

different virus particles varies between different species, and as a result, preclinical studies in mice often do not accurately reflect results in primates, including humans. As such there exists a need for improved rAAVs for use in the treatment of various genetic diseases.

SUMMARY

[0004] In one aspect, described herein are compositions comprising: a targeting moiety effective to target a muscle cell, wherein the targeting moiety comprises one or more n-mer motif, wherein at least one n-mer motif of the one or more n-mer motifs comprises or consists of $X_m\text{RGDX}_n$, wherein X_m and X_n are each independently selected from any amino acid, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, or 9, and wherein m is 1-4; and optionally a cargo, wherein the cargo is coupled to or is otherwise associated with the targeting moiety.

[0005] In certain examples, the at least one n-mer motif is as in any one of **Table 2, Table 3, FIG. 14**, or any combination thereof.

[0006] In certain examples, the targeting moiety comprises a polypeptide, a polynucleotide, a lipid, a polymer, a sugar, or a combination thereof.

[0007] In certain examples, the targeting moiety comprises a viral protein.

[0008] In certain examples, the viral protein is a capsid protein.

[0009] In certain examples, the viral protein is an adeno associated virus (AAV) protein.

[0010] In certain examples, the n-mer motif is located between two amino acids of the viral protein such that the n-mer motif is external to a viral capsid.

[0011] In certain examples, the n-mer motif is inserted between any two contiguous amino acids between amino acids 262-269, 327-332, 382-386, 452-460, 488-505, 527-539, 545-558, 581-593, 704-714, or any combination thereof in an AAV9 capsid polypeptide or in an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, or AAV rh.10 capsid polypeptide.

[0012] In certain examples, the n-mer motif is inserted between amino acids 588 and 589 in an AAV9 capsid polypeptide or in an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, or AAV rh.10 capsid polypeptide.

[0013] In certain examples, the composition is an engineered viral particle.

[0014] In certain examples, the engineered viral particle is an engineered AAV viral particle.

[0015] In certain examples, the AAV viral particle is an engineered AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV rh.74, or AAV rh.10 viral particle.

[0016] In certain examples, the n-mer motif is 3-15 amino acids.

[0017] In certain examples, the optional cargo is capable of treating or preventing a muscle disease or disorder.

[0018] In certain examples, the muscle disease or disorder is

- (a) an auto immune disease;
- (b) a cancer;
- (c) a muscular dystrophy;
- (d) a neuro-muscular disease;
- (e) a sugar or glycogen storage disease;
- (f) an expanded repeat disease;
- (g) a dominant negative disease;
- (h) a cardiomyopathy;
- (i) a viral disease;
- (j) a progeroid disease; or
- (k) any combination thereof.

[0019] In certain examples, the cargo is a morpholino, a peptide-linked morpholino, an antisense oligonucleotide, a PMO, a therapeutic transgene, a polynucleotide encoding a therapeutic polypeptide or peptide, a PPMO, one or more peptides, one or more polynucleotides encoding a CRISPR-Cas protein, a guide RNA, or both, a ribonucleoprotein, wherein the ribonucleoprotein comprises a CRISPR-Cas system molecule, a therapeutic transgene RNA, or other gene modifying or therapeutic RNA and/or protein, or any combination thereof.

[0020] In certain examples, the cargo is capable of inducing exon skipping in a gene.

[0021] In certain examples, the cargo is capable of inducing exon skipping in a dystrophin gene.

[0022] In certain examples, the cargo is a mini- or micro-dystrophin gene.

[0023] In certain examples, the mini- or micro-dystrophin gene comprises spectrin-like repeats 1, 2, 3, and 24, and optionally an nNOS domain.

[0024] In certain example, the expanded repeat disease is Huntington's disease, a Myotonic Dystrophy, or Facioscapulohumeral muscular dystrophy (FSHD).

[0025] In certain examples, the muscular dystrophy is Duchene muscular dystrophy, Becker Muscular dystrophy, a Limb-Girdle muscular dystrophy, an Emery Dreifuss muscular dystrophy, a myotonic dystrophy, or FSHD.

[0026] In certain examples, the myotonic dystrophy is Type 1 or Type 2.

[0027] In certain examples, the cardiomyopathy is dilated cardiomyopathy, hypertrophic cardiomyopathy, DMD-associated cardiomyopathy, or Dannon disease.

[0028] In certain examples, the sugar or glycogen storage disease is a MPS type III disease or Pompe disease.

[0029] In certain examples, the MPS type III disease, is MPS Type IIIA, IIIB, IIIC, or IIID.

[0030] In certain examples, the neuro-muscular disease is Charcot-Marie-Tooth disease or Friedreich's Ataxia.

