heterologous nucleic acid sequence encodes LDHB (e.g., a polypeptide represented by UniProt Accession number P07195 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

944. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Lambert-Eaton Myasthenic Syndrome and/or wherein the heterologous nucleic acid sequence encodes CACNB2 (e.g., a polypeptide represented by UniProt Accession number Q08289 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

945. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Laing Distal Myopathy and/or wherein the heterologous nucleic acid sequence encodes MYH7 (e.g., a polypeptide represented by UniProt Accession number A7E2Y1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

946. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Limb Girdle Muscular Dystrophy Type 2C (LGMD-2C) and/or wherein the heterologous nucleic acid sequence encodes Gamma-sarcoglycan (e.g., a polypeptide represented by UniProt Accession number Q13326 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

947. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Limb Girdle Muscular Dystrophy Type 2D (LGMD-2D) and/or wherein the heterologous nucleic acid sequence encodes Alpha-sarcoglycan (e.g., a polypeptide represented by UniProt Accession number Q16586 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

948. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Limb Girdle Muscular Dystrophy Type2E (LGMD-2E) and/or wherein the heterologous nucleic acid sequence encodes Beta-sarcoglycan (e.g., a polypeptide represented by UniProt Accession number Q16585 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

949. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Limb Girdle Muscular Dystrophy Type 2F (LGMD-2F) and/or wherein the heterologous nucleic acid sequence encodes Delta-sarcoglycan (e.g., a polypeptide represented by UniProt Accession number Q92629 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

950. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Merosin-Deficient Congenital Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes LAMA2 (e.g., a polypeptide represented by UniProt Accession number P24043 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

951. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Muscle-Eye-Brain Disease and/or wherein the heterologous nucleic acid sequence encodes POMGNT1 (e.g., a polypeptide represented by UniProt Accession number Q8WZA1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

952. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Mitochondrial Myopathy and/or wherein the heterologous nucleic acid sequence encodes CHCHD10 (e.g., a polypeptide represented by UniProt Accession number Q8WYQ3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

953. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Miyoshi myopathy and/or wherein the heterologous nucleic acid sequence encodes DYSF (e.g., a polypeptide represented by UniProt Accession number O75923 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

954. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myoadenylate Deaminase Deficiency and/or wherein the heterologous nucleic acid sequence encodes AMPD1 (e.g., a polypeptide represented by UniProt Accession number P23109 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

955. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myofibrillar Myopathy 1 and/or wherein the heterologous nucleic acid sequence encodes DES (e.g., a polypeptide represented by UniProt Accession number P17661 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

956. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myofibrillar Myopathy 2 and/or wherein the heterologous nucleic acid sequence encodes CRYAB (e.g., a polypeptide represented by UniProt Accession number P02511 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

957. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myofibrillar Myopathy 3 and/or wherein the heterologous nucleic acid sequence encodes MYOT (e.g., a polypeptide represented by UniProt Accession number Q9UBF9 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

958. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myofibrillar Myopathy 4 (ZASP related myopathy) and/or wherein the heterologous nucleic acid sequence encodes LDB3, ZASP (e.g., a polypeptide represented by UniProt Accession number O75112 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

959. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myofibrillar Myopathy 5 and/or wherein the heterologous nucleic acid sequence encodes FLNC (e.g., a polypeptide represented by UniProt Accession number Q14315 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

960. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myofibrillar Myopathy 6 and/or wherein the heterologous nucleic acid sequence encodes BAG3 (e.g., a polypeptide represented by UniProt Accession number O95817 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

961. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myofibrillar Myopathy 7 and/or wherein the heterologous nucleic acid sequence encodes KY (e.g., a polypeptide represented by UniProt Accession number Q8NBH2 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

962. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myofibrillar Myopathy 8 and/or wherein the heterologous nucleic acid sequence encodes PYROXD1 (e.g., a polypeptide represented by UniProt Accession number Q8WU10 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

963. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myofibrillar Myopathy 9 and/or wherein the heterologous nucleic acid sequence encodes TTN

(e.g., a polypeptide represented by UniProt Accession number Q8WZ42 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

964. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myofibrillar Myopathy 10 and/or wherein the heterologous nucleic acid sequence encodes SVIL (e.g., a polypeptide represented by UniProt Accession number O95425 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

965. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myofibrillar Myopathy 11 and/or wherein the heterologous nucleic acid sequence encodes UNC45B (e.g., a polypeptide represented by UniProt Accession number Q8IWX7 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

966. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myofibrillar Myopathy 12 and/or wherein the heterologous nucleic acid sequence encodes MYL2 (e.g., a polypeptide represented by UniProt Accession number Q99972 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

967. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myotonic dystrophy Type 1 (Steinert Disease) and/or wherein the heterologous nucleic acid sequence encodes Myotonin-protein kinase (DMPK) (e.g., a polypeptide represented by UniProt Accession number Q09013 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

968. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myotonic dystrophy Type 2 and/or wherein the heterologous nucleic acid sequence encodes CNBP (e.g., a polypeptide represented by UniProt Accession number P62633 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

969. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myotubular Myopathy and/or wherein the heterologous nucleic acid sequence encodes MTM1 (e.g., a polypeptide represented by UniProt Accession number Q13496 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

970. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Nemaline Myopathy 1 and/or wherein the heterologous nucleic acid sequence encodes TPM3 (e.g., a polypeptide represented by UniProt Accession number P06753 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

971. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Nemaline Myopathy 2 and/or wherein the heterologous nucleic acid sequence encodes NEB (e.g., a polypeptide represented by UniProt Accession number P20929 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

972. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Nemaline Myopathy 5A, 5B, 5C and/or wherein the heterologous nucleic acid sequence encodes TNNT1 (e.g., a polypeptide represented by UniProt Accession number P13805 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

973. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Nemaline Myopathy 3 and/or wherein the heterologous nucleic acid sequence encodes ACTA1 (e.g., a polypeptide represented by UniProt Accession number P68133 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

974. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Nemaline Myopathy 6 and/or wherein the heterologous nucleic acid sequence encodes KBTBD13 (e.g., a polypeptide represented by UniProt Accession number C9JR72 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

975. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Nemaline Myopathy 4 and/or wherein the heterologous nucleic acid sequence encodes TPM2 (e.g., a polypeptide represented by UniProt Accession number P07951 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

976. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Nemaline Myopathy 7 and/or wherein the heterologous nucleic acid sequence encodes CFL2 (e.g., a polypeptide represented by UniProt Accession number Q9Y281 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

977. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Nemaline Myopathy 8 and/or wherein the heterologous nucleic acid sequence encodes KLHL40 (e.g., a polypeptide represented by UniProt Accession number Q2TBA0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

978. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Nemaline Myopathy 9 and/or wherein the heterologous nucleic acid sequence encodes KLHL41 (e.g., a polypeptide represented by UniProt Accession number O60662 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

979. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Nemaline Myopathy 10 and/or wherein the heterologous nucleic acid sequence encodes LMOD3 (e.g., a polypeptide represented by UniProt Accession number Q0VAK6 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

980. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Nonaka Distal Myopathy and/or wherein the heterologous nucleic acid sequence encodes GNE (e.g., a polypeptide represented by UniProt Accession number Q9Y223 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

981. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Oculopharynggeal muscular dystrophy and/or wherein the heterologous nucleic acid sequence encodes PABPN1 (e.g., a polypeptide represented by UniProt Accession number Q86U42 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

982. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Omithine Transcarbamylase deficiency and/or wherein the heterologous nucleic acid sequence encodes OTC (e.g., a polypeptide represented by UniProt Accession number P00480 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

983. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Paramyotonia Congenita and/or wherein the heterologous nucleic acid sequence encodes SCN4A (e.g., a polypeptide represented by UniProt Accession number P35499 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

984. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Periodic Paralysis, hypokalemic and/or wherein the heterologous nucleic acid sequence encodes CACNA1S (e.g., a polypeptide represented by UniProt Accession number Q13698 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

985. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Periodic Paralysis, hyperkalemic and/or wherein the heterologous nucleic acid sequence encodes SCN4A (e.g., a polypeptide represented by UniProt Accession number P35499 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

986. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Phosphoglycerate Kinase Deficiency and/or wherein the heterologous nucleic acid sequence encodes PGK1 (e.g., a polypeptide represented by UniProt Accession number P00558 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

987. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Polymyositis and/or wherein the heterologous nucleic acid sequence encodes PMSCL2 (e.g., a polypeptide represented by UniProt Accession number Q01780 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

988. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Polymyositis and/or wherein the heterologous nucleic acid sequence encodes PMSCL1 (e.g., a polypeptide represented by UniProt Accession number Q06265 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

989. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Progressive External Ophthalmoplegia and/or wherein the heterologous nucleic acid sequence encodes POLG (e.g., a polypeptide represented by UniProt Accession number P54098 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

990. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Progressive External Ophthalmoplegia and/or wherein the heterologous nucleic acid sequence encodes POLG2 (e.g., a polypeptide represented by UniProt Accession number Q9UHN1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

991. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Progressive External Ophthalmoplegia and/or wherein the heterologous nucleic acid sequence encodes SLC25A4 (e.g., a polypeptide represented by UniProt Accession number P12235 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

992. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Progressive External Ophthalmoplegia and/or wherein the heterologous nucleic acid sequence encodes TWNK (e.g., a polypeptide represented by UniProt Accession number Q96RR1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

993. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Spinal Muscular Atrophy type 3 – Kugelberg-Welander Disease and/or wherein the heterologous nucleic acid sequence encodes Survival motor neuron protein (SMN), SMN1 (e.g., a polypeptide represented by UniProt Accession number Q16637 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

994. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Thomsen Disease (Myotonia Congenita (autosomal dominant)) and/or wherein the heterologous nucleic acid sequence encodes CLCN1 (e.g., a polypeptide represented by UniProt Accession number P35523 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

995. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Walker-Warburg Syndrome and/or wherein the heterologous nucleic acid sequence encodes POMT1 (e.g., a polypeptide represented by UniProt Accession number Q9Y6A1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

996. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is X-linked myotubular myopathy and/or wherein the heterologous nucleic acid sequence encodes Myotubularin (MTM1) (e.g., a polypeptide represented by UniProt Accession number Q13496 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

997. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Werdnig-Hoffmann Disease - Spinal Muscular Atrophy type 1 and/or wherein the heterologous nucleic acid sequence encodes SMN1 (e.g., a polypeptide represented by UniProt Accession number Q16637 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

998. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Carnitine Deficiency.

999. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Carnitine Palmityl Transferase Deficiency (CPT Deficiency).

1000. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Centronuclear Myopathy.

1001. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Debrancher Enzyme Deficiency.

1002. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Dermatomyositis (DM).

1003. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Distal Muscular Dystrophy (DD).

1004. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Dystrophia Myotonica (Myotonic Muscular Dystrophy).

1005. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Endocrine Myopathy.

1006. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Finnish (Tibial) Distal Myopathy.

1007. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Forbes Disease (Debrancher Enzyme Deficiency).

1008. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Gowers-Laing Distal Myopathy.

1009. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Hauptmann-Thanheuser MD (Emery- Dreifuss Muscular Dystrophy).

1010. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Hereditary Motor and Sensory Neuropathy (Charcot-Marie-Tooth Disease).

1011. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Hyperthyroid Myopathy.

1012. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Hypothyroid Myopathy.

1013. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Inclusion-Body Myositis (IBM).

1014. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Inherited Myopathies.

1015. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Lactate Dehydrogenase Deficiency.

1016. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Limb-Girdle Muscular Dystrophy (LGMD).

1017. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is McArdle Disease (Phosphorylase Deficiency).

1018. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Metabolic Diseases of Muscle.

1019. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Miyoshi Distal Myopathy.

1020. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Motor Neurone Disease.

1021. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myasthenia Gravis (MG).

1022. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myofibrillar Myopathy.

1023. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myophosphorylase Deficiency.

1024. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myotonia Congenita (MC).

1025. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Myotonic Muscular Dystrophy (MMD).

1026. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Nemaline Myopathy.

1027. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Pearson Syndrome.

1028. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Periodic Paralysis.

1029. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Peroneal Muscular Atrophy (Charcot-Marie-Tooth Disease).

1030. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Phosphofructokinase Deficiency.

1031. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Phosphogly cerate Kinase Deficiency.

1032. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Phosphorylase Deficiency.

1033. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Primary merosin deficiency (LAMA2).

1034. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Rod Body Disease (Nemaline Myopathy).

1035. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Spinal Muscular Atrophy (SMA).

1036. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Spinal-Bulbar Muscular Atrophy (SBMA).

1037. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Steinert Disease (Myotonic Muscular Dystrophy).

1038. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Tarui Disease (Phosphofructokinase Deficiency).

1039. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Thomsen Disease (Myotonia Congenita).

1040. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Ullrich Congenital Muscular Dystrophy.

1041. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is Welander Distal Myopathy.

1042. The method of any one of embodiments 190, 191, 858, and 859, wherein the disease or condition is ZASP-Related Myopathy.

1043. The method of embodiment 190 or embodiment 191, wherein the disease or condition is Osteogenesis imperfecta (brittle bone disease) Type I, II, III, or IV, Hereditary angioedema, Osteogenesis imperfecta Type V, Osteogenesis Imperfecta Type VI, Osteogenesis Imperfecta Type VII, Osteogenesis

Imperfecta Type VIII, Osteogenesis Imperfecta Type IX, Maple syrup urine disease, Alpha-mannosidosis, Beta-mannosidosis, Glycogen storage disease Ia (Von Gierke disease), Bloch-Sulzberger Syndrome, Cholesterol Ester Storage Disease, Danon Disease, Cystic Fibrosis, Rheumatoid Arthritis, Alpha-1 Antitrypsin Deficiency, Hemophilia A, Hemophilia B, Homozygous Familial Hypercholesterolemia (FHCL1) , Mucopolysaccharidosis Type VI, Familial Lipoprotein Lipase Deficiency, or Fragile X syndrome.

1044. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Osteogenesis imperfecta (brittle bone disease)Type I, II, III, or IV and/or wherein the heterologous nucleic acid sequence encodes COL1A1 (e.g., a polypeptide represented by UniProt Accession number P02452 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1045. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Osteogenesis imperfecta (brittle bone disease)Type I, II, III, or IV and/or wherein the heterologous nucleic acid sequence encodes COL1A2 (e.g., a polypeptide represented by UniProt Accession number P08123 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1046. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Hereditary angioedema and/or wherein the heterologous nucleic acid sequence encodes Plasma protease C1 inhibitor (SERPING1, C1NH) (e.g., a polypeptide represented by UniProt Accession number P05155 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1047. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Osteogenesis imperfecta Type V and/or wherein the heterologous nucleic acid sequence encodes Interferon-induced transmembrane protein 5 (IFITM5, IFM5) (e.g., a polypeptide represented by UniProt Accession number A6NNB3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1048. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Osteogenesis Imperfecta Type VI and/or wherein the heterologous nucleic acid sequence encodes Pigment epithelium-derived factor (SERPINF1, PEDF) (e.g., a polypeptide represented by UniProt Accession number P36955 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1049. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Osteogenesis Imperfecta Type VII and/or wherein the heterologous nucleic acid sequence encodes Cartilage-associated protein (CRTAP) (e.g., a polypeptide represented by UniProt Accession number O75718 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1050. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Osteogenesis Imperfecta Type VIII and/or wherein the heterologous nucleic acid sequence encodes Prolyl 3-hydroxylase 1 (P3H1, LEPRE1) (e.g., a polypeptide represented by UniProt Accession number Q32P28 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1051. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Osteogenesis Imperfecta Type IX and/or wherein the heterologous nucleic acid sequence encodes PPIB (e.g., a polypeptide represented by UniProt Accession number P23284 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1052. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Maple syrup urine disease and/or wherein the heterologous nucleic acid sequence encodes BCKDHA (e.g., a polypeptide represented by UniProt Accession number P12694 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1053. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Maple syrup urine disease and/or wherein the heterologous nucleic acid sequence encodes BCKDHB (e.g., a polypeptide represented by UniProt Accession number P21953 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1054. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Maple syrup urine disease and/or wherein the heterologous nucleic acid sequence encodes DBT (e.g., a polypeptide represented by UniProt Accession number P11182 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1055. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Alpha-mannosidosis and/or wherein the heterologous nucleic acid sequence encodes Lysosomal alpha-mannosidase (MAN2B1) (e.g., a polypeptide represented by UniProt Accession number O00754 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1056. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Beta-mannosidosis and/or wherein the heterologous nucleic acid sequence encodes Beta-mannosidase (MANBA) (e.g., a polypeptide represented by UniProt Accession number O00462 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1057. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Glycogen storage disease Ia (Von Gierke disease) and/or wherein the heterologous nucleic acid sequence encodes Glucose-6-phosphatase catalytic subunit 1 (G6PC1) (e.g., a polypeptide represented by UniProt Accession number P35575 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1058. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Bloch-Sulzberger Syndrome and/or wherein the heterologous nucleic acid sequence encodes IKBKG (e.g., a polypeptide represented by UniProt Accession number Q9Y6K9 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1059. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Cholesterol Ester Storage Disease and/or wherein the heterologous nucleic acid sequence encodes LIPA (e.g., a polypeptide represented by UniProt Accession number P38571 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1060. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Danon Disease and/or wherein the heterologous nucleic acid sequence encodes Lysosome-associated membrane glycoprotein 2 (LAMP2) (e.g., a polypeptide represented by UniProt Accession number

P13473 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1061. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Cystic Fibrosis and/or wherein the heterologous nucleic acid sequence encodes CTFR (e.g., a polypeptide represented by UniProt Accession number A4L9V0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1062. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Rheumatoid Arthritis and/or wherein the heterologous nucleic acid sequence encodes TNF (e.g., a polypeptide represented by UniProt Accession number P01375 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1063. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Alpha-1 Antitrypsin Deficiency and/or wherein the heterologous nucleic acid sequence encodes Alpha-1-antitrypsin (Alpha1-AT), AAT, SERPINA1 (e.g., a polypeptide represented by UniProt Accession number P01009 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1064. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Hemophilia A and/or wherein the heterologous nucleic acid sequence encodes Coagulation factor VIII (e.g., a polypeptide represented by UniProt Accession number P00451 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1065. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Hemophilia B and/or wherein the heterologous nucleic acid sequence encodes Coagulation factor IX (e.g., a polypeptide represented by UniProt Accession number P00740 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1066. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Homozygous Familial Hypercholesterolemia (FHCL1) and/or wherein the heterologous nucleic acid sequence encodes Low-density lipoprotein receptor (LDLR) (e.g., a polypeptide represented by UniProt Accession number P01130 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1067. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Mucopolysaccharidosis Type VI and/or wherein the heterologous nucleic acid sequence encodes Arylsulfatase B (ARSB) (e.g., a polypeptide represented by UniProt Accession number P15848 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1068. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Familial Lipoprotein Lipase Deficiency and/or wherein the heterologous nucleic acid sequence encodes LPL (e.g., a polypeptide represented by UniProt Accession number P06858 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1069. The method of any one of embodiments 190, 191, and 1043, wherein the disease or condition is Fragile X syndrome and/or wherein the heterologous nucleic acid sequence encodes FMR1 (e.g., a polypeptide represented by UniProt Accession number Q06787 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1070. The method of embodiment 190 or embodiment 191, wherein the disease or condition is a disease or condition of cardiac muscle.