[0031] In certain examples, the composition has increased muscle cell potency, muscle cell specificity, reduced immunogenicity, or any combination thereof.

[0032] Described in certain examples herein are vector systems comprising: a vector comprising: one or more polynucleotides each encoding all or part of one or more targeting moieties effective to target a muscle cell, wherein each targeting moiety comprises one or more n-mer motifs, wherein at least one n-mer motif of the one or more n-mer motifs comprises or consists of $X_m\text{RGDX}_n$, wherein X_m and X_n are each independently selected from any amino acid, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, or 9, and wherein m is 1-4, and wherein at least one of the one or more polynucleotides at least encodes the at least one n-mer motif; and optionally, a regulatory element operatively coupled to one or more of the polynucleotide(s).

[0033] In certain examples, at least one n-mer motif is as in any one of **Table 2**, **Table 3**, **FIG. 14F**, or any combination thereof.

[0034] In certain examples, the vector system further comprises a cargo.

[0035] In certain examples, the cargo is a cargo polynucleotide and is optionally coupled to one or more of the one or more polynucleotides encoding the targeting moiety.

[0036] In certain examples, the cargo polynucleotide is present on the same vector or a different vector than the one or more polynucleotides encoding the targeting moiety.

[0037] In certain examples, the vector system is capable of producing virus particles that contain the cargo when present.

[0038] In certain examples, the vector system is capable of producing a capsid polypeptide comprising one or more of the targeting moieties.

[0039] In certain examples, the vector system is capable of producing AAV virus particles.

[0040] In certain examples, the AAV viral particles are engineered AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV rh.74, or AAV rh.10 viral particle.

[0041] In certain examples, the capsid polypeptide is an engineered AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV rh.74, AAV rh.10 capsid polypeptide.

[0042] In certain examples of the vector system, the one or more polynucleotides encoding one n-mer motifs is inserted between two codons corresponding to two amino acids of the viral protein such that the n-mer motif(s) is external to the viral capsid.

[0043] In certain examples, the one or more polynucleotides encoding one or more n-mer motifs is/are inserted between two codons corresponding to any two contiguous amino acids between amino acids 262-269, 327-332, 382-386, 452-460, 488-505, 527-539, 545-558, 581-593, 704-714, or any combination thereof in an AAV9 capsid polypeptide or in an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, AAV rh.10 capsid polypeptide.

[0044] In certain examples, the one or more polynucleotides encoding one or more n-mer motifs is/are inserted between the codons corresponding to amino acid 588 and 589 in the AAV9 capsid polynucleotide or in an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, AAV rh.10 capsid polypeptide.

[0045] In another aspect, the present disclosure provides a vector system comprising: a vector comprising: one or more polynucleotides each encoding all or part of one or more targeting moieties effective to target a muscle cell, wherein each targeting moiety comprises one or more n-mer motifs, wherein at least one n-mer motif of the one or more n-mer motifs comprises or consists of $X_m\text{RGDX}_n$, wherein X_m and X_n are each independently selected from any amino acid, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, or 9, and wherein m is 1-4, and wherein at least one of the one or more polynucleotides at least encodes the at least one n-mer motif; and optionally, a regulatory element operatively coupled to one or more of the polynucleotide(s). In certain examples, the vector comprising the one or more polynucleotides each encoding all or part of one or more targeting moieties does not comprise splice regulatory elements.

[0046] In certain examples, the vector system further comprises a viral rep protein encoding polynucleotide.

[0047] In certain examples, the viral rep protein encoding polynucleotide is an AAV rep protein encoding polynucleotide.

[0048] In certain examples, the viral rep protein encoding polynucleotide is on the same vector or different vector as the one or more polynucleotides each encoding all or part of one or more targeting moieties.

[0049] In certain examples, the viral rep protein is operatively coupled to a regulatory element.

[0050] Described in certain examples herein are polynucleotides encoded by and/or produced by a vector system as in any of the preceding paragraphs or as described elsewhere herein.

[0051] In another aspect, the present disclosure provides a polypeptide encoded by and/or produced by a vector system as described herein. In certain examples, the polypeptide is a viral polypeptide.

[0052] In certain examples, the viral polypeptide is an AAV polypeptide.

[0053] In another aspect, described herein are particles produced by a vector system and/or including a polypeptide as described in any of the preceding paragraphs or as described elsewhere herein.

[0054] In certain examples, the particle is a viral particle.

[0055] In certain examples, the viral particle is an adeno-associated virus (AAV) particle, lentiviral particle, or a retroviral particle.

[0056] In certain examples, the viral particle has a muscle-specific tropism.

[0057] In certain examples, the cargo is capable of treating or preventing a muscle disease or disorder.