1071. The method of any one of embodiments 190, 191, and 1070, wherein the disease or condition is Acid maltase deficiency (Glycogen storage disease II), Advanced heart failure, Andersen-Tawil Syndrome, Arrhythmogenic right ventricular cardiomyopathy 1 (ARVD1), Arrhythmogenic right ventricular cardiomyopathy 5 (ARVD5), Arrhythmogenic right ventricular cardiomyopathy 8 (ARVD8), Arrhythmogenic right ventricular cardiomyopathy 9 (ARVD9), Arrhythmogenic right ventricular cardiomyopathy 10 (ARVD10), Arrhythmogenic right ventricular cardiomyopathy 11 (ARVD11), Arrhythmogenic right ventricular cardiomyopathy 12 (ARVD12), Arrhythmogenic right ventricular cardiomyopathy 13 (ARVD13), Arrhythmogenic right ventricular cardiomyopathy 14 (ARVD14), Arrhythmogenic right ventricular cardiomyopathy 15 (ARVD15), Atrial fibrillation 3 (ATFB3), Atrial fibrillation 4 (ATFB4), Atrial fibrillation 6 (ATFB6), Atrial fibrillation 7 (ATFB7), Atrial fibrillation 9 (ATFB9), Atrial fibrillation 10 (ATFB10), Atrial fibrillation 11 (ATFB11), Atrial fibrillation 12 (ATFB612), Atrial fibrillation 13 (ATFB6), Atrial fibrillation 14 (ATFB14), Atrial fibrillation 15 (ATFB15), Atrial fibrillation 16 (ATFB16), Atrial fibrillation 17 (ATFB17), Atrial fibrillation 18 (ATFB18), Atrial septal defect 2 (ASD2), Atrial septal defect 3 (ASD3), Atrial septal defect 4 (ASD4), Atrial septal defect 5 (ASD5), Atrial septal defect 6 (ASD6), Atrial septal defect 7 (ASD7), Atrial septal defect 8 (ASD8), Atrial septal defect 9 (ASD9), Atrial standstill 1, Atrial standstill 2, Barth syndrome , Becker Muscular Dystrophy (BMD), Brugada syndrome 1, Brugada syndrome 2, Brugada syndrome 3, Brugada syndrome 4, Brugada syndrome 5, Brugada syndrome 6, Brugada syndrome 7, Brugada syndrome 8, Brugada syndrome 9, Cardiac arrhythmia syndrome, Cardiac conduct defect, Cardiac conduction disease, Cardiac, facial, and digital anomalies with developmental delay (CAFDADD), Cardiofaciocutaneous syndrome 1, Cardiofaciocutaneous syndrome 2, Cardiofaciocutaneous syndrome 3, Cardiofaciocutaneous syndrome 4, Cardiac-urogenital syndrome, Cardiac valvular dysplasia, X-linked, Cardiac valvular dysplasia 2, Cardiomyopathy, dilated, 1A, Cardiomyopathy, dilated, 1AA, Cardiomyopathy, dilated, 1C, Cardiomyopathy, dilated, 1D, Cardiomyopathy, dilated, 1E, Cardiomyopathy, dilated, 1FF, Cardiomyopathy, dilated, 1MM, Cardiomyopathy, dilated, 1P, Cardiomyopathy, dilated, 1R, Cardiomyopathy, dilated, 1S, Cardiomyopathy, dilated, 1Y, Cardiomyopathy, dilated, 2A, Cardiomyopathy, dilated, 2E, Cardiomyopathy, familial restrictive, 1, Cardiomyopathy, familial restrictive, 3, Cardiomyopathy, hypertrophic, 1 (CMH1), Cardiomyopathy, hypertrophic, 2 (CMH2), Cardiomyopathy, hypertrophic, 3 (CMH3), Cardiomyopathy, hypertrophic 4 (CMH4), Cardiomyopathy, hypertrophic 6 (CMH6), Cardiomyopathy, hypertrophic, 7 (CMH7), Cardiomyopathy, hypertrophic, 8 (CMH8), Cardiomyopathy, hypertrophic, 9 (CMH9), Cardiomyopathy, hypertrophic, 10 (CMH10), Cardiomyopathy, hypertrophic, 11 (CMH11), Cardiomyopathy, hypertrophic, 12 (CMH12), Cardiomyopathy, hypertrophic, 13 (CMH13), Cardiomyopathy, hypertrophic, 14 (CMH14), Cardiomyopathy, hypertrophic, 15 (CMH15), Cardiomyopathy, hypertrophic, 16 (CMH16), Cardiomyopathy, hypertrophic, 17 (CMH17), Cardiomyopathy, hypertrophic, 18 (CMH18), Cardiomyopathy, hypertrophic, 20 (CMH20), Cardiomyopathy, hypertrophic, 23 (CMH23), Cardiomyopathy, hypertrophic, 25 (CMH25), Cardiomyopathy, hypertrophic, 26 (CMH26), Cardiomyopathy, hypertrophic, 27 (CMH27), Cardiomyopathy, hypertrophic, 28 (CMH28), Cardiomyopathy, hypertrophic, 29 (CMH29), Cardiomyopathy, restrictive 1 (RCM1), Cardiomyopathy, restrictive 3 (RCM3), Cardiomyopathy, restrictive 4 (RCM4), Cardiomyopathy, restrictive 5 (RCM5), Cardiomyopathy, restrictive 6 (RCM6),

Carnitine Deficiency, systemic primary, Catecholaminergic polymorphic ventricular tachycardia 2 (CPVT2), Combined oxidative phosphorylation deficiency 8, Combined oxidative phosphorylation deficiency 10, Congenital Myopathy, Congenital Myotonic Dystrophy, Conotruncal heart malformations, Coronary artery disease 1, Coronary artery disease 2, Cori Disease - Debrancher Enzyme Deficiency – Forbes Disease, Costello syndrome, Danon disease, Dextrocardia with other cardiac malformations, x-linked (visceral heterotaxy (HTX1)), Dilated Cardiomyopathy, Duchenne Muscular Dystrophy, Ehlers-Danlos syndrome, cardiac valvular type, Emery-Dreifuss Muscular Dystrophy, Fabry disease, cardiac variant, Frank-ter Haar syndrome, Friedreich's ataxia, Fukuyama Congenital Muscular Dystrophy, Glycogen storage disease III, GM1-gangliosidosis, type I with cardiac involvement, Heart failure, Hirschsprung disease (HCAD), Infantile hypertrophic cardiomyopathy, Ischemia-reperfusion injury, Jervell and Lange-Nielsen syndrome (JLNS1), Jervell and Lange-Nielsen syndrome 2 (JLNS2), Laing Distal Myopathy, Left ventricular noncompaction 1 (LVNC1), Left ventricular noncompaction 3 (LVNC3), Left ventricular noncompaction 4 (LVNC4), Left ventricular noncompaction 5 (LVNC5), Left ventricular noncompaction 6 (LVNC6), Left ventricular noncompaction 7 (LVNC7), Left ventricular noncompaction 8 (LVNC8), Left ventricular noncompaction 9 (LVNC9), Left ventricular noncompaction 10 (LVNC10), LEOPARD syndrome 1, LEOPARD syndrome 2, LEOPARD syndrome 3, Limb-girdle muscular dystrophy, type 25 (LGMDR25), Lodder-Merla syndrome, type 1, Long QT syndrome 1, Long QT syndrome 2, Long QT syndrome 3, Long QT syndrome 4, Long QT syndrome 5, Long QT syndrome 6, Long QT syndrome 7 (Andersen syndrome), Long QT syndrome 8, Long QT syndrome 9, Long QT syndrome 10, Long QT syndrome 11, Long QT syndrome 12, Long QT syndrome 13, Long QT syndrome 14, Long QT syndrome 15, Long QT syndrome 16, Metabolic encephalomyopathic crises (MECRCN), Microphthalmia, syndromic, type 9, Mitochondrial phosphate carrier deficiency (MPCD), Mitral valve prolapse 3 (MVP3), Mungan syndrome (MGS), Myocardial infarction, Myofibrillar Myopathy 1, Myofibrillar Myopathy 2, Myofibrillar Myopathy 6, Myofibrillar Myopathy 10, Myofibrillar Myopathy 11, Myofibrillar Myopathy 12, Myotonic dystrophy Type 1 - Steinert Disease, Myotonic dystrophy Type 2, Naxos disease (NXD), Nemaline Myopathy 1, Nemaline Myopathy 3, Nonprogressive hear block, Orthostatic intolerance (soldiers heart), Progeria syndrome, Progressive familial heart block type IA, Progressive familial heart block type IB, RYR2 calcium release deficiency syndrome, Sengers syndrome, Sick sinus syndrome 1 (SSS1), Sick sinus syndrome 2 (SSS2), Sick sinus syndrome 3 (SSS3), Sick sinus syndrome 4 (SSS4), Sudden cardiac failure, infantile (SCFI), TARP syndrome, Timothy syndrome, Valvular heart disease, congenital, Ventricular fibrillation 1 (VF1), Ventricular tachycardia, Vertebral, cardiac, renal, and limb defects syndrome 1 (VCRL1), Vertebral, cardiac, renal, and limb defects syndrome 2 (VCRL2), or Vertebral, cardiac, renal, and limb defects syndrome 3 (VCRL3).

1072. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Acid maltase deficiency (Glycogen storage disease II) and/or wherein the heterologous nucleic acid sequence encodes GAA (e.g., a polypeptide represented by UniProt Accession number P10253 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1073. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Advanced heart failure and/or wherein the heterologous nucleic acid sequence encodes ATP2A2 (e.g., a polypeptide represented by UniProt Accession number P16615 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1074. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Andersen-Tawil Syndrome and/or wherein the heterologous nucleic acid sequence encodes KCNJ2 (e.g., a polypeptide represented by UniProt Accession number P63252 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1075. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Arrhythmogenic right ventricular cardiomyopathy 1 (ARVD1) and/or wherein the heterologous nucleic acid sequence encodes TGFB3 (e.g., a polypeptide represented by UniProt Accession number P10600 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1076. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Arrhythmogenic right ventricular cardiomyopathy 5 (ARVD5) and/or wherein the heterologous nucleic acid sequence encodes TMEM43 (e.g., a polypeptide represented by UniProt Accession number Q9BTV4 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1077. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Arrhythmogenic right ventricular cardiomyopathy 8 (ARVD8) and/or wherein the heterologous nucleic acid sequence encodes DSP (e.g., a polypeptide represented by UniProt Accession number P15924 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1078. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Arrhythmogenic right ventricular cardiomyopathy 9 (ARVD9) and/or wherein the heterologous nucleic acid sequence encodes PKP2 (e.g., a polypeptide represented by UniProt Accession number Q99959 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1079. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Arrhythmogenic right ventricular cardiomyopathy 10 (ARVD10) and/or wherein the heterologous nucleic acid sequence encodes DSG2 (e.g., a polypeptide represented by UniProt Accession number Q14126 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1080. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Arrhythmogenic right ventricular cardiomyopathy 11 (ARVD11) and/or wherein the heterologous nucleic acid sequence encodes DSC2 (e.g., a polypeptide represented by UniProt Accession number Q02487 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1081. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Arrhythmogenic right ventricular cardiomyopathy 12 (ARVD12) and/or wherein the heterologous nucleic acid sequence encodes JUP (e.g., a polypeptide represented by UniProt Accession number P14923 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1082. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Arrhythmogenic right ventricular cardiomyopathy 13 (ARVD13) and/or wherein the

heterologous nucleic acid sequence encodes CTNNA3 (e.g., a polypeptide represented by UniProt Accession number Q9UI47 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1083. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Arrhythmogenic right ventricular cardiomyopathy 14 (ARVD14) and/or wherein the heterologous nucleic acid sequence encodes CDH2 (e.g., a polypeptide represented by UniProt Accession number P19022 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1084. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Arrhythmogenic right ventricular cardiomyopathy 15 (ARVD15) and/or wherein the heterologous nucleic acid sequence encodes FLNC (e.g., a polypeptide represented by UniProt Accession number Q14315 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1085. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 3 (ATFB3) and/or wherein the heterologous nucleic acid sequence encodes KCNQ1 (e.g., a polypeptide represented by UniProt Accession number P51787 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1086. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 4 (ATFB4) and/or wherein the heterologous nucleic acid sequence encodes KCNE2 (e.g., a polypeptide represented by UniProt Accession number Q9Y6J6 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1087. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 6 (ATFB6) and/or wherein the heterologous nucleic acid sequence encodes NPPA (e.g., a polypeptide represented by UniProt Accession number P01160 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1088. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 7 (ATFB7) and/or wherein the heterologous nucleic acid sequence encodes KCNA5 (e.g., a polypeptide represented by UniProt Accession number P22460 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1089. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 9 (ATFB9) and/or wherein the heterologous nucleic acid sequence encodes KCNJ2 (e.g., a polypeptide represented by UniProt Accession number P63252 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1090. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 10 (ATFB10) and/or wherein the heterologous nucleic acid sequence encodes SCN5A (e.g., a polypeptide represented by UniProt Accession number Q14524 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1091. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 11 (ATFB11) and/or wherein the heterologous nucleic acid sequence

encodes GJA5 (e.g., a polypeptide represented by UniProt Accession number P36382 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1092. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 12 (ATFB612) and/or wherein the heterologous nucleic acid sequence encodes ABCC9 (e.g., a polypeptide represented by UniProt Accession number O60706 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1093. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 13 (ATFB6) and/or wherein the heterologous nucleic acid sequence encodes SCN1B (e.g., a polypeptide represented by UniProt Accession number Q07699 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1094. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 14 (ATFB14) and/or wherein the heterologous nucleic acid sequence encodes SCN2B (e.g., a polypeptide represented by UniProt Accession number O60939 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1095. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 15 (ATFB15) and/or wherein the heterologous nucleic acid sequence encodes NUP155 (e.g., a polypeptide represented by UniProt Accession number O75694 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1096. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 16 (ATFB16) and/or wherein the heterologous nucleic acid sequence encodes SCN3B (e.g., a polypeptide represented by UniProt Accession number Q9NY72 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1097. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 17 (ATFB17) and/or wherein the heterologous nucleic acid sequence encodes SCN4B (e.g., a polypeptide represented by UniProt Accession number Q8IWT1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1098. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial fibrillation 18 (ATFB18) and/or wherein the heterologous nucleic acid sequence encodes MYL4 (e.g., a polypeptide represented by UniProt Accession number P12829 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1099. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial septal defect 2 (ASD2) and/or wherein the heterologous nucleic acid sequence encodes GATA4 (e.g., a polypeptide represented by UniProt Accession number P43694 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1100. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial septal defect 3 (ASD3) and/or wherein the heterologous nucleic acid sequence encodes MYH6 (e.g., a polypeptide represented by UniProt Accession number P13533 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1101. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial septal defect 4 (ASD4) and/or wherein the heterologous nucleic acid sequence

encodes TBX20 (e.g., a polypeptide represented by UniProt Accession number Q9UMR3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1102. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial septal defect 5 (ASD5) and/or wherein the heterologous nucleic acid sequence encodes ACTC1 (e.g., a polypeptide represented by UniProt Accession number P68032 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1103. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial septal defect 6 (ASD6) and/or wherein the heterologous nucleic acid sequence encodes TLL1 (e.g., a polypeptide represented by UniProt Accession number O43897 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1104. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial septal defect 7 (ASD7) and/or wherein the heterologous nucleic acid sequence encodes NKX2-5 (e.g., a polypeptide represented by UniProt Accession number P52952 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1105. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial septal defect 8 (ASD8) and/or wherein the heterologous nucleic acid sequence encodes CITED2 (e.g., a polypeptide represented by UniProt Accession number Q99967 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1106. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial septal defect 9 (ASD9) and/or wherein the heterologous nucleic acid sequence encodes GATA6 (e.g., a polypeptide represented by UniProt Accession number Q92908 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1107. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial standstill 1 and/or wherein the heterologous nucleic acid sequence encodes GJA5 (e.g., a polypeptide represented by UniProt Accession number P36382 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1108. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Atrial standstill 2 and/or wherein the heterologous nucleic acid sequence encodes NPPA (e.g., a polypeptide represented by UniProt Accession number P01160 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1109. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Barth syndrome and/or wherein the heterologous nucleic acid sequence encodes TAFAZZIN (e.g., a polypeptide represented by UniProt Accession number Q16635 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1110. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Becker Muscular Dystrophy (BMD) and/or wherein the heterologous nucleic acid sequence encodes DMD (e.g., a polypeptide represented by UniProt Accession number P11532 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1111. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Brugada syndrome 1 and/or wherein the heterologous nucleic acid sequence encodes

SCN5A (e.g., a polypeptide represented by UniProt Accession number Q14524 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1112. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Brugada syndrome 2 and/or wherein the heterologous nucleic acid sequence encodes GPD1L (e.g., a polypeptide represented by UniProt Accession number Q8N335 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1113. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Brugada syndrome 3 and/or wherein the heterologous nucleic acid sequence encodes CACNA1C (e.g., a polypeptide represented by UniProt Accession number Q13936 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1114. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Brugada syndrome 4 and/or wherein the heterologous nucleic acid sequence encodes CACNB2 (e.g., a polypeptide represented by UniProt Accession number Q08289 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1115. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Brugada syndrome 5 and/or wherein the heterologous nucleic acid sequence encodes SCN1B (e.g., a polypeptide represented by UniProt Accession number Q07699 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1116. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Brugada syndrome 6 and/or wherein the heterologous nucleic acid sequence encodes KCNE3 (e.g., a polypeptide represented by UniProt Accession number Q9Y6H6 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1117. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Brugada syndrome 7 and/or wherein the heterologous nucleic acid sequence encodes SCN3B (e.g., a polypeptide represented by UniProt Accession number Q9NY72 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1118. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Brugada syndrome 8 and/or wherein the heterologous nucleic acid sequence encodes HCN4 (e.g., a polypeptide represented by UniProt Accession number Q9Y3Q4 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1119. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Brugada syndrome 9 and/or wherein the heterologous nucleic acid sequence encodes KCND3 (e.g., a polypeptide represented by UniProt Accession number Q9UK17 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1120. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiac arrhythmia syndrome and/or wherein the heterologous nucleic acid sequence encodes TRDN (e.g., a polypeptide represented by UniProt Accession number Q13061 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1121. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiac conduct defect and/or wherein the heterologous nucleic acid sequence encodes

AKAP10 (e.g., a polypeptide represented by UniProt Accession number O43572 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1122. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiac conduction disease and/or wherein the heterologous nucleic acid sequence encodes TNNI3K (e.g., a polypeptide represented by UniProt Accession number Q59H18 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1123. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiac, facial, and digital anomalies with developmental delay (CAFDADD) and/or wherein the heterologous nucleic acid sequence encodes TRAF7 (e.g., a polypeptide represented by UniProt Accession number Q6Q0C0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1124. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiofaciocutaneous syndrome 1 and/or wherein the heterologous nucleic acid sequence encodes BRAF (e.g., a polypeptide represented by UniProt Accession number P15056 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1125. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiofaciocutaneous syndrome 2 and/or wherein the heterologous nucleic acid sequence encodes KRAS (e.g., a polypeptide represented by UniProt Accession number P01116 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1126. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiofaciocutaneous syndrome 3 and/or wherein the heterologous nucleic acid sequence encodes MAP2K1 (e.g., a polypeptide represented by UniProt Accession number Q02750 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1127. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiofaciocutaneous syndrome 4 and/or wherein the heterologous nucleic acid sequence encodes MAP2K2 (e.g., a polypeptide represented by UniProt Accession number P36507 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1128. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiac-urogenital syndrome and/or wherein the heterologous nucleic acid sequence encodes MYRF (e.g., a polypeptide represented by UniProt Accession number Q9Y2G1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1129. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiac valvular dysplasia, X-linked and/or wherein the heterologous nucleic acid sequence encodes FLNA (e.g., a polypeptide represented by UniProt Accession number P21333 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1130. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiac valvular dysplasia 2 and/or wherein the heterologous nucleic acid sequence encodes ADAMTS19 (e.g., a polypeptide represented by UniProt Accession number Q8TE59 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1131. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 1A and/or wherein the heterologous nucleic acid sequence encodes LMNA (e.g., a polypeptide represented by UniProt Accession number P02545 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1132. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 1AA and/or wherein the heterologous nucleic acid sequence encodes ACTN2 (e.g., a polypeptide represented by UniProt Accession number P35609 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1133. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 1C and/or wherein the heterologous nucleic acid sequence encodes LDB3 (e.g., a polypeptide represented by UniProt Accession number O75112 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1134. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 1D and/or wherein the heterologous nucleic acid sequence encodes TNNT2 (e.g., a polypeptide represented by UniProt Accession number P45379 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1135. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 1E and/or wherein the heterologous nucleic acid sequence encodes SCN5A (e.g., a polypeptide represented by UniProt Accession number Q14524 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1136. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 1FF and/or wherein the heterologous nucleic acid sequence encodes TNNI3 (e.g., a polypeptide represented by UniProt Accession number P19429 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1137. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 1FF and/or wherein the heterologous nucleic acid sequence encodes MYPN (e.g., a polypeptide represented by UniProt Accession number Q86TC9 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1138. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 1MM and/or wherein the heterologous nucleic acid sequence encodes MYBPC3 (e.g., a polypeptide represented by UniProt Accession number Q14896 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1139. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 1P and/or wherein the heterologous nucleic acid sequence encodes PLN (e.g., a polypeptide represented by UniProt Accession number P26678 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1140. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 1R and/or wherein the heterologous nucleic acid sequence encodes ACTC1 (e.g., a polypeptide represented by UniProt Accession number P68032 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1141. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 1S and/or wherein the heterologous nucleic acid sequence encodes MYH7 (e.g., a polypeptide represented by UniProt Accession number P12883 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1142. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 1Y and/or wherein the heterologous nucleic acid sequence encodes TPM1 (e.g., a polypeptide represented by UniProt Accession number P09493 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1143. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 2A and/or wherein the heterologous nucleic acid sequence encodes TNNI3 (e.g., a polypeptide represented by UniProt Accession number P19429 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1144. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, dilated, 2E and/or wherein the heterologous nucleic acid sequence encodes JPH2 (e.g., a polypeptide represented by UniProt Accession number Q9BR39 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1145. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, familial restrictive, 1 and/or wherein the heterologous nucleic acid sequence encodes TNNI3 (e.g., a polypeptide represented by UniProt Accession number P19429 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1146. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, familial restrictive, 3 and/or wherein the heterologous nucleic acid sequence encodes TNNT2 (e.g., a polypeptide represented by UniProt Accession number P45379 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1147. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 1 (CMH1) and/or wherein the heterologous nucleic acid sequence encodes MYH7 (e.g., a polypeptide represented by UniProt Accession number P12883 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1148. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 1 (CMH1) and/or wherein the heterologous nucleic acid sequence encodes CAV3 (e.g., a polypeptide represented by UniProt Accession number P56539 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1149. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 1 (CMH1) and/or wherein the heterologous nucleic acid sequence encodes MYLK2 (e.g., a polypeptide represented by UniProt Accession number or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1150. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 2 (CMH2) and/or wherein the heterologous nucleic acid sequence encodes TNNT2 (e.g., a polypeptide represented by UniProt Accession number P45379 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1151. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 3 (CMH3) and/or wherein the heterologous nucleic acid sequence encodes TPM1 (e.g., a polypeptide represented by UniProt Accession number P09493 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1152. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic 4 (CMH4) and/or wherein the heterologous nucleic acid sequence encodes MYBPC3 (e.g., a polypeptide represented by UniProt Accession number Q14896 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1153. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic 6 (CMH6) and/or wherein the heterologous nucleic acid sequence encodes PRKAG2 (e.g., a polypeptide represented by UniProt Accession number Q9UGJ0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1154. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 7 (CMH7) and/or wherein the heterologous nucleic acid sequence encodes TNNI3 (e.g., a polypeptide represented by UniProt Accession number P19429 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1155. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 8 (CMH8) and/or wherein the heterologous nucleic acid sequence encodes MYL3 (e.g., a polypeptide represented by UniProt Accession number P08590 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1156. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 9 (CMH9) and/or wherein the heterologous nucleic acid sequence encodes TTN (e.g., a polypeptide represented by UniProt Accession number Q8WZ42 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1157. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 10 (CMH10) and/or wherein the heterologous nucleic acid sequence encodes MYL2 (e.g., a polypeptide represented by UniProt Accession number P10916 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1158. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 11 (CMH11) and/or wherein the heterologous nucleic acid sequence encodes ACTC1 (e.g., a polypeptide represented by UniProt Accession number P68032 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1159. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 12 (CMH12) and/or wherein the heterologous nucleic acid sequence encodes CSRP3 (e.g., a polypeptide represented by UniProt Accession number P50461 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1160. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 13 (CMH13) and/or wherein the heterologous nucleic acid sequence encodes TNNC1 (e.g., a polypeptide represented by UniProt Accession number P63316 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1161. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 14 (CMH14) and/or wherein the heterologous nucleic acid sequence encodes MYH6 (e.g., a polypeptide represented by UniProt Accession number P13533 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1162. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 15 (CMH15) and/or wherein the heterologous nucleic acid sequence encodes VCL (e.g., a polypeptide represented by UniProt Accession number P18206 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1163. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 16 (CMH16) and/or wherein the heterologous nucleic acid sequence encodes MYOZ2 (e.g., a polypeptide represented by UniProt Accession number Q9NPC6 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1164. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 17 (CMH17) and/or wherein the heterologous nucleic acid sequence encodes JPH2 (e.g., a polypeptide represented by UniProt Accession number Q9BR39 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1165. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 18 (CMH18) and/or wherein the heterologous nucleic acid sequence encodes PLN (e.g., a polypeptide represented by UniProt Accession number P26678 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1166. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 20 (CMH20) and/or wherein the heterologous nucleic acid sequence encodes NEXN (e.g., a polypeptide represented by UniProt Accession number Q0ZGT2 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1167. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 23 (CMH23) and/or wherein the heterologous nucleic acid sequence encodes ACTN2 (e.g., a polypeptide represented by UniProt Accession number P35609 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1168. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 25 (CMH25) and/or wherein the heterologous nucleic acid sequence encodes TCAP (e.g., a polypeptide represented by UniProt Accession number O15273 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1169. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 26 (CMH26) and/or wherein the heterologous nucleic acid sequence encodes FLNC (e.g., a polypeptide represented by UniProt Accession number Q14315 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1170. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 27 (CMH27) and/or wherein the heterologous nucleic acid sequence encodes ALPK3 (e.g., a polypeptide represented by UniProt Accession number Q96L96 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1171. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 28 (CMH28) and/or wherein the heterologous nucleic acid sequence encodes FHOD3 (e.g., a polypeptide represented by UniProt Accession number Q2V2M9 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1172. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, hypertrophic, 29 (CMH29) and/or wherein the heterologous nucleic acid sequence encodes KLHL24 (e.g., a polypeptide represented by UniProt Accession number Q6TFL4 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1173. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, restrictive 1 (RCM1) and/or wherein the heterologous nucleic acid sequence encodes TNNI3 (e.g., a polypeptide represented by UniProt Accession number P19429 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1174. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, restrictive 3 (RCM3) and/or wherein the heterologous nucleic acid sequence encodes TNNT2 (e.g., a polypeptide represented by UniProt Accession number P45379 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1175. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, restrictive 4 (RCM4) and/or wherein the heterologous nucleic acid sequence encodes MYPN (e.g., a polypeptide represented by UniProt Accession number Q86TC9 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1176. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, restrictive 5 (RCM5) and/or wherein the heterologous nucleic acid sequence encodes FLNC (e.g., a polypeptide represented by UniProt Accession number Q14315 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1177. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cardiomyopathy, restrictive 6 (RCM6) and/or wherein the heterologous nucleic acid sequence encodes KIF20A (e.g., a polypeptide represented by UniProt Accession number O95235 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1178. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Carnitine Deficiency, systemic primary and/or wherein the heterologous nucleic acid sequence encodes SLC22A5 (e.g., a polypeptide represented by UniProt Accession number O76082 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1179. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Catecholaminergic polymorphic ventricular tachycardia 2 (CPVT2) and/or wherein the heterologous nucleic acid sequence encodes Calsequestrin-2 (CASQ2) (e.g., a polypeptide represented by UniProt Accession number O14958 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1180. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Combined oxidative phosphorylation deficiency 8 and/or wherein the heterologous nucleic

acid sequence encodes AARS2 (e.g., a polypeptide represented by UniProt Accession number Q5JTZ9 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1181. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Combined oxidative phosphorylation deficiency 10 and/or wherein the heterologous nucleic acid sequence encodes MTO1 (e.g., a polypeptide represented by UniProt Accession number Q9Y2Z2 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1182. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Congenital Myopathy and/or wherein the heterologous nucleic acid sequence encodes ACTA1 (e.g., a polypeptide represented by UniProt Accession number P68133 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1183. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Congenital Myopathy and/or wherein the heterologous nucleic acid sequence encodes STAC3 (e.g., a polypeptide represented by UniProt Accession number Q96MF2 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1184. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Congenital Myopathy and/or wherein the heterologous nucleic acid sequence encodes TPM3 (e.g., a polypeptide represented by UniProt Accession number P06753 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1185. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Congenital Myotonic Dystrophy and/or wherein the heterologous nucleic acid sequence encodes DMPK (e.g., a polypeptide represented by UniProt Accession number Q09013 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1186. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Conotruncal heart malformations and/or wherein the heterologous nucleic acid sequence encodes NKX2-5 (e.g., a polypeptide represented by UniProt Accession number P52952 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1187. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Conotruncal heart malformations and/or wherein the heterologous nucleic acid sequence encodes NKX2-6 (e.g., a polypeptide represented by UniProt Accession number A6NCS4 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1188. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Conotruncal heart malformations and/or wherein the heterologous nucleic acid sequence encodes TBX1 (e.g., a polypeptide represented by UniProt Accession number O43435 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1189. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Conotruncal heart malformations and/or wherein the heterologous nucleic acid sequence encodes GATA6 (e.g., a polypeptide represented by UniProt Accession number Q92908 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1190. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Coronary artery disease 1 and/or wherein the heterologous nucleic acid sequence encodes

MEF2A (e.g., a polypeptide represented by UniProt Accession number Q02078 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1191. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Coronary artery disease 2 and/or wherein the heterologous nucleic acid sequence encodes LRP6 (e.g., a polypeptide represented by UniProt Accession number O75581 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1192. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Cori Disease - Debrancher Enzyme Deficiency – Forbes Disease and/or wherein the heterologous nucleic acid sequence encodes AGL (e.g., a polypeptide represented by UniProt Accession number P35573 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1193. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Costello syndrome and/or wherein the heterologous nucleic acid sequence encodes HRAS (e.g., a polypeptide represented by UniProt Accession number P01112 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1194. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Danon disease and/or wherein the heterologous nucleic acid sequence encodes LAMP2 (e.g., a polypeptide represented by UniProt Accession number P13473 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1195. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Dextrocardia with other cardiac malformations, x-linked (visceral heterotaxy (HTX1)) and/or wherein the heterologous nucleic acid sequence encodes ZIC3 (e.g., a polypeptide represented by UniProt Accession number O60481 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1196. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Dilated Cardiomyopathy and/or wherein the heterologous nucleic acid sequence encodes BAG3 (e.g., a polypeptide represented by UniProt Accession number O95817 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1197. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Duchenne Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes Dystrophin (DMD) (e.g., a polypeptide represented by UniProt Accession number P11532 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1198. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Duchenne Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes B4GALNT2 (e.g., a polypeptide represented by UniProt Accession number Q8NHY0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1199. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Ehlers-Danlos syndrome, cardiac valvular type and/or wherein the heterologous nucleic acid sequence encodes COL1A2 (e.g., a polypeptide represented by UniProt Accession number P08123 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1200. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Emery-Dreifuss Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes EMD (e.g., a polypeptide represented by UniProt Accession number P50402 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1201. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Emery-Dreifuss Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes SYNE1 (e.g., a polypeptide represented by UniProt Accession number Q8NF91 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1202. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Emery-Dreifuss Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes SYNE2 (e.g., a polypeptide represented by UniProt Accession number Q8WXH0 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1203. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Emery-Dreifuss Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes TMEM43 (e.g., a polypeptide represented by UniProt Accession number Q9BTV4 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1204. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Emery-Dreifuss Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes LMNA (e.g., a polypeptide represented by UniProt Accession number P02545 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1205. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Fabry disease, cardiac variant and/or wherein the heterologous nucleic acid sequence encodes GLA (e.g., a polypeptide represented by UniProt Accession number P06280 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1206. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Frank-ter Haar syndrome and/or wherein the heterologous nucleic acid sequence encodes SH3PXD2B (e.g., a polypeptide represented by UniProt Accession number A1X283 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1207. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Friedreich's ataxia and/or wherein the heterologous nucleic acid sequence encodes Frataxin (FXN) (e.g., a polypeptide represented by UniProt Accession number Q16595 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1208. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Fukuyama Congenital Muscular Dystrophy and/or wherein the heterologous nucleic acid sequence encodes FKTN (e.g., a polypeptide represented by UniProt Accession number O75072 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1209. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Glycogen storage disease III and/or wherein the heterologous nucleic acid sequence encodes AGL (e.g., a polypeptide represented by UniProt Accession number P35573 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1210. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is GM1-gangliosidosis, type I with cardiac involvement and/or wherein the heterologous nucleic acid sequence encodes GLB1 (e.g., a polypeptide represented by UniProt Accession number P16278 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1211. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Heart failure and/or wherein the heterologous nucleic acid sequence encodes SOD3 (e.g., a polypeptide represented by UniProt Accession number P08294 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1212. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Hirschsprung disease (HCAD) and/or wherein the heterologous nucleic acid sequence encodes ECE1 (e.g., a polypeptide represented by UniProt Accession number P42892 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1213. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Infantile hypertrophic cardiomyopathy and/or wherein the heterologous nucleic acid sequence encodes MTATP6 (e.g., a polypeptide represented by UniProt Accession number P00846 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1214. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Infantile hypertrophic cardiomyopathy and/or wherein the heterologous nucleic acid sequence encodes MTATP8 (e.g., a polypeptide represented by UniProt Accession number P03928 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1215. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Ischemia-reperfusion injury and/or wherein the heterologous nucleic acid sequence encodes SOD3 (e.g., a polypeptide represented by UniProt Accession number P08294 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1216. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Ischemia-reperfusion injury and/or wherein the heterologous nucleic acid sequence encodes YY1 (e.g., a polypeptide represented by UniProt Accession number P25490 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1217. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Ischemia-reperfusion injury and/or wherein the heterologous nucleic acid sequence encodes BMP7 (e.g., a polypeptide represented by UniProt Accession number P18075 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1218. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Jervell and Lange-Nielsen syndrome (JLNS1) and/or wherein the heterologous nucleic acid sequence encodes KCNQ1 (e.g., a polypeptide represented by UniProt Accession number P51787 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1219. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Jervell and Lange-Nielsen syndrome 2 (JLNS2) and/or wherein the heterologous nucleic acid sequence encodes KCNE1 (e.g., a polypeptide represented by UniProt Accession number P15382 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1220. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Laing Distal Myopathy and/or wherein the heterologous nucleic acid sequence encodes MYH7 (e.g., a polypeptide represented by UniProt Accession number P12883 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1221. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Left ventricular noncompaction 1 (LVNC1) and/or wherein the heterologous nucleic acid sequence encodes DTNA (e.g., a polypeptide represented by UniProt Accession number or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1222. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Left ventricular noncompaction 3 (LVNC3) and/or wherein the heterologous nucleic acid sequence encodes LDB3 (e.g., a polypeptide represented by UniProt Accession number O75112 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1223. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Left ventricular noncompaction 4 (LVNC4) and/or wherein the heterologous nucleic acid sequence encodes ACTC1 (e.g., a polypeptide represented by UniProt Accession number P68032 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1224. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Left ventricular noncompaction 5 (LVNC5) and/or wherein the heterologous nucleic acid sequence encodes MYH7 (e.g., a polypeptide represented by UniProt Accession number P12883 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1225. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Left ventricular noncompaction 6 (LVNC6) and/or wherein the heterologous nucleic acid sequence encodes TNNT2 (e.g., a polypeptide represented by UniProt Accession number P45379 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1226. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Left ventricular noncompaction 7 (LVNC7) and/or wherein the heterologous nucleic acid sequence encodes MIB1 (e.g., a polypeptide represented by UniProt Accession number Q86YT6 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1227. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Left ventricular noncompaction 8 (LVNC8) and/or wherein the heterologous nucleic acid sequence encodes PRDM16 (e.g., a polypeptide represented by UniProt Accession number Q9HAZ2 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1228. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Left ventricular noncompaction 9 (LVNC9) and/or wherein the heterologous nucleic acid sequence encodes TPM1 (e.g., a polypeptide represented by UniProt Accession number P09493 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1229. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Left ventricular noncompaction 10 (LVNC10) and/or wherein the heterologous nucleic acid sequence encodes MYBPC3 (e.g., a polypeptide represented by UniProt Accession number Q14896 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1230. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is LEOPARD syndrome 1 and/or wherein the heterologous nucleic acid sequence encodes PTPN11 (e.g., a polypeptide represented by UniProt Accession number Q06124 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1231. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is LEOPARD syndrome 2 and/or wherein the heterologous nucleic acid sequence encodes RAF1 (e.g., a polypeptide represented by UniProt Accession number P04049 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1232. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is LEOPARD syndrome 3 and/or wherein the heterologous nucleic acid sequence encodes BRAF (e.g., a polypeptide represented by UniProt Accession number P15056 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1233. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Limb-girdle muscular dystrophy, type 25 (LGMDR25) and/or wherein the heterologous nucleic acid sequence encodes BVES (e.g., a polypeptide represented by UniProt Accession number Q8NE79 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1234. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Lodder-Merla syndrome, type 1 and/or wherein the heterologous nucleic acid sequence encodes GNB5 (e.g., a polypeptide represented by UniProt Accession number O14775 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1235. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 1 and/or wherein the heterologous nucleic acid sequence encodes KCNQ1 (e.g., a polypeptide represented by UniProt Accession number P51787 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1236. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 2 and/or wherein the heterologous nucleic acid sequence encodes KCNH2, ERG (e.g., a polypeptide represented by UniProt Accession number Q12809 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1237. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 3 and/or wherein the heterologous nucleic acid sequence encodes SCN5A (e.g., a polypeptide represented by UniProt Accession number Q14524 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1238. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 4 and/or wherein the heterologous nucleic acid sequence encodes ANK2 (e.g., a polypeptide represented by UniProt Accession number Q01484 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1239. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 5 and/or wherein the heterologous nucleic acid sequence encodes

KCNE1 (e.g., a polypeptide represented by UniProt Accession number P15382 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1240. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 6 and/or wherein the heterologous nucleic acid sequence encodes KCNE2 (e.g., a polypeptide represented by UniProt Accession number Q9Y6J6 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1241. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 7 (Andersen syndrome) and/or wherein the heterologous nucleic acid sequence encodes KCNJ2 (e.g., a polypeptide represented by UniProt Accession number P63252 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1242. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 8 and/or wherein the heterologous nucleic acid sequence encodes CACNA1C (e.g., a polypeptide represented by UniProt Accession number Q13936 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1243. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 9 and/or wherein the heterologous nucleic acid sequence encodes CAV3 (e.g., a polypeptide represented by UniProt Accession number P56539 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1244. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 10 and/or wherein the heterologous nucleic acid sequence encodes SCN4B (e.g., a polypeptide represented by UniProt Accession number Q8IWT1 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1245. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 11 and/or wherein the heterologous nucleic acid sequence encodes AKAP9 (e.g., a polypeptide represented by UniProt Accession number Q99996 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1246. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 12 and/or wherein the heterologous nucleic acid sequence encodes SNTA1 (e.g., a polypeptide represented by UniProt Accession number Q13424 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1247. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 13 and/or wherein the heterologous nucleic acid sequence encodes KCNJ5 (e.g., a polypeptide represented by UniProt Accession number P48544 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1248. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 14 and/or wherein the heterologous nucleic acid sequence encodes CALM1 (e.g., a polypeptide represented by UniProt Accession number P0DP23 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1249. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 15 and/or wherein the heterologous nucleic acid sequence encodes