[0058] In certain examples, the muscle disease or disorder is

- a. an auto immune disease;
- b. a cancer;
- c. a muscular dystrophy;
- d. a neuro-muscular disease;
- e. a sugar or glycogen storage disease;
- f. an expanded repeat disease;
- g. a dominant negative disease;
- h. a cardiomyopathy;
- i. a viral disease;
- j. a progeroid disease; or
- k. any combination thereof.

[0059] In certain examples, the cargo is a morpholino, a peptide-linked morpholino, an antisense oligonucleotide, a PMO, a therapeutic transgene, a polynucleotide encoding a therapeutic polypeptide or peptide, a PPMO, one or more peptides, one or more polynucleotides encoding a CRISPR-Cas protein, a guide RNA, or both, a ribonucleoprotein, wherein the ribonucleoprotein comprises a CRISPR-Cas system molecule, a therapeutic transgene RNA, or other gene modifying or therapeutic RNA and/or protein, or any combination thereof.

[0060] In certain examples, the cargo is capable of inducing exon skipping in a gene.

[0061] In certain examples, the cargo is capable of inducing exon skipping in a dystrophin gene.

[0062] In certain examples, the cargo is a mini- or micro-dystrophin gene.

[0063] In certain examples, the mini- or micro-dystrophin gene comprises spectrin-like repeats 1, 2, 3, and 24, and optionally an nNOS domain.

[0064] In certain examples, the expanded repeat disease is Huntington's disease, a Myotonic Dystrophy, or Facioscapulohumeral muscular dystrophy (FSHD).

[0065] In certain examples, the muscular dystrophy is Duchene muscular dystrophy, Becker Muscular dystrophy, a Limb-Girdle muscular dystrophy, an Emery Dreifuss muscular dystrophy, a myotonic dystrophy, or FSHD.

[0066] In certain examples, the myotonic dystrophy is Type 1 or Type 2.

[0067] In certain examples, the cardiomyopathy is dilated cardiomyopathy, hypertrophic cardiomyopathy, DMD-associated cardiomyopathy, or Dannon disease.

[0068] In certain examples, the sugar or glycogen storage disease is a MPS type III disease or Pompe disease.

[0069] In certain examples, the MPS type III disease, is MPS Type IIIA, IIIB, IIIC, or IIID.

[0070] In certain examples, the neuro-muscular disease is Charcot-Marie-Tooth disease or Friedreich's Ataxia.

[0071] In certain examples, the polypeptide, the particle, or both have increased muscle cell potency, muscle cell specificity, reduced immunogenicity, or any combination thereof.

[0072] In yet another aspect, described herein are cells comprising:

- a. a composition as in any of the preceding paragraphs or described elsewhere herein;
- b. a vector system as in of the preceding paragraphs or described elsewhere herein;
- c. a polypeptide as in of the preceding paragraphs or described elsewhere herein;
- d. a particle as in any of the preceding paragraphs or described elsewhere herein;
- or
- e. a combination thereof.

[0073] In certain examples, the cell is prokaryotic.

[0074] In certain examples, the cell is eukaryotic.

[0075] In yet another aspect, described herein are pharmaceutical formulations comprising:

- a. a composition as in any of the preceding paragraphs or described elsewhere herein;
- b. a vector system as in any of the preceding paragraphs or described elsewhere herein;
- c. a polypeptide as in any of the preceding paragraphs or described elsewhere herein;
- d. a particle as in any of the preceding paragraphs or described elsewhere herein;
- e. a cell as in any of the preceding paragraphs or described elsewhere herein; or
- f. a combination thereof; and

a pharmaceutically acceptable carrier.

[0076] In a further aspect, the present disclosure provides a composition as described herein; a vector system as described herein; a polypeptide as described herein; a particle as described herein; a cell as described herein; a pharmaceutical formulation as described herein; or combination thereof for use in therapy. In a further aspect, the present disclosure provides use of composition as described herein; a vector system as described herein; a particle as described herein; a cell as described herein; a pharmaceutical formulation as described herein; or combination thereof in the manufacture of a medicament for treating muscle disease or disorder. In certain examples , described herein are methods comprising:

administering, to a subject in need thereof, a

- a. composition as in any of the preceding paragraphs or described elsewhere herein;
- b. vector system as in any of the preceding paragraphs or described elsewhere herein;

- c. polypeptide as in any of the preceding paragraphs or described elsewhere herein;
- d. particle as in any of the preceding paragraphs or described elsewhere herein;
- e. cell as in any of the preceding paragraphs or described elsewhere herein;