CALM2 (e.g., a polypeptide represented by UniProt Accession number P0DP24 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1250. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Long QT syndrome 16 and/or wherein the heterologous nucleic acid sequence encodes CALM3 (e.g., a polypeptide represented by UniProt Accession number P0DP25 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1251. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Metabolic encephalomyopathic crises (MECRCN) and/or wherein the heterologous nucleic acid sequence encodes TANGO2 (e.g., a polypeptide represented by UniProt Accession number Q6ICL3 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1252. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Microphthalmia, syndromic, type 9 and/or wherein the heterologous nucleic acid sequence encodes STRA6 (e.g., a polypeptide represented by UniProt Accession number Q9BX79 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1253. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Mitochondrial phosphate carrier deficiency (MPCD) and/or wherein the heterologous nucleic acid sequence encodes SLC25A3 (e.g., a polypeptide represented by UniProt Accession number Q00325 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1254. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Mitral valve prolapse 3 (MVP3) and/or wherein the heterologous nucleic acid sequence encodes DZIP1 (e.g., a polypeptide represented by UniProt Accession number Q86YF9 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1255. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Mungan syndrome (MGS) and/or wherein the heterologous nucleic acid sequence encodes RAD21 (e.g., a polypeptide represented by UniProt Accession number O60216 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1256. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Myocardial infarction and/or wherein the heterologous nucleic acid sequence encodes SOD3 (e.g., a polypeptide represented by UniProt Accession number P08294 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1257. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Myocardial infarction and/or wherein the heterologous nucleic acid sequence encodes CDK9 (e.g., a polypeptide represented by UniProt Accession number P50750 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1258. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Myofibrillar Myopathy 1 and/or wherein the heterologous nucleic acid sequence encodes DES (e.g., a polypeptide represented by UniProt Accession number P17661 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1259. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Myofibrillar Myopathy 2 and/or wherein the heterologous nucleic acid sequence encodes CRYAB (e.g., a polypeptide represented by UniProt Accession number P02511 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1260. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Myofibrillar Myopathy 6 and/or wherein the heterologous nucleic acid sequence encodes BAG3 (e.g., a polypeptide represented by UniProt Accession number O95817 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1261. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Myofibrillar Myopathy 10 and/or wherein the heterologous nucleic acid sequence encodes SVIL (e.g., a polypeptide represented by UniProt Accession number O95425 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1262. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Myofibrillar Myopathy 11 and/or wherein the heterologous nucleic acid sequence encodes UNC45B (e.g., a polypeptide represented by UniProt Accession number Q8IWX7 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1263. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Myofibrillar Myopathy 12 and/or wherein the heterologous nucleic acid sequence encodes MYL2 (e.g., a polypeptide represented by UniProt Accession number P10916 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1264. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Myotonic dystrophy Type 1 - Steinert Disease and/or wherein the heterologous nucleic acid sequence encodes Myotonin-protein kinase (DMPK) (e.g., a polypeptide represented by UniProt Accession number Q09013 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1265. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Myotonic dystrophy Type 2 and/or wherein the heterologous nucleic acid sequence encodes CNBP (e.g., a polypeptide represented by UniProt Accession number P62633 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1266. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Naxos disease (NXD) and/or wherein the heterologous nucleic acid sequence encodes JUP (e.g., a polypeptide represented by UniProt Accession number P14923 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1267. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Nemaline Myopathy 1 and/or wherein the heterologous nucleic acid sequence encodes TPM3 (e.g., a polypeptide represented by UniProt Accession number P06753 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1268. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Nemaline Myopathy 3 and/or wherein the heterologous nucleic acid sequence encodes

ACTA1 (e.g., a polypeptide represented by UniProt Accession number P68133 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1269. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Nonprogressive hear block and/or wherein the heterologous nucleic acid sequence encodes SCN5A (e.g., a polypeptide represented by UniProt Accession number Q14524 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1270. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Orthostatic intolerance (soldiers heart) and/or wherein the heterologous nucleic acid sequence encodes SLC6A2 (e.g., a polypeptide represented by UniProt Accession number P23975 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1271. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Progeria syndrome and/or wherein the heterologous nucleic acid sequence encodes LMNA (e.g., a polypeptide represented by UniProt Accession number P02545 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1272. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Progressive familial heart block type IA and/or wherein the heterologous nucleic acid sequence encodes SCN5A (e.g., a polypeptide represented by UniProt Accession number Q14524 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1273. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Progressive familial heart block type IB and/or wherein the heterologous nucleic acid sequence encodes TRPM4 (e.g., a polypeptide represented by UniProt Accession number Q8TD43 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1274. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is RYR2 calcium release deficiency syndrome and/or wherein the heterologous nucleic acid sequence encodes RYR2 (e.g., a polypeptide represented by UniProt Accession number Q92736 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1275. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Sengers syndrome and/or wherein the heterologous nucleic acid sequence encodes AGK (e.g., a polypeptide represented by UniProt Accession number Q53H12 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1276. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Sick sinus syndrome 1 (SSS1) and/or wherein the heterologous nucleic acid sequence encodes SCN5A (e.g., a polypeptide represented by UniProt Accession number Q14524 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1277. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Sick sinus syndrome 2 (SSS2) and/or wherein the heterologous nucleic acid sequence encodes HCN4 (e.g., a polypeptide represented by UniProt Accession number Q9Y3Q4 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1278. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Sick sinus syndrome 3 (SSS3) and/or wherein the heterologous nucleic acid sequence

encodes MYH6 (e.g., a polypeptide represented by UniProt Accession number P13533 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1279. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Sick sinus syndrome 4 (SSS4) and/or wherein the heterologous nucleic acid sequence encodes GNB2 (e.g., a polypeptide represented by UniProt Accession number P62879 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1280. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Sudden cardiac failure, infantile (SCFI) and/or wherein the heterologous nucleic acid sequence encodes PPA2 (e.g., a polypeptide represented by UniProt Accession number Q9H2U2 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1281. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is TARP syndrome and/or wherein the heterologous nucleic acid sequence encodes RBM10 (e.g., a polypeptide represented by UniProt Accession number P98175 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1282. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Timothy syndrome and/or wherein the heterologous nucleic acid sequence encodes CACNA1C (e.g., a polypeptide represented by UniProt Accession number Q13936 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1283. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Valvular heart disease, congenital and/or wherein the heterologous nucleic acid sequence encodes FLNA (e.g., a polypeptide represented by UniProt Accession number P21333 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1284. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Ventricular fibrillation 1 (VF1) and/or wherein the heterologous nucleic acid sequence encodes SCN5A (e.g., a polypeptide represented by UniProt Accession number Q14524 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1285. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Ventricular tachycardia and/or wherein the heterologous nucleic acid sequence encodes CASQ2 (e.g., a polypeptide represented by UniProt Accession number O14958 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1286. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Vertebral, cardiac, renal, and limb defects syndrome 1 (VCRL1) and/or wherein the heterologous nucleic acid sequence encodes HAAO (e.g., a polypeptide represented by UniProt Accession number P46952 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1287. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Vertebral, cardiac, renal, and limb defects syndrome 2 (VCRL2) and/or wherein the heterologous nucleic acid sequence encodes KYNU (e.g., a polypeptide represented by UniProt Accession number Q16719 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1288. The method of any one of embodiments 190, 191, 1070, and 1071, wherein the disease or condition is Vertebral, cardiac, renal, and limb defects syndrome 3 (VCRL3) and/or wherein the heterologous nucleic acid sequence encodes NADSYN1 (e.g., a polypeptide represented by UniProt Accession number Q6IA69 or a polypeptide comprising an amino acid sequence having at least 95% sequence identity thereto).

1289. The method of any one of embodiments 190 to 192, wherein the disease or condition is a disease or condition identified in Section 6.6, 6.6.1, or 6.6.2 and/or wherein the heterologous nucleic acid sequence encodes a protein identified in Section 6.6, 6.6.1, or 6.6.2.

1290. The method of any one of embodiments 189 to 1289, wherein the subject is a mammal, *e.g.*, a human.

1291. A cell, cell-free system, or other translation system, comprising the capsid polypeptide of any one of embodiments 1 to 130, the nucleic acid molecule of any one of embodiments 131 to 150, or virus particle of any one of embodiments 151 to 188.

1292. A method of making a virus (*e.g.*, a dependoparvovirus particle such as an adeno-associated virus (AAV) particle), comprising:

(a) providing a cell, cell-free system, or other translation system, comprising the nucleic acid molecule of any one of embodiments 131 to 150; and

(b) cultivating the cell, cell-free system, or other translation system, under conditions suitable for the production of the virus particle,

(c) thereby making the virus particle.

1293. The method of embodiment 1292, wherein the cell, cell-free system, or other translation system comprises a second nucleic acid molecule and at least a portion of said second nucleic acid molecule is packaged in the dependoparvovirus particle.

1294. The method of embodiment 1293, wherein the second nucleic acid molecule comprises a payload, *e.g.*, a heterologous nucleic acid sequence encoding a therapeutic product, *e.g.*, as described herein.

1295. The method of any one of embodiments 1292 to 1294, wherein the nucleic acid molecule of any one of embodiments 131 to 150 mediates the production of a virus particle which does not include said nucleic acid molecule of any one of embodiments 131 to 150 or fragment thereof.

1296. The method of any one of embodiments 1292 to 1295, wherein the nucleic acid molecule of any one of embodiments 131 to 150 mediates the production of a virus particle at a level similar, or at least 10% greater than the production level mediated by a nucleic acid comprising SEQ ID NO:2 in an otherwise similar production system.

1297. In a method of making a virus (*e.g.*, a dependoparvovirus particle such as an adeno-associated virus (AAV) particle) that comprises providing a cell, cell-free system, or other translation system comprising a nucleic acid molecule encoding a capsid polypeptide; and cultivating the cell, cell-free system, or other translation system under conditions suitable for the production of the virus particle, the improvement comprising utilizing a nucleic acid molecule encoding a capsid polypeptide comprising:

(a) a threonine at a position corresponding to Q579 of the VP1 capsid polypeptide of SEQ ID NO:1;

(b) a valine at a position corresponding to Q592 of the VP1 capsid polypeptide of SEQ ID NO:1;

(c) an alanine at a position corresponding to T593 of the VP1 capsid polypeptide of SEQ ID NO:1;

(d) an alanine at a position corresponding to W595 of the VP1 capsid polypeptide of SEQ ID NO:1;

(e) a leucine at a position corresponding to V596 of the VP1 capsid polypeptide of SEQ ID NO:1;

(f) a serine at a position corresponding to N598 of the VP1 capsid polypeptide of SEQ ID NO:1; and

(g) an alanine at a position corresponding to I601 of the VP1 capsid polypeptide of SEQ ID NO:1.

1298. The method of embodiment 1297, wherein the cell, cell-free system, or other translation system comprises a second nucleic acid molecule and at least a portion of said second nucleic acid molecule is packaged in the dependoparvovirus particle.

1299. The method of embodiment 1298, wherein the second nucleic acid molecule comprises a payload, *e.g.*, a heterologous nucleic acid sequence encoding a therapeutic product, *e.g.*, as described herein.

1300. The method of any one of embodiments 1297 to 1299, wherein the nucleic acid molecule encoding the capsid polypeptide mediates the production of a virus particle which does not include said nucleic acid molecule encoding the capsid polypeptide or fragment thereof.

1301. The method of any one of embodiments 1297 to 1300, wherein the nucleic acid molecule encoding the capsid polypeptide mediates the production of a virus particle at a level similar, or at least 10% greater than the production level mediated by a nucleic acid molecule comprising SEQ ID NO:2 in an otherwise similar production system.

1302. A composition, *e.g.*, a pharmaceutical composition, comprising a virus particle of any one of embodiments 151 to 188, or a virus particle produced by the method of any one of embodiments 1292 to 1301, and a pharmaceutically acceptable carrier or excipient.

1303. The capsid polypeptide of any one of embodiments 1 to 130, the nucleic acid molecule of any one of embodiments 131 to 150, the virus particle of any one of embodiments 151 to 188, or the composition of embodiment 1302, for use in treating a disease or condition in a subject, optionally wherein (a) the subject is as defined in embodiment 1290 and/or (b) the disease or condition is as defined in any one of embodiments 189 to 1288.

1304. The capsid polypeptide of any one of embodiments 1 to 130, the nucleic acid molecule of any one of embodiments 131 to 150, or the virus particle of any one of embodiments 151 to 188, or the composition of embodiment 1302, for use in the manufacture of a medicament for use in treating a disease or condition in a subject, optionally wherein (a) the subject is as defined in embodiment 1290 and/or (b) the disease or condition is as defined in any one of embodiments 189 to 1288.

1305. A host cell comprising the nucleic acid of any one of embodiments 131 to 150.

1306. The host cell of embodiment 1305, wherein the host cell comprises a nucleic acid encoding a rep protein.

1307. The host cell of embodiment 1305 or 1306, wherein the host cell comprises a nucleic acid encoding a cap protein.

1308. The host cell of any one of embodiments 1305 to 1307, wherein the host cell comprises a nucleic acid comprising one or more helper sequences.

1309. The host cell of any one of embodiments 1305 to 1308, wherein the host cell comprises a nucleic acid comprising a payload, *e.g.*, a heterologous nucleic acid sequence encoding a therapeutic product, *e.g.*, as described herein.

1310. The host cell of any one of embodiments 1305 to 1309, which is a mammalian host cell.

1311. The host cell of embodiment 1310, which is a human host cell.

1312. The host cell of any one of embodiments 1305 to 1309, which is an insect host cell.

1313. The host cell of any one of embodiments 1305 to 1312, wherein the host cell is selected from cell types described in Section 6.5.

1314. The host cell of any one of embodiments 1305 to 1313, which is a packaging host cell.

1315. The host cell of embodiment 1314, which is configured to package a virus (a) according to any one of embodiments 151 to 188 and/or (b) useful for performing a method according to any one of embodiments 189 to 1290.

1316. The method of any one of embodiments 1292 to 1301, wherein the cell is a host cell according to any one of embodiments 1305 to 1315.

8. EXAMPLES

8.1. Example 1: *In vivo* Evaluation of Capsid Library in Non-Human Primate (NHP)

8.1.1. Materials and Methods

8.1.1.1. Variant Selection

[0282] A library of variants was created utilizing multiple sets of strategies of design and selection. The main objectives were to develop capsids capable of packaging into AAV particles efficiently, transducing central nervous system tissues effectively after intravenous administration, and detargeting the liver and other tissue types. The first set of variants were selected from internal data sets acquired from other non-human primate (NHP) experiments using either: (1) an algorithm that optimizes capsid performance while balancing sequence diversity and measurement uncertainty; (2) the reproducibility of capsid performance across brain regions; or (3) manual curation by examination of individual property performance and sequence diversity. The second set of variants were novel designs that utilized machine learning algorithms trained on extensive data from hundreds of thousands of capsid variants, focusing on optimizing capsid performance further while staying in distribution with respect to the original training set, as well as leveraging methods that exploit additivity observed in the fitness landscape. The study also included variants that contain stop codons in VP1 and VP2 as transduction negative controls (expected to produce virus but not transduce cells) and containing VP3 stop codons as production negative controls (not expected to produce virus). The study also included variants having WT-AAV9 capsid polypeptides as control.

8.1.1.2. Library Creation

[0283] The virus particles for the study, including Variant 1 ("V1"), having a VP1 polypeptide sequence as set forth in SEQ ID NO:12, were produced individually via separate transient triple transfection of adherent HEK293T cells followed by co-purification by iodixanol gradient. Each variant capsid was included in a virus particle that included a genome bearing identifying unique barcode sets of 8 as well as diverse random sequence IDs for quantification, providing a measure of biological replicates within the study. Each genome further contained a sequence encoding a fluorescent reporter gene under the control of a ubiquitous Cbh promoter.

[0284] The representation of each individual variant within the virus pool is measured via NGS via the unique barcode pools that are associated with each variant. Variants identified with low initial productivity yields were produced again individually in a separate production round and combined with virus from the previous productions to balance the representation of every variant to be within 10-fold range in the final test article. Final test article included each variant at an amount of 9e10-3e11 vg/kg in the IV test article, as measured by ddPCR for final titer and NGS analysis for variant representation. Production efficiencies for individual variants are calculated by NGS relative to production efficiency of wild-type AAV9 in each round of production. For variants that were produced in multiple rounds, production rates were calculated as a mean of production rates across rounds.

8.1.1.3. *In-vivo* Evaluation of Capsid Library in NHP

[0285] All NHP experiments were conducted in accordance with institutional policies and NIH guidelines. One young adult male and one adult female cynomolgus macaques (Macaca fascicularis) weighing 2.2-2.9 kg, seronegative for anti-AAV9 neutralizing antibodies (NAb) were selected for the study (seronegativity status being serum NAb titers < 1:4 based on in vitro NAb assay). Prior to test article administrations, samples of blood were collected. The animals were anesthetized with ketamine and xylazine and received an intravenous injection (doses: 1.22e13vg/kg. and 1.27e13vg/kg). During the in-life period the animals were monitored for signs of inflammation and were treated with weekly IM injections of steroids (methylprednisolone, 8 mg/kg), and dexamethasone as needed according to the animal facility's SOPs and recommendations from the veterinarian. Serum samples were collected at 1 h, 12 h and 24 h, 48 h, and weekly after the injections. The animals were sacrificed 4 weeks after the injections and tissues were collected for biodistribution and transduction analyses. The non-brain tissues collected are shown in Table 6A and the brain tissues collected are shown in Table 6B. Peripheral tissue samples were collected into RNAlater® (Sigma-Aldrich) and incubated overnight at 4°C, after which the RNAlater® was drained and samples were frozen at -80°C. The entire brain was sliced into 4mm coronal slabs using a chilled species-specific brain matrix. Slabs will be arranged in sequential order (rostral to caudal). Each slab was bisected into left and right hemispheres along the sagittal midline. The slabs from the right hemisphere were immersed in RNAlater®, drained and frozen as previously described. The left hemisphere slabs were sub-dissected for sub regions of the brain, placed into cryo tubes and immediately frozen on dry-ice.

Table 6A: List of Non-Brain Tissues Collected
Adipose tissue (abdominal, subcutaneous)
Aorta
Bone marrow, femur
Carotid artery (left)
Dorsal root ganglion: cervical (bilateral)

Table 6A: List of Non-Brain Tissues Collected
Dorsal root ganglion: thoracic (bilateral)
Dorsal root ganglion: lumbar (bilateral)
Dorsal root ganglion: sacral (bilateral)
Gland, adrenal
Gonad: testes or ovaries
Heart, atria (right)
Heart, apex
Heart, ventricle (left)
Kidney
Liver, right lateral lobe
Liver, left lateral lobe
Lung, cranial lobe (bilateral)
Lymph nodes, cervical
Nerve, sciatic (right)
Skeletal muscle, biceps brachii (bilateral)
Skeletal muscle, diaphragm
Skeletal muscle, gastrocnemius
Skeletal muscle, quadriceps (bilateral)
Spinal cord, cervical
Spinal cord, cranial thoracic
Spinal cord, caudal thoracic
Spinal cord, lumbar
Spleen

Table 6B: List of Brain Tissues Collected
Basal ganglia (caudate, globus pallidus, putamen)
Brainstem (medula, pons)
Cerebellum
Forebrain (frontal cortex, motor cortex)
Hippocampus
Midbrain
Parietal cortex
Substantia nigra
Temporal cortex
Thalamus

8.1.1.4. Bulk Sequencing NGS Library Preparation

[0286] Brain slices were dissected to isolate regions including, but not limited to, frontal cortex, temporal cortex, motor cortex, hippocampus, basal ganglia, midbrain, brainstem, and cerebellum. For all biodistribution and transduction analyses, total DNA and RNA was extracted from tissue samples with Trizol/chloroform using DNeasy Blood & Tissue kit (Qiagen) and RNeasy kit respectively. RNA was extracted from the upper aqueous phase using an RNeasy® (QIAGEN) kit according to the manufacturer's recommendations, and was further treated with Turbo™ DNase (Thermo Fisher Scientific) to remove any vector DNA contamination in the RNA sample. Reverse transcription was done with Protoscript® II Reverse Transcriptase (New England Biolabs) utilizing primers that were specific to the vector transgene and included unique molecular identifiers (UMIs). Control reactions lacking the reverse transcriptase enzyme (-RT control) were also prepared. Finally, samples were prepared for next-generation sequencing by amplifying the transgene barcode regions with primers compatible with Illumina NGS platform and sequenced with NextSeq™ 550 (Illumina).