- f. pharmaceutical formulation as of the preceding paragraphs or described elsewhere herein; or
 - g. combination thereof
- [0077]** In certain examples, the subject has a muscle disease or disorder.
- [0078]** In certain examples, the muscle disease or disorder is
- a. an auto immune disease;
 - b. a cancer;
 - c. a muscular dystrophy;
 - d. a neuro-muscular disease;
 - e. a sugar or glycogen storage disease;
 - f. an expanded repeat disease;
 - g. a dominant negative disease;
 - h. a cardiomyopathy;
 - i. a viral disease;
 - j. a progeroid disease; or
 - k. any combination thereof.
- [0079]** In certain examples, the expanded repeat disease is Huntington's disease, a Myotonic Dystrophy, or Facioscapulohumeral muscular dystrophy (FSHD).
- [0080]** In certain examples, the muscular dystrophy is Duchene muscular dystrophy, Becker Muscular dystrophy, a Limb-Girdle muscular dystrophy, an Emery Dreifuss muscular dystrophy, a myotonic dystrophy, or FSHD.
- [0081]** In certain examples, the myotonic dystrophy is Type 1 or Type 2.
- [0082]** In certain examples, the cardiomyopathy is dilated cardiomyopathy, hypertrophic cardiomyopathy, DMD-associated cardiomyopathy, or Dannon disease.
- [0083]** In certain examples, the sugar or glycogen storage disease is a MPS type III disease or Pompe disease.
- [0084]** In certain examples, the MPS type III disease, is MPS Type IIIA, IIIB, IIIC, or IIID.
- [0085]** In certain examples, the neuro-muscular disease is Charcot-Marie-Tooth disease or Friedreich's Ataxia.

[0086] In certain examples, the compositions have reduced or eliminated targeting or specificity for a non-muscle cell. In certain examples, the non-muscle cells is a liver cell.

[0087] These and other examples, objects, features, and advantages of the examples will become apparent to those having ordinary skill in the art upon consideration of the following detailed description of illustrated example.

BRIEF DESCRIPTION OF THE DRAWINGS

[0088] An understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention may be utilized, and the accompanying drawings of which:

[0089] **FIG. 1** – The adeno-associated virus (AAV) transduction mechanism, which results in production of mRNA from the transgene.

[0090] **FIG. 2** - mRNA-based selection of AAV variants can be more stringent than DNA-based selection. The virus library was expressed under the control of a CMV promoter.

[0091] **FIGS. 3A-3B** – A correlation between the virus library and vector genome DNA (FIG. 3A) and mRNA (FIG. 3B) in the liver.

[0092] **FIGS. 4A-4F** - Capsid variants present at the DNA level and expressed at the mRNA level identified in different tissues. For this experiment, the virus library was expressed under the control of a CMV promoter.

[0093] **FIGS. 5A-5C** - Capsid mRNA expression in different tissues under the control of cell-type specific promoters (as noted on x-axis). CMV was included as an exemplary constitutive promoter. CK8 is a muscle-specific promoter. MHCK7 is a muscle-specific promoter. hSyn is a neuron specific promoter. Expression levels from the cell type-specific promoters have been normalized based on expression levels from the constitutive CMV promoter in each tissue.

[0094] **FIG. 6** - A schematic demonstrating embodiments of a method of producing and selecting capsid variants for tissue-specific gene delivery across species.

[0095] **FIG. 7** -A schematic demonstrating embodiments of generating an AAV capsid variant library, particularly insertion of a random *n*-mer (*n*=3-15 amino acids) into a wild-type AAV, e.g., AAV9.

CLAIMS

What is claimed is:

1. A composition comprising:

a targeting moiety effective to target a muscle cell, wherein the targeting moiety comprises one or more n-mer motif, wherein at least one n-mer motif of the one or more n-mer motifs comprises or consists of $X_m\text{RGDX}_n$, wherein X_m and X_n are each independently selected from any amino acid, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, or 9, and wherein m is 1-4; and

optionally a cargo, wherein the cargo is coupled to or is otherwise associated with the targeting moiety.
2. The composition of claim 1, wherein the at least one n-mer motif is as in any one of Table 2 (SEQ ID NO: 2-7, 20-21, 41-409), Table 3 (SEQ ID NO: 2, 28, 30-32, 55, 76, 96, 103, 135, 158, 207, 214, 252, 306, 316, 398, 410-768), FIG. 14F (SEQ ID NO: 8-12, 14-18), or any combination thereof.
3. The composition of any one of claims 1-2, wherein the targeting moiety comprises a polypeptide, a polynucleotide, a lipid, a polymer, a sugar, or a combination thereof.
4. The composition of any one of claims 1-3, wherein the targeting moiety comprises a viral protein.
5. The composition of claim 4, wherein the viral protein is a capsid protein.
6. The composition of any one of claims 4-5, wherein the viral protein is an adeno associated virus (AAV) protein.
7. The composition of any one of claims 5-6, wherein the n-mer motif is located between two amino acids of the viral protein such that the n-mer motif is external to a viral capsid.

8. The composition of any one of claims 6-7, wherein the n-mer motif is inserted between any two contiguous amino acids between amino acids 262-269, 327-332, 382-386, 452-460, 488-505, 527-539, 545-558, 581-593, 704-714, or any combination thereof in an AAV9 capsid polypeptide or in an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, AAV rh.10 capsid polypeptide.
9. The composition of any one of claims 6-8, wherein the n-mer motif is inserted between amino acids 588 and 589 in an AAV9 capsid polypeptide or in an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, AAV rh.10 capsid polypeptide.
10. The composition of any one of claims 1-9, wherein the composition is an engineered viral particle.
11. The composition of claim 10, wherein the engineered viral particle is an engineered AAV viral particle.
12. The composition of claim 11, wherein the AAV viral particle is an engineered AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV rh.74, or AAV rh.10 viral particle.
13. The composition of any one of claims 1-12, wherein the n-mer motif is 3-15 amino acids.
14. The composition of any one of the preceding claims, wherein the composition has a reduced or eliminated specificity for a non-muscle cell.
15. The composition of claim 14, wherein the non-muscle cell is a liver cell.
16. The composition of any one of claims 5-14, wherein the viral capsid is an engineered AAV capsid protein having reduced or eliminated uptake in a non-muscle cell as compared to a corresponding wild-type AAV capsid polypeptide.

17. The composition of claim 16, wherein wild-type capsid polypeptide is an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV rh.74, or AAV rh.10 capsid polypeptide.
18. The composition of any one of claims 16-17, wherein the engineered AAV capsid protein comprises one or more mutations that result in reduced or eliminated uptake in a non-muscle cell.
19. The composition of claim 18, wherein the one or more mutations are
- in position 267,
 - in position 269,
 - in position 504,
 - in position 505,
 - in position 590,
 - or any combination thereof
- AAV9 capsid protein (SEQ ID NO: 1) or in one or more positions corresponding thereto in a non-AAV9 capsid polypeptide.
20. The composition of claim 19, wherein the non-AAV9 capsid protein is an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, or AAV rh.10 capsid polypeptide.
21. The composition of claim 19, wherein the mutation in position 267 in the AAV9 capsid protein (SEQ ID NO: 1) or position corresponding thereto in a non-AAV9 capsid polypeptide is a G or X mutation to A, wherein X is any amino acid.
22. The composition of claim 19, wherein the mutation in position 269 in the AAV9 capsid protein (SEQ ID NO: 1) or position corresponding thereto in a non-AAV9 capsid polypeptide is an S or X to T mutation, wherein X is any amino acid.

23. The composition of claim 19, wherein the mutation in position 504 in the AAV9 capsid protein (SEQ ID NO: 1) or position corresponding thereto in a non-AAV9 capsid polypeptide is a G or X to A mutation, wherein X is any amino acid.
24. The composition of claim 19, wherein the mutation in position 505 in the AAV9 capsid protein (SEQ ID NO: 1) or position corresponding thereto in a non-AAV9 capsid polypeptide is a P or X to A mutation, wherein X is any amino acid.
25. The composition of claim 19, wherein the mutation in position 590 in the AAV9 capsid protein (SEQ ID NO: 1) or position corresponding thereto in a non-AAV9 capsid polypeptide is a Q or X to A mutation, wherein X is any amino acid.
26. The composition of claim 18, wherein the engineered AAV capsid protein is an engineered AAV9 capsid polypeptide comprising a mutation at position 267, position 269 or both of a wild-type AAV9 capsid protein (SEQ ID NO: 1), wherein the mutation at position 267 is a G to A mutation and wherein the mutation at position 269 is an S to T mutation.
27. The composition of claim 18, wherein the engineered AAV capsid protein is an engineered AAV9 capsid polypeptide comprising a mutation at position 590 of a wild-type AAV9 capsid protein (SEQ ID NO: 1), wherein the mutation at position 509 is a Q to A mutation.
28. The composition of claim 18, wherein the engineered AAV capsid protein is an engineered AAV9 capsid polypeptide comprising a mutation at position 504, position 505, or both of a wild-type AAV9 capsid protein (SEQ ID NO: 1), wherein the mutation at position 504 is a G to A mutation and wherein the mutation at position 505 is a P to A mutation.
29. The composition of any one of claims 1-28, wherein the optional cargo is capable of treating or preventing a muscle disease or disorder.