8.1.1.5. Bulk Tissue NGS Sample Parsing and Analysis

[0287] After sequencing, the barcode tags were extracted from reads with the expected amplicon structure, and the abundance (number of reads, number of UMIs, or number of unique id tags) of each barcode was recorded. Analyses were restricted to the set of barcodes that were present in the input virus sample, as measured by a separate sequencing assay of the input virus sample. To aggregate biodistribution samples, read counts from samples from the same tissue were summed. To aggregate brain transduction samples, the number of transduction events (measured by unique id tags detected) from samples from the same tissue were summed. To aggregate all other transduction samples, the number of UMIs from samples from the same tissue were summed.

[0288] Biodistribution and transduction of tissue were calculated by normalizing aggregated biodistribution or transduction counts with input virus abundance. The transduction and biodistribution rates were calculated as fold change relative to the wild-type (WT) AAV9. The measurements are reported as mean and standard deviation of barcode replicates (n=8-16).

8.1.1.6. Single-nuclei RNA Sequencing and Analysis

[0289] Single-cell RNA sequencing has been previously demonstrated to allow characterization of cell-type specific tropism of barcoded rAAVs (Brown et al., 2021, Front. Immunol. 12:730825, which is incorporated herein by reference in its entirety). However, obtaining single cell suspension from certain tissue types and/or flash frozen samples from externally-sourced NHP studies can be extremely challenging. An approach was developed that combines single-nuclei RNA sequencing (snRNA-Seq) with targeted amplicon sequencing to reliably detect cell-type specific transduction from up to 50-100 barcoded rAAVs with minimal sequencing depth. To implement this approach: 1) protocols for isolation of high quality single nuclei suspensions from flash frozen NHP brain tissues (e.g. prefrontal cortex, motor cortex, caudate, putamen, hippocampus and substantia nigra) were developed, 2) flow cytometry was used to sort nuclei transduced with a rAAV (H2B-GFP reporter expressing), 3) the 10X Genomics Chromium X platform was used to encapsulate these nuclei and generate gene expression libraries for reliable identification of cell types, 4) barcoded viral transcripts that were captured using the 10X oligo dT capture probes were selectively amplified (for sequencing), and 5) viral transcripts identified from the targeted libraries were computationally mapped to cells identified using the gene expression libraries. Using this approach, cell-type specific tropism of multiple rAAVs in Cynomolgus macaque cortex (prefrontal + motor cortex) and basal ganglia regions (putamen) was investigated. The snRNA-seq gene expression analysis identified all the major central nervous system (CNS) cell types including therapeutically relevant cells such as neurons, excitatory neurons, interneurons, oligodendrocytes, and astrocytes. Viral transduction events, as assessed from our targeted library sequencing, were detected in almost all clusters and we could successfully quantify differences in transduction rates between rAAVs and benchmarks within a cell type of interest. Overall, it was demonstrated that transduced nuclei from the primate CNS can be selectively enriched, snRNA-seq performed, and relative transduction between multiple rAAVs in major cell types of interest can be quantitated.

[0290] Details of the single nuclear experimental workflow are described below.

8.1.1.6.1. Materials

[0291] Materials included the following:

EZ lysis buffer + 0.2 U/µl of murine RNAse inhibitor

1x PBS + 20% BSA + 0.2 U/µl of murine RNase inhibitor
1X PBS + 5% BSA + 0.2 U/µl of murine RNAse inhibitor/Wash
1X PBS + 2% BSA + 0.2 U/µl of murine RNAse inhibitor
Eight 15 ml tubes pre-coated with 1x PBS+2% BSA + 0.2 U/µl RNAse inhibitor
Two 50 ml tubes pre-coated with 1x PBS+2% BSA + 0.2 U/µl RNAse inhibitor
Two polypropylene FACS tubes pre-coated with 1x PBS + 2% BSA + 0.2 U/µl RNAse inhibitor, one with 100uL 1x PBS + 5% BSA + 0.2 U/µl RNAse inhibitor in the bottom for collection
Four 7 ml dounce homogenizer + Pestle A and Pestle B
2x Dissection Scissors
2x 0.4 µm filters
2x 0.7 µm filters
1 ml wide bore pipette tips
Hemocytometer
Six 0.5 ml protein lobind tube with 15 µl of 1 x PBS + 5% BSA + 0.2U/µl murine RNase inhibitor + 1:100 Propidium Iodide
Two 0.5 ml protein lobind tube with 1uL Propidium Iodide
Sony MA900 Cell Sorter

8.1.1.6.2. Single nuclei dissociation from Prefrontal Cortex, Motor Cortex, and Putamen

[0292] Mincing: All CNS tissue pieces were cut into four ~25 mg pieces on a cryostat and weighed. The 25 mg tissue samples were placed in a tube on ice and 200 µl of EZ lysis buffer + RNAse inhibitor was added. The tissue was minced with a pair of microscissors for about 1 min and transferred to a 7ml dounce homogenizer using a wide bore pipette. Each ~25 mg tissue piece was homogenized in a separate 7ml dounce.

[0293] Dounce homogenization: EZ lysis buffer + RNAse inhibitor was added to the sample in the dounce homogenizer for a total volume of 7 ml. A loose-fitting pestle (Pestle A) was used to dounce the sample with steady strokes (about 1 stroke per second) followed by a tight fitting pestle (Pestle B). The number of dounces varies by tissue type and is indicated in the table below.

Tissue	Dounce A	Dounce B
Frontal Cortex	10x	5x, wait 20 seconds on ice, 5x
Motor Cortex	10x	5x, wait 20 seconds on ice, 5x
Putamen	10x	5x, wait 20 seconds on ice, 5x

[0294] Filtration and clean up: Post dounce, a 70 µm filter was stacked on top of a 40 µm filter over a 50 mL conical centrifuge tube pre-coated with 1X PBS + 2% BSA + 0.2 U/µl of murine RNAse inhibitor. Using a funnel, the sample (7 ml) was passed through the filters by pouring. Next, 7ml of 1X PBS + 20% BSA + 0.2 U/µl of murine RNAse inhibitor was passed through the funnel and filters to rinse. Mincing, douncing and filtration was repeated with a second 25 mg tissue piece such that both pieces of tissue

were combined during the filtering step. A small (10 µl) aliquot of the filtered sample was transferred to a 0.5 ml protein lobind tube with 1 µl Propidium Iodide for counting. The filtered sample was divided into 4 pre-coated 15 ml conical centrifuge tubes with 7 ml sample each. The tubes were centrifuged at 200 RCF for 10 mins at 4°C. The supernatant was discarded and the pellet was resuspended in appropriate volume of 1 x PBS + 5% BSA + RNAse-Inhibitor to obtain ~3 million nuclei/ml. A small (5 µl) aliquot of the sample was transferred to a 0.5 ml protein lobind tube with 15 µl of 1xPBS+5%BSA+0.2U/µl murine RNase inhibitor+1:100 Propidium Iodide for counting. The remaining sample was stained with 1:100 Draq7.

[0295] FACS cleanup: The nuclei were sorted on a Sony MA900 cell sorter by gating for intact nuclei that were positively stained for Draq7 and discarding any doublets. The intact nuclei were further gated for GFP positivity and generous gates for sorting were implemented to maximize capture of even faintly GFP positive nuclei. The FACS cleaned nuclei were centrifuged at 200 RCF for 10 mins at 4°C in a final concentration of 10% BSA. The pellet was resuspended in 1 x PBS + 2% BSA+RNAse-inhibitor and counted. Final nuclei concentration was adjusted as needed for 10x encapsulation.

[0296] 10x Encapsulation and library preparation: The 10X Chromium X platform (10x Genomics) was used for single cell encapsulation as per the manufacturer's standard instructions. Reverse transcription was performed as per 10X protocols. cDNA amplification was performed using the 10X cDNA amplification kit which allows for amplification of oligo-dT captured transcripts. A viral transcript specific primer was added during cDNA amplification to enable early amplification and purification of viral transcripts. Post cDNA amplification a portion of the cDNA library was used to generate a gene expression library as per 10x standard protocol and the library was quality controlled and sequenced as per standard 10X protocols. A small portion of the cDNA library was used to generate targeted libraries by PCR amplifying the Dyno barcode region. For targeted amplification of viral transcripts captured by oligo-dT, primers binding to the TruSeq Handle in combination with a viral transcript specific primer were used. Once the targeted product was amplified we performed pre-indexing and indexing PCRs and sequenced the libraries using an Illumina NextSeq2000 sequencer.

8.1.1.6.3. Single Nuclei RNA Sequencing Data Analysis

[0297] Gene expression data processing: 10X gene expression libraries were sequenced at a depth of 5000 reads per nuclei. Gene expression sequencing data was demultiplexed using Illumina bcl-convert with default settings, then aligned to *Macaca fascicularis* reference genome (v6.0, assembly GCA_011100615.1) and quantified using the CellRanger pipeline v7.1.0 with intron mode activated. Doublet detection and filtering was performed using Scrublet package v0.2.3. Dimensionality reduction, batch effect removal, clustering, and identification of marker genes were carried out using Scanpy v1.9.3.

[0298] Cell type annotation: 10X gene expression RNA transcript data was plotted on a UMAP plot (Leiden clustering) to reveal the cell clusters. Identification of cell types was performed with an in-house algorithm that projects cell type labels from reference datasets, which were curated from published literature (Siletti et al., 2023, Science, 382(6667):eadd7046, which is incorporated herein by reference in its entirety). This allowed for the annotation of major cell types in the CNS tissues, including neurons, oligodendrocytes, oligodendrocyte precursors, astrocytes, microglia, and vascular cells. To validate the annotations, curated cell type specific markers from the literature were used (Khrameeva et al., 2020, Genome Res. 30(5):776-789; Han et al., 2022, Nature 604(7907):723-731; He et al., 2021, Current

Biology 31(24):5473-5486.e6; Agarwal et al., 2020, Nature Comms. 11:4183, each of which is incorporated herein by reference in its entirety) and it was confirmed that these markers follow the expected expression patterns in the data.

[0299] Targeted library data processing: Targeted libraries were processed using an in-house pipeline to obtain the identities of transducing variants and the 10X feature barcode. To completely remove chimeric molecules, transcript per transcript (TPT) filtering (Dixit, 2021, bioRxiv 093237, which is incorporated herein by reference in its entirety) was performed with a threshold of 0.5 and 0.02 for forward and reverse molecules, respectively. Targeted libraries were then filtered against gene expression libraries to associate cell type information and limit the analysis to valid cell barcodes. The data was further filtered with cut-offs of 250-1000 reads per molecule to remove any remaining sequencing artifacts. Finally, nuclei with more than 3 observed transduction events, which likely represent clumping artifacts, were excluded from downstream analysis.

[0300] Determination of transduction rates: To calculate the normalized transduction rate of variant 'i' in cell type 'j', the number of transduction events for variant 'i' observed in cell type 'j' was divided by the population count of cell type 'j'. To generate the data shown in FIGS. 2-4, this value was further normalized by the amount of vector genome (vg) dosed, which is defined as the fraction of reads (DNAseq) belonging to variant 'i' in the test article, multiplied by total vg dosed into the brain [transduction efficiency of variant 'i' in cell type 'j' = (transduction events 'i' / number of cells 'j') / # of dose vector genomes for variant 'i']. The error bars were computed by bootstrapping cell barcodes (N=2000), calculating the resulting resampled rates, and identifying the 5th and 95th percentiles of the sampled distributions.

8.1.2. Results

[0301] Capsid polypeptide Variant 1 ("V1"), having a VP1 polypeptide sequence as set forth in SEQ ID NO:12, resulted in viral particles with an improved CNS, cardiac, and skeletal muscle delivery profile, as well as improved liver detargeting, as compared to viral particles with wild type AAV9 capsid sequences having a VP1 capsid polypeptide as set forth in SEQ ID NO:1.

[0302] The changes in biodistribution and transduction in brain and non-brain tissues (including skeletal and cardiac muscle) are shown in Tables 7-9 below:

Table 7: Biodistribution of V1 in NHP Non-Brain Samples. All values reported as fold change relative to WT AAV9, with the standard deviation shown in parentheses following each value.

Sample	Relative Fold Change
Dorsal root ganglion (aggregated)	2.79 (1.05)
Liver (aggregated)	0.23 (1.35)
Cardiac muscle (aggregated)	4.79 (1.07)
Skeletal muscle (aggregated)	6.15 (1.04)
Skeletal muscle (biceps)	5.69 (1.06)
Skeletal muscle (gastrocnemius)	7.22 (1.06)
Skeletal muscle (quadriceps)	5.39 (1.07)
Spinal cord (aggregated)	16.31 (1.11)
Spleen (aggregated)	0.51 (1.18)

Table 8: Transduction of V1 in NHP Brain Samples. All values reported as fold change (standard deviation) relative to WT AAV9. "Aggregated Brain Tissue" is an aggregate across all brain samples analyzed from each NHP animal in the study.

Sample	Relative Fold Change
Aggregated Brain Tissue	210.58 (1.04)
Basal Ganglia (Aggregated)	207.29 (1.04)
Basal Ganglia (Caudate)	202.9 (1.05)
Basal Ganglia (Globus Pallidus)	189.62 (1.08)
Basal Ganglia (Putamen)	222.56 (1.03)
Brainstem (Aggregated)	134.43 (1.07)
Cerebellum (Aggregated)	258.29 (1.06)
Forebrain (Aggregated)	241.03 (1.05)
Forebrain (Frontal Cortex)	219.71 (1.06)
Forebrain (Motor Cortex)	248.54 (1.05)
Hippocampus (Aggregated)	324.55 (1.05)
Midbrain (Aggregated)	175.74 (1.07)
Parietal Cortex (Aggregated)	275.85 (1.05)
Substantia Nigra (Aggregated)	143.72 (1.07)
Temporal Cortex (Aggregated)	442.57 (1.04)
Thalamus (Aggregated)	286.76 (1.06)

Table 9: Transduction of V1 in NHP Non-Brain Samples. All values reported as fold change (standard deviation) relative to WT AAV9.

Sample	Relative Fold Change
Dorsal root ganglion (aggregated)	3.23 (1.29)
Liver (aggregated)	0.26 (1.08)
Cardiac muscle (aggregated)	7.94 (1.13)
Skeletal muscle (aggregated)	21.5 (1.06)
Skeletal muscle (biceps)	19.13 (1.06)
Skeletal muscle (gastrocnemius)	22.34 (1.06)
Skeletal muscle (quadriceps)	22.1 (1.08)
Spinal cord (aggregated)	197.6 (1.2)
Spleen (aggregated)	0.93 (1.51)

[0303] Single nuclei RNA sequencing results providing cell-type specific transduction rates for V1 relative to "VAR-1" as disclosed in WO 2023/060264 A1 (amino acid sequence - SEQ ID NO:14 of WO 2023/060264 A1, SEQ ID NO:38 herein; nucleotide sequence - SEQ ID NO:15 of WO 2023/060264 A1, SEQ ID NO:39 herein) are shown in FIG. 2 (prefrontal cortex), FIG. 3 (motor cortex) and FIG. 4 (putamen). These results demonstrate increased transduction to all measured cell types relative to VAR-1.

[0304] V1 had 1.27-fold the production efficiency of AAV9 in HEK293.

[0305] Overall, V1 demonstrated significantly improved CNS and muscle targeting, and liver detargeting, as well as improved production efficiency relative to wild type AAV9.

8.2. Example 2: Single Capsid *In vivo* Evaluation of V1 in NHP

[0306] In order to confirm the performance of virus particles comprising the capsid polypeptide of V1 and further investigate its properties, virus particle comprising the V1 capsid polypeptide and carrying a transgene encoding a fluorescent protein was synthesized and tested in *in vivo* studies.

8.2.1. Materials and Methods

8.2.1.1. Virus Design and Production

[0307] Virus particles comprising the V1 capsid polypeptide were produced individually via transient triple transfection of adherent HEK293T cells (pRepCap(V1), pHELP (pALD X-80, Aldevron), pITR.Cbh.GFP) followed by purification as described in Section 8.1. Each variant capsid was produced with a self-complementary (scAAV) genome containing 5 distinct regions: One, the ubiquitous CBh promoter (CMV enhancer, Cba promoter, CBA/MVM hybrid intron); two, a Green Fluorescent Protein with a nuclear localization signal (NLS) tag; three, a unique barcode (the genome was produced with eight unique barcodes per fluorescent reporter, which were included to provide technical replicates for each capsid within the single study); four, the SV40 PolyA termination signal; and five, left and right ITRs capable of enabling self-complementary genome packaging in the virus particles. After individual purification of each virus, concentrations and amounts were quantified using ddPCR and a final test article was formulated at $4.68e^{11}$ vg/mL (low dose) and $3.42e^{12}$ vg/mL (high dose).

8.2.1.2. *In vivo* Study Design

[0308] All non-human primate (NHP) experiments were conducted in accordance with institutional policies and NIH guidelines. Two female Cynomolgus macaque NHPs weighing 2-3 kg and seronegative for anti-AAV9 and V1 neutralizing antibodies (serum NAb titers <1:4 based on *in vitro* NAb assay) were selected for the study. Animals were treated with methylprednisolone (40mg, IM) on Day -7 and -1 and then weekly for the duration of the study. Prior to test article administration, samples of blood were collected. The animals received an intravenous injection of the final test article virus containing V1 ($3.9e^{12}$ vg/kg (low dose) and $3.0e^{13}$ vg/kg (high dose)). During the in-life period the animals were monitored according to the animal facility's SOPs. Serum samples were collected at 1 day, 2 days, 4 days, and weekly post injection. The animals were sacrificed 4 weeks after the injections, perfused with cold saline, and tissues were collected for biodistribution, transduction, and histology analyses. The tissues and collection methods are shown in Table 10. For the brain, the left hemisphere was dissected, and flash frozen in 4 mm slices (stored at -80°C) and the right hemisphere was sliced at 4 mm and fixed in 10% naturally buffered formalin at room temperature for 48 hours before being moved to cold PBS. Other samples were collected and either flash frozen, formalin fixed, or collected into RNAlater® (Sigma-Aldrich), as indicated in Table 4. Samples collected in RNAlater® were incubated overnight at 4°C, after which the RNAlater® was drained and samples were frozen at -80°C. In addition, serum samples were collected at necropsy and stored at -80°C.

Table 10: List of Tissues Collected
Caudate
Putamen

Table 10: List of Tissues Collected
Motor cortex
Frontal cortex
Temporal cortex
Hippocampus
Thalamus
Midbrain
Substantia Nigra
Diaphragm
Gastrocnemius
Quadriceps
Atrium
Ventricle
Liver
Kidney
Gonads

8.2.1.3. Tissue Biodistribution and Transduction Analysis

[0309] Skeletal muscle tissue samples from the diaphragm, gastrocnemius, quadriceps muscles and cardiac muscle samples from atrium and ventricle areas were analyzed. Left hemisphere flash frozen brain slices were dissected to isolate regions including, but not limited to, frontal cortex, temporal cortex, motor cortex, hippocampus, basal ganglia, midbrain, brainstem, and cerebellum. Liver, Spleen, kidney, gonad, and DRG samples were also analyzed.

8.2.1.4. Vector Genome Biodistribution Assay

[0310] DNA was extracted from 10 mg of frozen tissue samples per replicate on the Kingfisher Apex automated platform using the MagMAX™ DNA Multi-Sample Ultra Kit (Thermofisher). Sample quality of extracted DNA samples was assessed using the Agilent 4200 TapeStation. Abundance of vector genomes in the DNA samples was measured using two single-plex qPCR reactions using Luna 2X Master Mix (NEB) and Taqman probes, one targeting the reporter transgene (eGFP) and another targeting RPP30, a reference gene for genomic DNA. qPCR reactions were run for 35 cycles using standard cycling conditions on a QuantStudio 5 real-time PCR instrument and the data was analyzed using QuantStudio Design and Analysis Software. The number of viral genomes present in a sample were calculated by reference to the relevant standard curve and were expressed as vector genome copies per diploid genome (VG/dg), where diploid genome values were calculated based on observed copies of the standard reference gene RPP30.