30. The composition of claim 29, wherein the muscle disease or disorder is
- a. an auto immune disease;
 - b. a cancer;
 - c. a muscular dystrophy;
 - d. a neuro-muscular disease;
 - e. a sugar or glycogen storage disease;
 - f. an expanded repeat disease;
 - g. a dominant negative disease;
 - h. a cardiomyopathy;
 - i. a viral disease;
 - j. a progeroid disease; or
 - k. any combination thereof.
31. The composition of any one of claims 1-30, wherein the cargo is a morpholino, a peptide-linked morpholino, an antisense oligonucleotide, a PMO, a therapeutic transgene, a polynucleotide encoding a therapeutic polypeptide or peptide, a PPMO, one or more peptides, one or more polynucleotides encoding a CRISPR-Cas protein, a guide RNA, or both, a ribonucleoprotein, wherein the ribonucleoprotein comprises a CRISPR-Cas system molecule, a therapeutic transgene RNA, or other gene modifying or therapeutic RNA and/or protein, or any combination thereof.
32. The composition of any one of claims 1-31, wherein the cargo is capable of inducing exon skipping in a gene.
33. The composition of any one of claims 1-32, wherein the cargo is capable of inducing exon skipping in a dystrophin gene.
34. The composition of any one of claims 1-33, wherein the cargo is a mini- or micro-dystrophin gene.
35. The composition of claim 34, wherein the mini- or micro-dystrophin gene comprises spectrin-like repeats 1, 2, 3, and 24, and optionally an nNOS domain.

36. The composition of any of claims 29-35, wherein the expanded repeat disease is Huntington's disease, a Myotonic Dystrophy, or Facioscapulohumeral muscular dystrophy (FSHD).
37. The composition of any of claims 29-36, wherein the muscular dystrophy is Duchene muscular dystrophy, Becker Muscular dystrophy, a Limb-Girdle muscular dystrophy, an Emery Dreifuss muscular dystrophy, a myotonic dystrophy, or FSHD.
38. The composition of claim 36, wherein the myotonic dystrophy is Type 1 or Type 2.
39. The composition of any of claims 29-38, wherein the cardiomyopathy is dilated cardiomyopathy, hypertrophic cardiomyopathy, DMD-associated cardiomyopathy, or Dannon disease.
40. The composition of any of claims 29-39, wherein the sugar or glycogen storage disease is a MPS type III disease or Pompe disease.
41. The composition of claim 40, wherein the MPS type III disease, is MPS Type IIIA, IIIB, IIIC, or IIID.
42. The composition of any of claims 29-41, wherein the neuro-muscular disease is Charcot-Marie-Tooth disease or Friedreich's Ataxia.
43. The composition of any one of claims 1-42, wherein the composition has increased muscle cell potency, muscle cell specificity, reduced immunogenicity, or any combination thereof.
44. A vector system comprising:
a vector comprising:
one or more polynucleotides each encoding all or part of one or more targeting moieties effective to target a muscle cell, wherein each targeting moiety comprises one or more n-mer motifs, wherein at least one n-mer motif of the one or more n-mer motifs

comprises or consists of $X_m\text{RGDX}_n$, wherein X_m and X_n are each independently selected from any amino acid, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, or 9, and wherein m is 1-4, and wherein at least one of the one or more polynucleotides at least encodes the at least one n -mer motif; and

optionally, a regulatory element operatively coupled to one or more of the polynucleotide(s).

45. The vector system of claim 44, wherein the at least one n -mer motif is as in any one of **Table 2 (SEQ ID NO: 2-7, 20-21, 41-409)**, **Table 3 (SEQ ID NO: 2, 28, 30-32, 55, 76, 96, 103, 135, 158, 207, 214, 252, 306, 316, 398, 410-768)**, **FIG. 14F (SEQ ID NO: 8-12, 14-18)**, or any combination thereof.
46. The vector system of any one of claims 44-45, further comprising a cargo.
47. The vector system of claim 46, wherein the cargo is a cargo polynucleotide and is optionally coupled to one or more of the one or more polynucleotides encoding the targeting moiety.
48. The vector system of any of claims 46-47, wherein the cargo polynucleotide is present on the same vector or a different vector than the one or more polynucleotides encoding the targeting moiety.
49. The vector system of any of claims 44-48, wherein the vector system is capable of producing virus particles that contain the cargo when present.
50. The vector system of any of claims 44-49, wherein the vector system is capable of producing a viral polypeptide comprising one or more of the targeting moieties.
51. The vector system of claim 50, wherein the viral polypeptide is a capsid polypeptide.
52. The vector system of claim 51, wherein the capsid polypeptide is an AAV capsid polypeptide.

53. The vector system. of any of claims 44-51, wherein the vector system is capable of producing AAV virus particles.
54. The vector system of claim 53, wherein the AAV viral particles are engineered AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV rh.74, or AAV rh.10 viral particle.
55. The vector system of any one of claims 51-54, wherein the capsid polypeptide is an engineered AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV rh.74, AAV rh.10 capsid polypeptide.
56. The vector system of any of claims 50-55, wherein the one or more polynucleotides encoding one n-mer motifs is inserted between two codons corresponding to two amino acids of the viral polypeptide such that the n-mer motif(s) is external to the viral capsid.
57. The vector system of claim 56, wherein the one or more polynucleotides encoding one or more n-mer motifs is/are inserted between two codons corresponding to any two contiguous amino acids between amino acids 262-269, 327-332, 382-386, 452-460, 488-505, 527-539, 545-558, 581-593, 704-714, or any combination thereof in an AAV9 capsid polypeptide or in an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, AAV rh.10 capsid polypeptide.
58. The vector system of claim 57, wherein the one or more polynucleotides encoding one or more n-mer motifs is/are inserted between the codons corresponding to amino acid 588 and 589 in the AAV9 capsid polynucleotide or in an analogous position in an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV rh.74, AAV rh.10 capsid polypeptide.
59. The vector system of any one of claims 51-58, wherein the capsid protein is an engineered AAV capsid protein having reduced or eliminated uptake in a non-muscle cell as compared to a corresponding wild-type AAV capsid polypeptide.

60. The vector system of claim 59, wherein the non-muscle cell is a liver cell.
61. The vector system of any one of claims 59-60, wherein the wild-type capsid polypeptide is an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV rh.74, or AAV rh.10 capsid polypeptide.
62. The vector system of any one of claims 69-61, wherein the engineered AAV capsid protein comprises one or more mutations that result in reduced or eliminated uptake in a non-muscle cell.
63. The vector system of claim 62, wherein the one or more mutations are
- a. in position 267,
 - b. in position 269,
 - c. in position 504,
 - d. in position 505,
 - e. in position 590,
 - f. or any combination thereof
- in the AAV9 capsid protein (SEQ ID NO: 1) or in one or more positions corresponding thereto in a non-AAV9 capsid polypeptide.
64. The vector system of claim 63, wherein the non-AAV9 capsid protein is an AAV1, AAV2, AAV3, AAV4, AAV5, AV6, AAV7, AAV8, AAV rh.74, or AAV rh.10 capsid polypeptide.
65. The vector system of claim 63, wherein the mutation in position 267 in the AAV9 capsid protein (SEQ ID NO: 1) or position corresponding thereto in a non-AAV9 capsid polypeptide is a G or X mutation to A, wherein X is any amino acid.
66. The vector system of claim 63, wherein the mutation in position 269 in the AAV9 capsid protein (SEQ ID NO: 1) or position corresponding thereto in a non-AAV9 capsid polypeptide is an S or X to T mutation, wherein X is any amino acid.

67. The vector system of claim 63, wherein the mutation in position 504 in the AAV9 capsid protein (SEQ ID NO: 1) or position corresponding thereto in a non-AAV9 capsid polypeptide is a G or X to A mutation, wherein X is any amino acid.
68. The vector system of claim 63, wherein the mutation in position 505 in the AAV9 capsid protein (SEQ ID NO: 1) or position corresponding thereto in a non-AAV9 capsid polypeptide is a P or X to A mutation, wherein X is any amino acid.
69. The vector system of claim 63, wherein the mutation in position 590 in the AAV9 capsid protein (SEQ ID NO: 1) or position corresponding thereto in a non-AAV9 capsid polypeptide is a Q or X to A mutation, wherein X is any amino acid.
70. The vector system of claim 62, wherein the engineered AAV capsid protein is an engineered AAV9 capsid polypeptide comprising a mutation at position 267, position 269 or both of a wild-type AAV9 capsid protein (SEQ ID NO: 1), wherein the mutation at position 267 is a G to A mutation and wherein the mutation at position 269 is an S to T mutation.
71. The vector system of claim 62, wherein the engineered AAV capsid protein is an engineered AAV9 capsid polypeptide comprising a mutation at position 590 of a wild-type AAV9 capsid protein (SEQ ID NO: 1), wherein the mutation at position 509 is a Q to A mutation.
72. The vector system of claim 62, wherein the engineered AAV capsid protein is an engineered AAV9 capsid polypeptide comprising a mutation at position 504, position 505, or both of a wild-type AAV9 capsid protein (SEQ ID NO: 1), wherein the mutation at position 504 is a G to A mutation and wherein the mutation at position 505 is a P to A mutation.
73. The vector system of any one of claims 44-72, wherein the vector comprising the one or more polynucleotides each encoding all or part of one or more targeting moieties does not comprise splice regulatory elements.