8.2.1.5. NHP Tissue Immunofluorescence

[0311] Tissues fixed in 10% NBF, including right hemisphere brain slabs, DRG, spinal cord, biceps, diaphragm, gastrocnemius and cardiac muscle sections, were paraffin embedded, sectioned at 5 uM per slice, and placed in 1" x 3" glass slides.

[0312] Immunofluorescence (IF) staining of FFPE tissue slides was performed using Leica BOND RX Autostainer, CNS tissue was probed for NeuN a neuronal marker (Millipore MAB377 1:500), GFAP an

astrocyte marker (CST #3670 1:200), and GFP as the transduction reporter (Fisher #A-11122, 1:500); skeletal and cardiac muscle tissue was probed for Dystrophin a muscle fiber marker (Abcam #ab15277, 1:300) and GFP as the transduction reporter (Fisher #A-11122, 1:900), immunoreactivity was detected using tyramide signal amplification (TSA), and Nuclei were counterstained with DAPI.

[0313] Multiplexed fluorescent RNAscope staining was performed on FFPE tissue slides using Leica BOND RX Autostainer, CNS tissue was probed for RBFOX3 a neuronal marker (ACD #486788-C2, 1:1000) and GFP the transduction reporter (ACD #400288-C1, 1:1500). Detection was performed using TSA Opal fluorophores.

[0314] All stained tissue slides were scanned using a 3D Histech Pannoramic Midi II slide scanner to produce whole-slide digital images. Image analysis was performed in both IF and RNAScope images to quantify percent transduction on all cells and specific cell types for specific tissue regions was performed using QuPath software (Bankhead et al., 2017). In short, DAPI signal was used to segment nuclei, cell type classification and transduction state was assigned to each nuclei based on fluorescence intensity properties classifiers created using the same software.

8.2.1.6. Brain Histology Protocol

[0315] Formalin fixed right hemisphere brain slabs, spinal cord, DRG, heart, and skeletal muscle samples were paraffin embedded, sliced at 5 microns, and stained for GFP, NeuN (a neuronal marker), and glial fibrillary acidic protein (GFAP, an astrocyte marker). The GFP/NeuN/GFAP staining was performed on the Leica BOND RX Autostainer. The primary antibodies used include GFP (A-11122, Thermo-Fisher), NeuN (MAB377, Millipore), and GFAP (#3670, Cell Signaling Technology). Immunofluorescence-stained tissue 75 x 26mm glass slides were scanned using a 3DHistech PANNORAMIC Midi slide scanner (50X total magnification) to produce whole-slide digital images.

[0316] Each brain region was samples across 1-2 slabs at 4 depths with 200 microns between sectioning depths. 6-8 replicates from each region were quantified to calculate the transduction rate. Quantification was done in Qupath with an automated analysis pipeline. First, the Stardist Python module was used to segment the DAPI channel, and the footprint of the nuclei was expanded to detect any adjacent fluorescence. Next, nuclei were categorized using a 2-layer random forest classifier. The first layer classified nuclei as positive or negative depending on the GFP intensity and was used to calculate the percentage of all cells transduced. The second classified cells as positive or negative for NeuN or GFAP. The overlap of GFP/NeuN and GFP/GFAP was used to calculate the percentage of neurons or astrocytes transduced. Brain regions of interest were annotated manually using a Rhesus Monkey Brain Atlas (Saleem & Logothetis, 2012) and guided by H&E images from adjacent sections.

8.2.2. Results

[0317] The V1 AAV capsid (having a VP1 polypeptide sequence as set forth in SEQ ID NO:12) demonstrated efficient transduction and biodistribution of cardiac and skeletal muscles as measured by payload expression (FIG. 5A) and viral genome quantification (FIG. 5B). Biodistribution to DRG and off-target peripheral organ samples was low (FIG. 5B).

[0318] Representative images displaying V1 and staining for tissue-specific markers are shown in FIGS. 6A (muscle tissues) and 6B (brain tissues). Quantification of transduction revealed that V1 transduced 30-52% of cardiomyocytes in NHP heart tissues with the high dose ($3e^{13}$ vg/kg) application and 32-66%

of cardiomyocytes in NHP heart tissues with the low dose ($4e^{12}$ vg/kg) application (FIG. 6C-6D). Transduction values in NHP skeletal muscle tissues ranged from 85 to 90% with the high dose application and from 57 to 90 % with the low dose application (FIG. 6E-6F).

[0319] Transduction in NHP brain tissues ranged between 2 to 6 % with the high dose application and between 1 to 5% with the low dose application (FIG. 6G-6H), demonstrating that the V1 AAV capsid effectively crosses the blood brain barrier. Liver biodistribution was 43 vg/dg with the high dose ($3e^{13}$ vg/kg) application and 10 vg/dg with the low dose ($4e^{12}$ vg/kg) application, demonstrating effective liver detargeting.

[0320] The results from the studies described in Example 2 are summarized in Table 11 below. These studies demonstrate that the V1 AAV capsid (having a VP1 polypeptide sequence as set forth in SEQ ID NO:12) transduces skeletal and heart muscles with high efficiency and crosses the blood brain barrier, even at low IV doses, and effectively detargets the liver.

Table 11

Dose	**$4e^{12}$ vg/kg ("high dose")**	**$3e^{13}$ vg/kg ("low dose")**
Skeletal muscle	57-90% of myofibers transduced	85-90% of myofibers transduced
Heart	32-66% of cardiomyocytes transduced	30-52% of cardiomyocytes transduced
CNS	1-5% of neurons transduced	2-6% of neurons transduced
Liver detargeting	10 vg/dg	43 vg/dg

9. SEQUENCE LISTING

[0321] Exemplary sequences of the present disclosure are provided in Table 12 below.

Table 12

Description	Sequence	SEQ ID NO
AAV9 VP1 wild-type reference amino acid sequence	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLV LPGYKYLGPGNGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKY NHADAEFQERLKEDTSFGGNLGRAVFQAKKRLLEPLGLVEEAAKTAP GKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVPDPQ PIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDS QWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYST PWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVT DNNGVKTIANNLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMI PQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENVP FHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGSGQNQQTLKFSVAGPS NMAVQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRN SLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVDADKVMITN EEEIKTTNPVATESYGQVATNHQSAQAQAQTGWVQNQGILPGMVWQ DRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPA DPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSN YYKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL	1
AAV9 VP1 wild-type reference nucleotide sequence	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTTA GTGAAGGTATTCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTC AACCCAAGGCAAATCAACAACATCAAGACAACGCTCGAGGTCTTGT GCTTCCGGGTTACAAATACCTTGGACCCGGCAACGGACTCGACAA GGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCACG ACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACC TCAAGTACAACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAG AAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCAGTCTTCCAGG CCAAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTTGAGGAAGCGGC TAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTCCTCA GGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCC CGCTAAAAAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCA GTCCCAGACCCTCAACCAATCGGAGAACCTCCCGCAGCCCCCTCA GGTGTGGGATCTCTTACAATGGCTTCAGGTGGTGGCGCACCAGTG GCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCCTCGGGA AATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCA CCAGCACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCT ACAAGCAAATCTCCAACAGCACATCTGGAGGATCTTCAAATGACAA CGCCTACTTCGGCTACAGCACCCCCTGGGGGTATTTTGACTTCAAC AGATTCCACTGCCACTTCTCACCACGTGACTGGCAGCGACTCATCA ACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCTT CAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACC ATCGCCAATAACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAG ACTATCAGCTCCCGTACGTGCTCGGGTCGGCTCACGAGGGCTGCC TCCCGCCGTTCCCAGCGGACGTTTTCATGATTCCTCAGTACGGGTA TCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCGTCCTTT TACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACA ACTTCCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAG CTACGCTCACAGCCAAAGCCTGGACCGACTAATGAATCCACTCATC GACCAATACTTGTACTATCTCTCAAAGACTATTAACGGTTCTGGACA GAATCAACAAACGCTAAAATTCAGTGTGGCCGGACCCAGCAACATG GCTGTCCAGGGAAGAAACTACATACCTGGACCCAGCTACCGACAA CAACGTGTCTCAACCACTGTGACTCAAAACAACAACAGCGAATTTG CTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGA CCGTTTCTTTCCTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAA CTGGAAGAGACAACGTGGATGCGGACAAAGTCATGATAACCAACG AAGAAGAAATTAAAACTACTAACCCGGTAGCAACGGAGTCCTATGG ACAAGTGGCCACAAACCACCAGAGTGCCCAAGCACAGGCGCAGAC	2

Table 12		
Description	**Sequence**	**SEQ ID NO**
	CGGCTGGGTTCAAAACCAAGGAATACTTCCGGGTATGGTTTGGCA GGACAGAGATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCT CACACGGACGGCAACTTTCACCCTTCTCCGCTGATGGGAGGGTTT GGAATGAAGCACCCGCCTCCTCAGATCCTCATCAAAAACACACCTG TACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAGCTGAACTC TTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAG TGGGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATC CAGTACACTTCCAACTATTACAAGTCTAATAATGTTGAATTTGCTGTT AATACTGAAGGTGTATATAGTGAACCCCGCCCCATTGGCACCAGAT ACCTGACTCGTAATCTGTAA	
AAV2 VP1 wild-type reference amino acid sequence	MAADGYLPDWLEDTLSEGIRQWWKLKPGPPPPKPAERHKDDSRGLV LPGYKYLGPFNGLDKGEPVNEADAAALEHDKAYDRQLDSGDNPYLKY NHADAEFQERLKEDTSFGGNLGRAVFQAKKRVLEPLGLVEEPVKTAP GKKRPVEHSPVEPDSSSGTGKAGQQPARKRLNFGQTGDADSVPDPQ PLGQPPAAPSGLGTNTMATGSGAPMADNNEGADGVGNSSGNWHCD STWMGDRVITTSTRTWALPTYNNHLYKQISSQSGASNDNHYFGYSTP WGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVTQ NDGTTTIANNLTSTVQVFTDSEYQLPYVLGSAHQGCLPPFPADVFMVP QYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFTFSYTFEDVPF HSSYAHSQSLDRLMNPLIDQYLYYLSRTNTPSGTTTQSRLQFSQAGAS DIRDQSRNWLPGPCYRQQRVSKTSADNNNSEYSWTGATKYHLNGRD SLVNPGPAMASHKDDEEKFFPQSGVLIFGKQGSEKTNVDIEKVMITDE EEIRTTNPVATEQYGSVSTNLQRGNRQAATADVNTQGVLPGMVWQD RDVYLQGPIWAKIPHTDGHFHPSPLMGGFGLKHPPPQILIKNTPVPANP STTFSAAKFASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNYN KSVNVDFTVDTNGVYSEPRPIGTRYLTRNL	3
AAV2 VP1 wild-type reference nucleotide sequence	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACACTCTCT CTGAAGGAATAAGACAGTGGTGGAAGCTCAAACCTGGCCCACCAC CACCAAAGCCCGCAGAGCGGCATAAGGACGACAGCAGGGGTCTTG TGCTTCCTGGGTACAAGTACCTCGGACCCTTCAACGGACTCGACAA GGGAGAGCCGGTCAACGAGGCAGACGCCGCGGCCCTCGAGCACG ACAAAGCCTACGACCGGCAGCTCGACAGCGGAGACAACCCGTACC TCAAGTACAACCACGCCGACGCGGAGTTTCAGGAGCGCCTTAAAG AAGATACGTCTTTTGGGGGCAACCTCGGACGAGCAGTCTTCCAGG CGAAAAAGAGGGTTCTTGAACCTCTGGGCCTGGTTGAGGAACCTG TTAAGACGGCTCCGGGAAAAAAGAGGCCGGTAGAGCACTCTCCTG TGGAGCCAGACTCCTCCTCGGGAACCGGAAAGGCGGGCCAGCAG CCTGCAAGAAAAAGATTGAATTTTGGTCAGACTGGAGACGCAGACT CAGTACCTGACCCCCAGCCTCTCGGACAGCCACCAGCAGCCCCCT CTGGTCTGGGAACTAATACGATGGCTACAGGCAGTGGCGCACCAA TGGCAGACAATAACGAGGGCGCCGACGGAGTGGGTAATTCCTCGG GAAATTGGCATTGCGATTCCACATGGATGGGCGACAGAGTCATCAC CACCAGCACCCGAACCTGGGCCCTGCCCACCTACAACAACCACCT CTACAAACAAATTTCCAGCCAATCAGGAGCCTCGAACGACAATCAC TACTTTGGCTACAGCACCCCTTGGGGGTATTTTGACTTCAACAGATT CCACTGCCACTTTTCACCACGTGACTGGCAAAGACTCATCAACAAC AACTGGGGATTCCGACCCAAGAGACTCAACTTCAAGCTCTTTAACA TTCAAGTCAAAGAGGTCACGCAGAATGACGGTACGACGACGATTG CCAATAACCTTACCAGCACGGTTCAGGTGTTTACTGACTCGGAGTA CCAGCTCCCGTACGTCCTCGGCTCGGCGCATCAAGGATGCCTCCC GCCGTTCCCAGCAGACGTCTTCATGGTGCCACAGTATGGATACCTC ACCCTGAACAACGGGAGTCAGGCAGTAGGACGCTCTTCATTTTACT GCCTGGAGTACTTTCCTTCTCAGATGCTGCGTACCGGAAACAACTT TACCTTCAGCTACACTTTTGAGGACGTTCCTTTCCACAGCAGCTAC GCTCACAGCCAGAGTCTGGACCGTCTCATGAATCCTCTCATCGACC AGTACCTGTATTACTTGAGCAGAACAAACACTCCAAGTGGAACCAC CACGCAGTCAAGGCTTCAGTTTTCTCAGGCCGGAGCGAGTGACATT	4

Table 12		
Description	**Sequence**	**SEQ ID NO**
	CGGGACCAGTCTAGGAACTGGCTTCCTGGACCCTGTTACCGCCAG CAGCGAGTATCAAAGACATCTGCGGATAACAACAACAGTGAATACT CGTGGACTGGAGCTACCAAGTACCACCTCAATGGCAGAGACTCTCT GGTGAATCCGGGCCCGGCCATGGCAAGCCACAAGGACGATGAAG AAAAGTTTTTTCCTCAGAGCGGGGTTCTCATCTTTGGGAAGCAAGG CTCAGAGAAAACAAATGTGGACATTGAAAAGGTCATGATTACAGAC GAAGAGGAAATCAGGACAACCAATCCCGTGGCTACGGAGCAGTAT GGTTCTGTATCTACCAACCTCCAGAGAGGCAACAGACAAGCAGCTA CCGCAGATGTCAACACACAAGGCGTTCTTCCAGGCATGGTCTGGC AGGACAGAGATGTGTACCTTCAGGGGCCCATCTGGGCAAAGATTC CACACACGGACGGACATTTTCACCCCTCTCCCCTCATGGGTGGATT CGGACTTAAACACCCTCCTCCACAGATTCTCATCAAGAACACCCCG GTACCTGCGAATCCTTCGACCACCTTCAGTGCGGCAAAGTTTGCTT CCTTCATCACACAGTACTCCACGGGACAGGTCAGCGTGGAGATCG AGTGGGAGCTGCAGAAGGAAAACAGCAAACGCTGGAATCCCGAAA TTCAGTACACTTCCAACTACAACAAGTCTGTTAATGTGGACTTTACT GTGGACACTAATGGCGTGTATTCAGAGCCTCGCCCCATTGGCACC AGATACCTGACTCGTAATCTGTAA	
AAV5 VP1 wild-type reference amino acid sequence	MSFVDHPPDWLEEVGEGLREFLGLEAGPPKPKPNQQHQDQARGLVL PGYNYLGPGNGLDRGEPVNRADEVAREHDISYNEQLEAGDNPYLKYN HADAEFQEKLADDTSFGGNLGKAVFQAKKRVLEPFGLVEEGAKTAPT GKRIDDHFPKRKKARTEEDSKPSTSSDAEAGPSGSQQLQIPAQPASSL GADTMSAGGGGPLGDNNQGADGVGNASGDWHCDSTWMGDRVVTK STRTWVLPSYNNHQYREIKSGSVDGSNANAYFGYSTPWGYFDFNRF HSHWSPRDWQRLINNYWGFRPRSLRVKIFNIQVKEVTVQDSTTTIANN LTSTVQVFTDDDYQLPYVVGNGTEGCLPAFPPQVFTLPQYGYATLNR DNTENPTERSSFFCLEYFPSKMLRTGNNFEFTYNFEEVPFHSSFAPSQ NLFKLANPLVDQYLYRFVSTNNTGGVQFNKNLAGRYANTYKNWFPGP MGRTQGWNLGSGVNRASVSAFATTNRMELEGASYQVPPQPNGMTN NLQGSNTYALENTMIFNSQPANPGTTATYLEGNMLITSESETQPVNRV AYNVGGQMATNNQSSTTAPATGTYNLQEIVPGSVWMERDVYLQGPI WAKIPETGAHFHPSPAMGGFGLKHPPPMMLIKNTPVPGNITSFSDVPV SSFITQYSTGQVTVEMEWELKKENSKRWNPEIQYTNNYNDPQFVDFA PDSTGEYRTTRPIGTRYLTRPL	5
AAV5 VP1 wild-type reference nucleotide sequence	ATGTCTTTTGTTGATCACCCTCCAGATTGGTTGGAAGAAGTTGGTG AAGGTCTTCGCGAGTTTTTGGGCCTTGAAGCGGGCCCACCGAAAC CAAAACCCAATCAGCAGCATCAAGATCAAGCCCGTGGTCTTGTGCT GCCTGGTTATAACTATCTCGGACCCGGAAACGGGCTCGATCGAGG AGAGCCTGTCAACAGGGCAGACGAGGTCGCGCGAGAGCACGACA TCTCGTACAACGAGCAGCTTGAGGCGGGAGACAACCCCTACCTCA AGTACAACCACGCGGACGCCGAGTTTCAGGAGAAGCTCGCCGACG ACACATCCTTCGGGGGAAACCTCGGAAAGGCAGTCTTTCAGGCCA AGAAAAGGGTTCTCGAACCTTTTGGCCTGGTTGAAGAGGGTGCTAA GACGGCCCCTACCGGAAAGCGGATAGACGACCACTTTCCAAAAAG AAAGAAGGCTCGGACCGAAGAGGACTCCAAGCCTTCCACCTCGTC AGACGCCGAAGCTGGACCCAGCGGATCCCAGCAGCTGCAAATCCC AGCCCAACCAGCCTCAAGTTTGGGAGCTGATACAATGTCTGCGGG AGGTGGCGGCCCATTGGGCGACAATAACCAAGGTGCCGATGGAGT GGGCAATGCCTCGGGAGATTGGCATTGCGATTCCACGTGGATGGG GGACAGAGTCGTCACCAAGTCCACCCGAACCTGGGTGCTGCCCAG CTACAACAACCACCAGTACCGAGAGATCAAAAGCGGCTCCGTCGA CGGAAGCAACGCCAACGCCTACTTTGGATACAGCACCCCCTGGGG GTACTTTGACTTTAACCGCTTCCACAGCCACTGGAGCCCCCGAGAC TGGCAAAGACTCATCAACAACTACTGGGGCTTCAGACCCCGGTCC CTCAGAGTCAAAATCTTCAACATTCAAGTCAAAGAGGTCACGGTGC AGGACTCCACCACCACCATCGCCAACAACCTCACCTCCACCGTCCA AGTGTTTACGGACGACGACTACCAGCTGCCCTACGTCGTCGGCAA	6

Table 12		
Description	**Sequence**	**SEQ ID NO**
	CGGGACCGAGGGATGCCTGCCGGCCTTCCCTCCGCAGGTCTTTAC GCTGCCGCAGTACGGTTACGCGACGCTGAACCGCGACAACACAGA AAATCCCACCGAGAGGAGCAGCTTCTTCTGCCTAGAGTACTTTCCC AGCAAGATGCTGAGAACGGGCAACAACTTTGAGTTTACCTACAACT TTGAGGAGGTGCCCTTCCACTCCAGCTTCGCTCCCAGTCAGAACCT GTTCAAGCTGGCCAACCCGCTGGTGGACCAGTACTTGTACCGCTT CGTGAGCACAAATAACACTGGCGGAGTCCAGTTCAACAAGAACCTG GCCGGGAGATACGCCAACACCTACAAAAACTGGTTCCCGGGGCCC ATGGGCCGAACCCAGGGCTGGAACCTGGGCTCCGGGGTCAACCG CGCCAGTGTCAGCGCCTTCGCCACGACCAATAGGATGGAGCTCGA GGGCGCGAGTTACCAGGTGCCCCCGCAGCCGAACGGCATGACCA ACAACCTCCAGGGCAGCAACACCTATGCCCTGGAGAACACTATGAT CTTCAACAGCCAGCCGGCGAACCCGGGCACCACCGCCACGTACCT CGAGGGCAACATGCTCATCACCAGCGAGAGCGAGACGCAGCCGG TGAACCGCGTGGCGTACAACGTCGGCGGGCAGATGGCCACCAACA ACCAGAGCTCCACCACTGCCCCCGCGACCGGCACGTACAACCTCC AGGAAATCGTGCCCGGCAGCGTGTGGATGGAGAGGGACGTGTAC CTCCAAGGACCCATCTGGGCCAAGATCCCAGAGACGGGGGCGCA CTTTCACCCCTCTCCGGCCATGGGCGGATTCGGACTCAAACACCC ACCGCCCATGATGCTCATCAAGAACACGCCTGTGCCCGGAAATATC ACCAGCTTCTCGGACGTGCCCGTCAGCAGCTTCATCACCCAGTACA GCACCGGGCAGGTCACCGTGGAGATGGAGTGGGAGCTCAAGAAG GAAAACTCCAAGAGGTGGAACCCAGAGATCCAGTACACAAACAACT ACAACGACCCCCAGTTTGTGGACTTTGCCCCGGACAGCACCGGGG AATACAGAACCACCAGACCTATCGGAACCCGATACCTTACCCGACC CCTTTAA	
AAV8 VP1 wild-type reference amino acid sequence	MAADGYLPDWLEDNLSEGIREWWALKPGAPKPKANQQKQDDGRGLV LPGYKYLGPFNGLDKGEPVNAADAAALEHDKAYDQQLQAGDNPYLRY NHADAEFQERLQEDTSFGGNLGRAVFQAKKRVLEPLGLVEEGAKTAP GKKRPVEPSPQRSPDSSTGIGKKGQQPARKRLNFGQTGDSESVPDP QPLGEPPAAPSGVGPNTMAAGGGAPMADNNEGADGVGSSSGNWHC DSTWLGDRVITTSTRTWALPTYNNHLYKQISNGTSGGATNDNTYFGYS TPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLSFKLFNIQVKEV TQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGSAHQGCLPPFPADVFMI PQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFQFTYTFEDVP FHSSYAHSQSLDRLMNPLIDQYLYYLSRTQTTGGTANTQTLGFSQGG PNTMANQAKNWLPGPCYRQQRVSTTTGQNNNSNFAWTAGTKYHLN GRNSLANPGIAMATHKDDEERFFPSNGILIFGKQNAARDNADYSDVML TSEEEIKTTNPVATEEYGIVADNLQQQNTAPQIGTVNSQGALPGMVWQ NRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPPQILIKNTPVPA DPPTTFNQSKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSN YYKSTSVDFAVNTEGVYSEPRPIGTRYLTRNL	7
AAV8 VP1 wild-type reference nucleotide sequence	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTCT CTGAGGGCATTCGCGAGTGGTGGGCGCTGAAACCTGGAGCCCCG AAGCCCAAAGCCAACCAGCAAAAGCAGGACGACGGCCGGGGTCT GGTGCTTCCTGGCTACAAGTACCTCGGACCCTTCAACGGACTCGA CAAGGGGGAGCCCGTCAACGCGGCGGACGCAGCGGCCCTCGAGC ACGACAAGGCCTACGACCAGCAGCTGCAGGCGGGTGACAATCCGT ACCTGCGGTATAACCACGCCGACGCCGAGTTTCAGGAGCGTCTGC AAGAAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCAGTCTTCC AGGCCAAGAAGCGGGTTCTCGAACCTCTCGGTCTGGTTGAGGAAG GCGCTAAGACGGCTCCTGGAAAGAAGAGACCGGTAGAGCCATCAC CCCAGCGTTCTCCAGACTCCTCTACGGGCATCGGCAAGAAAGGCC AACAGCCCGCCAGAAAAAGACTCAATTTTGGTCAGACTGGCGACTC AGAGTCAGTTCCAGACCCTCAACCTCTCGGAGAACCTCCAGCAGC GCCCTCTGGTGTGGGACCTAATACAATGGCTGCAGGCGGTGGCGC ACCAATGGCAGACAATAACGAAGGCGCCGACGGAGTGGGTAGTTC	8

Table 12		
Description	**Sequence**	**SEQ ID NO**
	CTCGGGAAATTGGCATTGCGATTCCACATGGCTGGGCGACAGAGT CATCACCACCAGCACCCGAACCTGGGCCCTGCCCACCTACAACAA CCACCTCTACAAGCAAATCTCCAACGGGACATCGGGAGGAGCCAC CAACGACAACACCTACTTCGGCTACAGCACCCCCTGGGGGTATTTT GACTTTAACAGATTCCACTGCCACTTTTCACCACGTGACTGGCAGC GACTCATCAACAACAACTGGGGATTCCGGCCCAAGAGACTCAGCTT CAAGCTCTTCAACATCCAGGTCAAGGAGGTCACGCAGAATGAAGG CACCAAGACCATCGCCAATAACCTCACCAGCACCATCCAGGTGTTT ACGGACTCGGAGTACCAGCTGCCGTACGTTCTCGGCTCTGCCCAC CAGGGCTGCCTGCCTCCGTTCCCGGCGGACGTGTTCATGATTCCC CAGTACGGCTACCTAACACTCAACAACGGTAGTCAGGCCGTGGGA CGCTCCTCCTTCTACTGCCTGGAATACTTTCCTTCGCAGATGCTGA GAACCGGCAACAACTTCCAGTTTACTTACACCTTCGAGGACGTGCC TTTCCACAGCAGCTACGCCCACAGCCAGAGCTTGGACCGGCTGAT GAATCCTCTGATTGACCAGTACCTGTACTACTTGTCTCGGACTCAAA CAACAGGAGGCACGGCAAATACGCAGACTCTGGGCTTCAGCCAAG GTGGGCCTAATACAATGGCCAATCAGGCAAAGAACTGGCTGCCAG GACCCTGTTACCGCCAACAACGCGTCTCAACGACAACCGGGCAAA ACAACAATAGCAACTTTGCCTGGACTGCTGGGACCAAATACCATCT GAATGGAAGAAATTCATTGGCTAATCCTGGCATCGCTATGGCAACA CACAAAGACGACGAGGAGCGTTTTTTTCCCAGTAACGGGATCCTGA TTTTTGGCAAACAAAATGCTGCCAGAGACAATGCGGATTACAGCGA TGTCATGCTCACCAGCGAGGAAGAAATCAAAACCACTAACCCTGTG GCTACAGAGGAATACGGTATCGTGGCAGATAACTTGCAGCAGCAAA ACACGGCTCCTCAAATTGGAACTGTCAACAGCCAGGGGGCCTTAC CCGGTATGGTCTGGCAGAACCGGGACGTGTACCTGCAGGGTCCCA TCTGGGCCAAGATTCCTCACACGGACGGCAACTTCCACCCGTCTC CGCTGATGGGCGGCTTTGGCCTGAAACATCCTCCGCCTCAGATCC TGATCAAGAACACGCCTGTACCTGCGGATCCTCCGACCACCTTCAA CCAGTCAAAGCTGAACTCTTTCATCACGCAATACAGCACCGGACAG GTCAGCGTGGAAATTGAATGGGAGCTGCAGAAGGAAAACAGCAAG CGCTGGAACCCCGAGATCCAGTACACCTCCAACTACTACAAATCTA CAAGTGTGGACTTTGCTGTTAATACAGAAGGCGTGTACTCTGAACC CCGCCCCATTGGCACCCGTTACCTCACCCGTAATCTGTAA	
AAVrh74 VP1 wild-type reference amino acid sequence	MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDNGRGLV LPGYKYLGPFNGLDKGEPVNAADAAALEHDKAYDQQLQAGDNPYLRY NHADAEFQERLQEDTSFGGNLGRAVFQAKKRVLEPLGLVESPVKTAP GKKRPVEPSPQRSPDSSTGIGKKGQQPAKKRLNFGQTGDSESVPDP QPIGEPPAGPSGLGSGTMAAGGGAPMADNNEGADGVGSSSGNWHC DSTWLGDRVITTSTRTWALPTYNNHLYKQISNGTSGGSTNDNTYFGYS TPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEV TQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGSAHQGCLPPFPADVFMI PQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFEFSYNFEDVP FHSSYAHSQSLDRLMNPLIDQYLYYLSRTQSTGGTAGTQQLLFSQAGP NNMSAQAKNWLPGPCYRQQRVSTTLSQNNNSNFAWTGATKYHLNG RDSLVNPGVAMATHKDDEERFFPSSGVLMFGKQGAGKDNVDYSSVM LTSEEEIKTTNPVATEQYGVVADNLQQQNAAPIVGAVNSQGALPGMV WQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPPQILIKNTPV PADPPTTFNQAKLASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYT SNYYKSTNVDFAVNTEGTYSEPRPIGTRYLTRNL	9
AAVrh74 wild-type reference nucleotide sequence	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTCT CTGAGGGCATTCGCGAGTGGTGGGACCTGAAACCTGGAGCCCCGA AACCCAAAGCCAACCAGCAAAAGCAGGACAACGGCCGGGGTCTGG TGCTTCCTGGCTACAAGTACCTCGGACCCTTCAACGGACTCGACAA GGGGGAGCCCGTCAACGCGGCGGACGCAGCGGCCCTCGAGCAC GACAAGGCCTACGACCAGCAGCTCCAAGCGGGTGACAATCCGTAC CTGCGGTATAATCACGCCGACGCCGAGTTTCAGGAGCGTCTGCAA	10

Table 12

Description	Sequence	SEQ ID NO
	GAAGATACGTCTTTTGGGGGCAACCTCGGGCGCGCAGTCTTCCAG GCCAAAAAGCGGGTTCTCGAACCTCTGGGCCTGGTTGAATCGCCG GTTAAGACGGCTCCTGGAAAGAAGAGGCCGGTAGAGCCATCACCC CAGCGCTCTCCAGACTCCTCTACGGGCATCGGCAAGAAAGGCCAG CAGCCCGCAAAAAAGAGACTCAATTTTGGGCAGACTGGCGACTCA GAGTCAGTCCCCGACCCTCAACCAATCGGAGAACCACCAGCAGGC CCCTCTGGTCTGGGATCTGGTACAATGGCTGCAGGCGGTGGCGCT CCAATGGCAGACAATAACGAAGGCGCCGACGGAGTGGGTAGTTCC TCAGGAAATTGGCATTGCGATTCCACATGGCTGGGCGACAGAGTC ATCACCACCAGCACCCGCACCTGGGCCCTGCCCACCTACAACAAC CACCTCTACAAGCAAATCTCCAACGGGACCTCGGGAGGAAGCACC AACGACAACACCTACTTCGGCTACAGCACCCCCTGGGGGTATTTTG ACTTCAACAGATTCCACTGCCACTTTTCACCACGTGACTGGCAGCG ACTCATCAACAACAACTGGGGATTCCGGCCCAAGAGGCTCAACTTC AAGCTCTTCAACATCCAAGTCAAGGAGGTCACGCAGAATGAAGGCA CCAAGACCATCGCCAATAACCTTACCAGCACGATTCAGGTCTTTAC GGACTCGGAATACCAGCTCCCGTACGTGCTCGGCTCGGCGCACCA GGGCTGCCTGCCTCCGTTCCCGGCGGACGTCTTCATGATTCCTCA GTACGGGTACCTGACTCTGAACAATGGCAGTCAGGCTGTGGGCCG GTCGTCCTTCTACTGCCTGGAGTACTTTCCTTCTCAAATGCTGAGAA CGGGCAACAACTTTGAATTCAGCTACAACTTCGAGGACGTGCCCTT CCACAGCAGCTACGCGCACAGCCAGAGCCTGGACCGGCTGATGAA CCCTCTCATCGACCAGTACTTGTACTACCTGTCCCGGACTCAAAGC ACGGGCGGTACTGCAGGAACTCAGCAGTTGCTATTTTCTCAGGCC GGGCCTAACAACATGTCGGCTCAGGCCAAGAACTGGCTACCCGGT CCCTGCTACCGGCAGCAACGTGTCTCCACGACACTGTCGCAGAAC AACAACAGCAACTTTGCCTGGACGGGTGCCACCAAGTATCATCTGA ATGGCAGAGACTCTCTGGTGAATCCTGGCGTTGCCATGGCTACCC ACAAGGACGACGAAGAGCGATTTTTTCCATCCAGCGGAGTCTTAAT GTTTGGGAAACAGGGAGCTGGAAAAGACAACGTGGACTATAGCAG CGTGATGCTAACCAGCGAGGAAGAAATAAAGACCACCAACCCAGT GGCCACAGAACAGTACGGCGTGGTGGCCGATAACCTGCAACAGCA AAACGCCGCTCCTATTGTAGGGGCCGTCAATAGTCAAGGAGCCTTA CCTGGCATGGTGTGGCAGAACCGGGACGTGTACCTGCAGGGTCCC ATCTGGGCCAAGATTCCTCATACGGACGGCAACTTTCATCCCTCGC CGCTGATGGGAGGCTTTGGACTGAAGCATCCGCCTCCTCAGATCC TGATTAAAAACACACCTGTTCCCGCGGATCCTCCGACCACCTTCAA TCAGGCCAAGCTGGCTTCTTTCATCACGCAGTACAGTACCGGCCAG GTCAGCGTGGAGATCGAGTGGGAGCTGCAGAAGGAGAACAGCAAA CGCTGGAACCCAGAGATTCAGTACACTTCCAACTACTACAAATCTA CAAATGTGGACTTTGCTGTCAATACTGAGGGTACTTATTCCGAGCC TCGCCCCATTGGCACCCGTTACCTCACCCGTAATCTGTAA	
AAVrh74 VP1 alternative reference amino acid sequence	MAADGYLPDWLEDNLSEGIREWWDLKPGAPKPKANQQKQDNGRGLV LPGYKYLGPFNGLDKGEPVNAADAAALEHDKAYDQQLQAGDNPYLRY NHADAEFQERLQEDTSFGGNLGRAVFQAKKRVLEPLGLVESPVKTAP GKKRPVEPSPQRSPDSSTGIGKKGQQPAKKRLNFGQTGDSESVPDP QPIGEPPAGPSGLGSGTMAAGGGAPMADNNEGADGVGSSSGNWHC DSTWLGDRVITTSTRTWALPTYNNHLYKQISNGTSGGSTNDNTYFGYS TPWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEV TQNEGTKTIANNLTSTIQVFTDSEYQLPYVLGSAHQGCLPPFPADVFMI PQYGYLTLNNGSQAVGRSSFYCLEYFPSQMLRTGNNFEFSYNFEDVP FHSSYAHSQSLDRLMNPLIDQYLYYLSRTQSTGGTAGTQQLLFSQAGP NNMSAQAKNWLPGPCYRQQRVSTTLSQNNNSNFAWTGATKYHLNG RDSLVNPGVAMATHKDDEERFFPSSGVLMFGKQGAGKDNVDYSSVM LTSEEEIKTTNPVATEQYGVVADNLQQQNAAPIVGAVNSQGALPGMV WQNRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGLKHPPPQILIKNTPV	11

Table 12		
Description	**Sequence**	**SEQ ID NO**
	PADPPTTFTKAKLASFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTS NYYKSTNVDFAVNTEGTYSEPRPIGTRYLTRNL	
Variant 1 ("V1") amino acid sequence	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLV LPGYKYLGPGNGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKY NHADAEFQERLKEDTSFGGNLGRAVFQAKKRLLEPLGLVEEAAKTAP GKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVPDPQ PIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDS QWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYST PWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVT DNNGVKTIANNLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMI PQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENVP FHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGSGQNQQTLKFSVAGPS NMAVQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRN SLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVDADKVMITN EEEIKTTNPVATESYGTVATNHQSAQAQAVAGALQSQGALPGMVWQ DRDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPA DPPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSN YYKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL	12
Variant 1 ("V1") nucleotide sequence	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTTA GTGAAGGTATTCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTC AACCCAAGGCAAATCAACAACATCAAGACAACGCTCGAGGTCTTGT GCTTCCGGGTTACAAATACCTTGGACCCGGCAACGGACTCGACAA GGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCACG ACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACC TCAAGTACAACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAG AAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCAGTCTTCCAGG CCAAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTTGAGGAAGCGGC TAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTCCTCA GGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCC CGCTAAAAAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCA GTCCCAGACCCTCAACCAATCGGAGAACCTCCCGCAGCCCCCTCA GGTGTGGGATCTCTTACAATGGCTTCAGGTGGTGGCGCACCAGTG GCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCCTCGGGA AATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCA CCAGCACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCT ACAAGCAAATCTCCAACAGCACATCTGGAGGATCTTCAAATGACAA CGCCTACTTCGGCTACAGCACCCCCTGGGGGTATTTTGACTTCAAC AGATTCCACTGCCACTTCTCACCACGTGACTGGCAGCGACTCATCA ACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCTT CAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACC ATCGCCAATAACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAG ACTATCAGCTCCCGTACGTGCTCGGGTCGGCTCACGAGGGCTGCC TCCCGCCGTTCCCAGCGGACGTTTTCATGATTCCTCAGTACGGGTA TCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCGTCCTTT TACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACA ACTTCCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAG CTACGCTCACAGCCAAAGCCTGGACCGACTAATGAATCCACTCATC GACCAATACTTGTACTATCTCTCAAAGACTATTAACGGTTCTGGACA GAATCAACAAACGCTAAAATTCAGTGTGGCCGGACCCAGCAACATG GCTGTCCAGGGAAGAAACTACATACCTGGACCCAGCTACCGACAA CAACGTGTCTCAACCACTGTGACTCAAAACAACAACAGCGAATTTG CTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGA CCGTTTCTTTCCTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAA CTGGAAGAGACAACGTGGATGCGGACAAAGTCATGATAACCAACG AAGAAGAAATTAAAACTACTAACCCGGTAGCAACGGAGTCCTATGG AACTGTGGCCACAAACCACCAGAGTGCCCAAGCACAGGCGGTGGC	13

Table 12		
Description	**Sequence**	**SEQ ID NO**
	TGGCGCGTTGCAAAGCCAAGGAGCTCTTCCGGGTATGGTTTGGCA GGACAGAGATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCT CACACGGACGGCAACTTTCACCCTTCTCCGCTGATGGGAGGGTTT GGAATGAAGCACCCGCCTCCTCAGATCCTCATCAAAAACACACCTG TACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAGCTGAACTC TTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAG TGGGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATC CAGTACACTTCCAACTATTACAAGTCTAATAATGTTGAATTTGCTGTT AATACTGAAGGTGTATATAGTGAACCCCGCCCCATTGGCACCAGAT ACCTGACTCGTAATCTGTAA	
CBh promoter	CCAACCTGAAAAAAAGTGATTTCAGGCAGGTGCTCCAGGTAATTAA ACATTAATACCCCACCAACCAACCATCCCTTAAACCCTTACCTCTTG CTCAGCTAATTACAGCCCGGAGGAGAAGGGCCGTCCCGCCCGCTC ACCTGTGGGAGTAACGCGGTCAGTCAGAGCCGGGGCGGGCGGCG CGAGGCGGCGGCGGAGCGGGGCACGGGGCGAAGGCAGCGCGCA GCGACTCCCGCCCGCCGCGCGCTTCGCTTTTTATAGGGCCGCCGC CGCCGCCGCCTCGCCATAAAAGGAAACTTTCGGAGCGCGCCGCTC TGATTGGCTGCCGCCGCACCTCTCCGCCTCGCCCCGCCCCGCCCC TCGCCCCGCCCCGCCCCGCCTGGCGCGCGCCCCCCCCCCCCCCC CGCCCCCATCGCTGCACAAAATAATTAAAAAATAAATAAATACAAAA TTGGGGGTGGGGAGGGGGGGGAGATGGGGAGAGTGAAGCAGAAC GTGGGGCTCACCTCGACCATGGTAATAGCGATGACTAATACGTAGA TGTACTGCCAAGTAGGAAAGTCCCATAAGGTCATGTACTGGGCACA ATGCCAGGCGGGCCATTTACCGTCATTGACGTCAATAGGGGGCGT ACTTGGCATATGATACACTTGATGTACTGCCAAGTGGGCAGTTTAC CGTAAATACTCCACCCATTGACGTCAATGGAAAGTCCCTATTGGCG TTACTATTGACGTCAATGGGCGGGGGTCGTTGGGCGGTCAGCCAG GCGGGCCATTTACCGTAAGTTATGTAACG	14
hSYN promoter	AGTGCAAGTGGGTTTTAGGACCAGGATGAGGCGGGGTGGGGGTG CCTACCTGACGACCGACCCCGACCCACTGGACAAGCACCCAACCC CCATTCCCCAAATTGCGCATCCCCTATCAGAGAGGGGGAGGGGAA ACAGGATGCGGCGAGGCGCGTGCGCACTGCCAGCTTCAGCACCG CGGACAGTGCCTTCGCCCCCGCCTGGCGGCGCGCGCCACCGCCG CCTCAGCACTGAAGGCGCGCTGACGTCACTCGCCGGTCCCCCGCA AACTCCCCTTCCCGGCCACCTTGGTCGCGTCCGCGCCGCCGCCG GCCCAGCCGGACCGCACCACGCGAGGCGCGAGATAGGGGGGCAC GGGCGCGACCATCTGCGCTGCGGCGCCGGCGACTCAGCGCTGCC TCAGTCTGCGGTGGGCAGCGGAGGAGTCGTGTCGTGCCTGAGAG CGCAG	15
Targeting peptide	PLNGAVHLY	16
Targeting peptide	IVMNSLK	17
Targeting peptide	RDSPKGW	18
Targeting peptide	YSTDVRM	19
Targeting peptide	RESPRGL	20
Targeting peptide	GNNTRSV	21
Targeting peptide	GNNTRDT	22

Table 12		
Description	**Sequence**	**SEQ ID NO**
Targeting peptide	TNSTRPV	23
Targeting peptide	ASSLNIA	24
Targeting peptide	SLEEEWAQVECEVYGRGCPSGSLDESFYDWFERQL	25
Targeting peptide	TPFYPVGYTVKQPGTCGDGVLQPGEECDDGNPDVSDGCIDCHRAYC GDGYRHQGVEDCDGSDFGYLTCETYLPGSYGDLRCTQYCSIDSTPCR YFT	26
Targeting peptide	RGDX$_1$X$_2$X$_3$X$_4$, with X$_1$ to X$_4$ each being any amino acid In various aspects of SEQ ID NO:27, X$_1$, X$_2$, and X$_3$ are each independently selected from L, G, V, and A and/or X$_4$ is S, V, A, G, or L. In some embodiments, at least one of X$_2$ and X$_3$ is G.	27
Targeting peptide	RGDLGLS	28
Targeting peptide	RGDLSTP	29
Targeting peptide	SNSRGDYNSL	30
Targeting peptide	ENRRGDFNNT	31
Targeting peptide	SRGDYNSL	32
Targeting peptide	RGDYNSL	33
Targeting peptide	RGDLST	34
Targeting peptide	RGDYVGL	35
Targeting peptide	RGDAVGV	36
Amino acids 579 to 601 of SEQ ID NO:12	TVATNHQSAQAQAVAGALQSQGA	37
"VAR-1" disclosed in WO 2023/060264 A1 (amino acid)	MAADGYLPDWLEDNLSEGIREWWALKPGAPQPKANQQHQDNARGLV LPGYKYLGPGNGLDKGEPVNAADAAALEHDKAYDQQLKAGDNPYLKY NHADAEFQERLKEDTSFGGNLGRAVFQAKKRLLEPLGLVEEAAKTAP GKKRPVEQSPQEPDSSAGIGKSGAQPAKKRLNFGQTGDTESVPDPQ PIGEPPAAPSGVGSLTMASGGGAPVADNNEGADGVGSSSGNWHCDS QWLGDRVITTSTRTWALPTYNNHLYKQISNSTSGGSSNDNAYFGYST PWGYFDFNRFHCHFSPRDWQRLINNNWGFRPKRLNFKLFNIQVKEVT DNNGVKTIANNLTSTVQVFTDSDYQLPYVLGSAHEGCLPPFPADVFMI PQYGYLTLNDGSQAVGRSSFYCLEYFPSQMLRTGNNFQFSYEFENVP FHSSYAHSQSLDRLMNPLIDQYLYYLSKTINGSGQNQQTLKFSVAGPS NMAVQGRNYIPGPSYRQQRVSTTVTQNNNSEFAWPGASSWALNGRN SLMNPGPAMASHKEGEDRFFPLSGSLIFGKQGTGRDNVDADKVMITN EEEIKTTNPVATESYGVVATNHQSAQAQAIVGALQSQGALPGMVWQD	38

Table 12		
Description	**Sequence**	**SEQ ID NO**
	RDVYLQGPIWAKIPHTDGNFHPSPLMGGFGMKHPPPQILIKNTPVPAD PPTAFNKDKLNSFITQYSTGQVSVEIEWELQKENSKRWNPEIQYTSNY YKSNNVEFAVNTEGVYSEPRPIGTRYLTRNL	
"VAR-1" disclosed in WO 2023/060264 A1 (nucleotide)	ATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTTA GTGAAGGTATTCGCGAGTGGTGGGCTTTGAAACCTGGAGCCCCTC AACCCAAGGCAAATCAACAACATCAAGACAACGCTCGAGGTCTTGT GCTTCCGGGTTACAAATACCTTGGACCCGGCAACGGACTCGACAA GGGGGAGCCGGTCAACGCAGCAGACGCGGCGGCCCTCGAGCACG ACAAGGCCTACGACCAGCAGCTCAAGGCCGGAGACAACCCGTACC TCAAGTACAACCACGCCGACGCCGAGTTCCAGGAGCGGCTCAAAG AAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCAGTCTTCCAGG CCAAAAAGAGGCTTCTTGAACCTCTTGGTCTGGTTGAGGAAGCGGC TAAGACGGCTCCTGGAAAGAAGAGGCCTGTAGAGCAGTCTCCTCA GGAACCGGACTCCTCCGCGGGTATTGGCAAATCGGGTGCACAGCC CGCTAAAAAGAGACTCAATTTCGGTCAGACTGGCGACACAGAGTCA GTCCCAGACCCTCAACCAATCGGAGAACCTCCCGCAGCCCCCTCA GGTGTGGGATCTCTTACAATGGCTTCAGGTGGTGGCGCACCAGTG GCAGACAATAACGAAGGTGCCGATGGAGTGGGTAGTTCCTCGGGA AATTGGCATTGCGATTCCCAATGGCTGGGGGACAGAGTCATCACCA CCAGCACCCGAACCTGGGCCCTGCCCACCTACAACAATCACCTCT ACAAGCAAATCTCCAACAGCACATCTGGAGGATCTTCAAATGACAA CGCCTACTTCGGCTACAGCACCCCCTGGGGGTATTTTGACTTCAAC AGATTCCACTGCCACTTCTCACCACGTGACTGGCAGCGACTCATCA ACAACAACTGGGGATTCCGGCCTAAGCGACTCAACTTCAAGCTCTT CAACATTCAGGTCAAAGAGGTTACGGACAACAATGGAGTCAAGACC ATCGCCAATAACCTTACCAGCACGGTCCAGGTCTTCACGGACTCAG ACTATCAGCTCCCGTACGTGCTCGGGTCGGCTCACGAGGGCTGCC TCCCGCCGTTCCCAGCGGACGTTTTCATGATTCCTCAGTACGGGTA TCTGACGCTTAATGATGGAAGCCAGGCCGTGGGTCGTTCGTCCTTT TACTGCCTGGAATATTTCCCGTCGCAAATGCTAAGAACGGGTAACA ACTTCCAGTTCAGCTACGAGTTTGAGAACGTACCTTTCCATAGCAG CTACGCTCACAGCCAAAGCCTGGACCGACTAATGAATCCACTCATC GACCAATACTTGTACTATCTCTCAAAGACTATTAACGGTTCTGGACA GAATCAACAAACGCTAAAATTCAGTGTGGCCGGACCCAGCAACATG GCTGTCCAGGGAAGAAACTACATACCTGGACCCAGCTACCGACAA CAACGTGTCTCAACCACTGTGACTCAAAACAACAACAGCGAATTTG CTTGGCCTGGAGCTTCTTCTTGGGCTCTCAATGGACGTAATAGCTT GATGAATCCTGGACCTGCTATGGCCAGCCACAAAGAAGGAGAGGA CCGTTTCTTTCCTTTGTCTGGATCTTTAATTTTTGGCAAACAAGGAA CTGGAAGAGACAACGTGGATGCGGACAAAGTCATGATAACCAACG AAGAAGAAATTAAAACTACTAACCCGGTAGCAACGGAGTCCTATGG AGTAGTGGCCACAAACCACCAGAGTGCCCAAGCACAGGCGATTGT TGGCGCTCTTCAATCTCAAGGAGCGCTTCCGGGTATGGTTTGGCA GGACAGAGATGTGTACCTGCAAGGACCCATTTGGGCCAAAATTCCT CACACGGACGGCAACTTTCACCCTTCTCCGCTGATGGGAGGGTTT GGAATGAAGCACCCGCCTCCTCAGATCCTCATCAAAAACACACCTG TACCTGCGGATCCTCCAACGGCCTTCAACAAGGACAAGCTGAACTC TTTCATCACCCAGTATTCTACTGGCCAAGTCAGCGTGGAGATCGAG TGGGAGCTGCAGAAGGAAAACAGCAAGCGCTGGAACCCGGAGATC CAGTACACTTCCAACTATTACAAGTCTAATAATGTTGAATTTGCTGTT AATACTGAAGGTGTATATAGTGAACCCCGCCCCATTGGCACCAGAT ACCTGACTCGTAATCTGTAA	39

10. CITATION OF REFERENCES

[0322] All publications, patent applications, patents, and other publications and references (e.g., sequence database reference numbers) cited herein are incorporated by reference in their entirety. For example, all GenBank, Unigene, and Entrez sequences referred to herein, e.g., in any Table herein, are incorporated by reference. Unless otherwise specified, the sequence accession numbers specified herein, including in any Table herein, refer to the database entries current as of August 21, 2020. When one gene or protein references a plurality of sequence accession numbers, all of the sequence variants are encompassed.

WHAT IS CLAIMED IS:

1. A capsid polypeptide comprising:
   (a) a threonine at a position corresponding to Q579 of the VP1 capsid polypeptide of SEQ ID NO:1;
   (b) a valine at a position corresponding to Q592 of the VP1 capsid polypeptide of SEQ ID NO:1;
   (c) an alanine at a position corresponding to T593 of the VP1 capsid polypeptide of SEQ ID NO:1;
   (d) an alanine at a position corresponding to W595 of the VP1 capsid polypeptide of SEQ ID NO:1;
   (e) a leucine at a position corresponding to V596 of the VP1 capsid polypeptide of SEQ ID NO:1;
   (f) a serine at a position corresponding to N598 of the VP1 capsid polypeptide of SEQ ID NO:1; and
   (g) an alanine at a position corresponding to I601 of the VP1 capsid polypeptide of SEQ ID NO:1.

2. A capsid polypeptide comprising the peptide TVATNHQSAQAQAVAGALQSQGA (SEQ ID NO:37) or a peptide whose amino acid sequence has one to five amino acid substitutions as compared to the amino acid sequence of SEQ ID NO:37, provided that the amino acids at positions 1, 14, 15, 17, 18, 20, and 23 of the peptide are threonine, valine, alanine, alanine, leucine, serine, and alanine, respectively.

3. The capsid polypeptide of claim 2, wherein the peptide has the amino acid sequence of SEQ ID NO:37.

4. The capsid polypeptide of any claim 2 or 3, wherein the peptide is in a surface loop of the capsid polypeptide.

5. The capsid polypeptide of claim 4, wherein the surface loop comprises a VR-VIII variable region.

6. The capsid polypeptide of any one of claims 1 to 5, which comprises an amino acid sequence having at least 95% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

7. The capsid polypeptide of any one of claims 1 to 5, which comprises an amino acid sequence having at least 99% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:1 or the VP2 or VP3 portion thereof.

8. The capsid polypeptide of any one of claims 1 to 5, which comprises an amino acid sequence having at least 95% sequence identity ((a) calculated taking targeting peptide insertions into account or

(b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

9. The capsid polypeptide of any one of claims 1 to 5, which comprises an amino acid sequence having at least 99% sequence identity ((a) calculated taking targeting peptide insertions into account or (b) calculated without taking targeting peptide insertions into account) to a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

10. A capsid polypeptide which comprises the amino acid sequence of a VP1 capsid polypeptide of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

11. A capsid polypeptide which:

(a) comprises the mutations in the mutation set present in the amino acid sequence of SEQ ID NO:12 as compared to the amino acid sequence of SEQ ID NO:1; and

(b) comprises an amino acid sequence with an edit distance of 15 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

12. The capsid polypeptide of claim 11, comprising an amino acid sequence with an edit distance of 5 or less to the amino acid sequence of SEQ ID NO:12 (or to the VP2 or VP3 portion thereof).

13. The capsid polypeptide of any one of claims 1 to 12, whose sequence has an edit distance of (a) 12 or lower, (b) 11 or lower, or (c) 10 or lower to:

(a) a VP1 capsid polypeptide of SEQ ID NO:12;

(b) a VP2 capsid polypeptide corresponding to the VP2 portion of SEQ ID NO:12; or

(c) a VP3 capsid polypeptide corresponding to the VP3 portion of SEQ ID NO:12.

14. The capsid polypeptide of any one of claims 1 to 13, which is a VP1 capsid polypeptide.

15. The capsid polypeptide of any one of claims 1 to 13, which is a VP2 capsid polypeptide.

16. The capsid polypeptide of any one of claims 1 to 13, which is a VP3 capsid polypeptide.

17. A nucleic acid molecule encoding a capsid polypeptide of any one of claims 1 to 16.

18. The nucleic acid molecule of claim 17, wherein the nucleic acid molecule comprises a nucleotide sequence having at least 95% sequence identity to the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

19. The nucleic acid molecule of claim 17, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:13 or a fragment thereof (*e.g.*, a VP1-encoding, a VP2-encoding or a VP3-encoding fragment thereof).

20. A virus particle (*e.g.*, adeno-associated virus ("AAV") particle) comprising a capsid polypeptide of any one of claims 1 to 16 or comprising a capsid polypeptide encoded by the nucleic acid molecule of any one of claims 17 to 19.

21. The virus particle of claim 20, comprising a nucleic acid comprising a payload (*e.g.*, a heterologous transgene) and one or more regulatory elements.

22. The virus particle of claim 21, wherein the one or more regulatory elements comprise a promoter.

23. The virus particle of claim 22, wherein the promoter is a CNS-specific promoter.

24. The virus particle of claim 22, wherein the promoter is a muscle-specific promoter.

25. The virus particle of claim 24, wherein the muscle-specific promoter is a skeletal muscle-specific promoter.

26. The virus particle of claim 24, wherein the muscle-specific promoter is a cardiac muscle-specific promoter.

27. An adeno-associated virus particle comprising (a) a capsid polypeptide of any one of claims 1 to 16 or comprising a capsid polypeptide encoded by the nucleic acid molecule of any one of claims 17 to 19 and (b) a nucleic acid comprising a payload (*e.g.*, a heterologous transgene) and one or more regulatory elements.

28. The adeno-associated virus particle of claim 27, wherein the virus particle comprises a capsid polypeptide comprising the amino acid sequence of SEQ ID NO:12 or the VP2 or VP3 portion thereof.

29. The adeno-associated virus particle of claim 27 or 28, wherein the nucleic acid comprises AAV inverted terminal repeat sequences, optionally wherein the AAV inverted repeat sequences are AAV2 inverted terminal repeat sequences.

30. A method of treating a disease or condition in a subject, comprising administering to the subject in an amount effective to treat the disease or condition:

(a) a virus particle:

(i) comprising the capsid polypeptide of any one of claims 1 to 16 and a heterologous nucleic acid sequence encoding a therapeutic product suitable for treating the disease or condition;

(ii) comprising a capsid polypeptide encoded by the nucleic acid molecule of any one of claims 17 to 19 and a heterologous nucleic acid sequence encoding a therapeutic product suitable for treating the disease or condition, or

(iii) of any one of claims 20 to 29 comprising a heterologous nucleic acid sequence encoding a therapeutic product suitable for treating the disease or condition; or

(b) a composition, *e.g.*, a pharmaceutical composition, comprising the virus particle of (a) and, optionally, a pharmaceutically acceptable carrier.

31. The method of claim 30, wherein the disease or condition is a disease or condition of the CNS.

32. The method of claim 30, wherein the disease or condition is a muscle disease or condition.

33. The method of claim 30, wherein the disease or condition is a disease or condition of skeletal muscle.

34. The method of claim 30, wherein the disease or condition is a disease or condition of cardiac muscle.

35. A method of making a virus (*e.g.*, a dependoparvovirus particle such as an adeno-associated virus (AAV) particle), comprising:

(a) providing a cell, cell-free system, or other translation system, comprising the nucleic acid molecule of any one of claims 17 to 19; and

(b) cultivating the cell, cell-free system, or other translation system, under conditions suitable for the production of the virus particle,

thereby making the virus particle.

36. The method of claim 35, wherein the cell, cell-free system, or other translation system comprises a second nucleic acid molecule and at least a portion of said second nucleic acid molecule is packaged in the dependoparvovirus particle.

37. The method of claim 36, wherein the second nucleic acid molecule comprises a payload, *e.g.*, a heterologous nucleic acid sequence encoding a therapeutic product.

38. A composition, *e.g.*, a pharmaceutical composition, comprising a virus particle of any one of claims 20 to 29, or a virus particle produced by the method of any one of claims 35 to 37, and a pharmaceutically acceptable carrier or excipient.

39. The capsid polypeptide of any one of claims 1 to 16, the nucleic acid molecule of any one of claims 17 to 19, the virus particle of any one of claims 20 to 29, or the composition of claim 38, for use in treating a disease or condition in a subject.

40. The capsid polypeptide of any one of claims 1 to 16, the nucleic acid molecule of any one of claims 17 to 19, or the virus particle of any one of claims 20 to 29, or the composition of claim 38, for use in the manufacture of a medicament for use in treating a disease or condition in a subject.

41. A host cell comprising the nucleic acid molecule of any one of claims 17 to 19.

42. The host cell of claim 41, wherein the host cell comprises a nucleic acid encoding a rep protein.

43. The host cell of claim 41 or 42, wherein the host cell comprises a nucleic acid encoding a cap protein.

44. The host cell of any one of claims 41 to 43, wherein the host cell comprises a nucleic acid comprising one or more helper sequences.

45. The host cell of any one of claims 41 to 44, wherein the host cell comprises a nucleic acid comprising a payload, *e.g.*, a heterologous nucleic acid sequence encoding a therapeutic product, *e.g.*, as described herein.

46. A method of delivering a payload (e.g., a transgene) to a cell, comprising contacting the cell with the virus particle of any one of claims 20 to 29.

47. A method of delivering a payload (e.g., a transgene) to the CNS of a subject, comprising administering to the subject the virus particle of any one of claims 20 to 29.

48. A method of delivering a payload (e.g., a transgene) to the muscle of a subject, comprising administering to the subject the virus particle of any one of claims 20 to 29.

49. The method of claim 47 or 48, wherein the virus particle is administered systemically.