74. The vector system of any one of claims 43-73, further comprising a viral rep protein encoding polynucleotide.
75. The vector system of claim 74, wherein the viral rep protein encoding polynucleotide is an AAV rep protein encoding polynucleotide.
76. The vector system of any one of claims 74-75, wherein the viral rep protein encoding polynucleotide is on the same vector or different vector as the one or more polynucleotides each encoding all or part of one or more targeting moieties.
77. The vector system of any one of claims 74-76, wherein the viral rep protein is operatively coupled to a regulatory element.
78. A polypeptide encoded by and/or produced by a vector system as in any of claims 44-77.
79. The polypeptide of claim 78, wherein the polypeptide is a viral polypeptide.
80. The polypeptide of claim 79, wherein the viral polypeptide is an AAV polypeptide.
81. A particle produced by a vector system as in any one of claims 43-77 and/or including a polypeptide as in any one of claims 78-79.
82. The particle of claim 81, wherein the particle is a viral particle.
83. The particle of claim 82, wherein the viral particle is an adeno-associated virus (AAV) particle, lentiviral particle, or a retroviral particle.
84. The particle of claim 83, wherein the viral particle has a muscle-specific tropism.

85. The vector system of any one of claims 46-77, a polypeptide as in any one of claims 78-80, or a particle of any one of claims 81-84, wherein the cargo is capable of treating or preventing a muscle disease or disorder.
86. The vector system, the polypeptide, or the particle of claim 85, wherein the muscle disease or disorder is
- (a) an auto immune disease;
 - (b) a cancer;
 - (c) a muscular dystrophy;
 - (d) a neuro-muscular disease;
 - (e) a sugar or glycogen storage disease;
 - (f) an expanded repeat disease;
 - (g) a dominant negative disease;
 - (h) a cardiomyopathy;
 - (i) a viral disease;
 - (j) a progeroid disease; or
 - (k) any combination thereof.
87. The vector system, the polypeptide, or the particle of any one of claims 85-86, wherein the cargo is a morpholino, a peptide-linked morpholino, an antisense oligonucleotide, a PMO, a therapeutic transgene, a polynucleotide encoding a therapeutic polypeptide or peptide, a PPMO, one or more peptides, one or more polynucleotides encoding a CRISPR-Cas protein, a guide RNA, or both, a ribonucleoprotein, wherein the ribonucleoprotein comprises a CRISPR-Cas system molecule, a therapeutic transgene RNA, or other gene modifying or therapeutic RNA and/or protein, or any combination thereof.
88. The vector system, the polypeptide, or the particle of any one of claims 85-87, wherein the cargo is capable of inducing exon skipping in a gene.
89. The vector system, the polypeptide, or the particle of any one of claims 85-88, wherein the cargo is capable of inducing exon skipping in a dystrophin gene.

90. The vector system, the polypeptide, or the particle of any of claims 85-89, wherein the cargo is a mini- or micro-dystrophin gene.
91. The vector system, the polypeptide, or the particle of claim 90, wherein the mini- or micro-dystrophin gene comprises spectrin-like repeats 1, 2, 3, and 24, and optionally an nNOS domain.
92. The vector system, the polypeptide, or the particle of any one of claims 86-91, wherein the expanded repeat disease is Huntington's disease, a Myotonic Dystrophy, or Facioscapulohumeral muscular dystrophy (FSHD).
93. The vector system, the polypeptide, or the particle of any one of claims 86-92, wherein the muscular dystrophy is Duchene muscular dystrophy, Becker Muscular dystrophy, a Limb-Girdle muscular dystrophy, an Emery Dreifuss muscular dystrophy, a myotonic dystrophy, or FSHD.
94. The vector system, the polypeptide, or the particle of claim 93, wherein the myotonic dystrophy is Type 1 or Type 2.
95. The vector system, the polypeptide, or the particle of any of claims 85-94, wherein the cardiomyopathy is dilated cardiomyopathy, hypertrophic cardiomyopathy, DMD-associated cardiomyopathy, or Dannon disease.
96. The vector system, the polypeptide, or the particle of any of claims 85-95, wherein the sugar or glycogen storage disease is a MPS type III disease or Pompe disease.
97. The vector system, the polypeptide, or the particle of claim 96, wherein the MPS type III disease, is MPS Type IIIA, IIIB, IIIC, or IIID.
98. The vector system, the polypeptide, or the particle of any of claims 85-97, wherein the neuro-muscular disease is Charcot-Marie-Tooth disease or Friedreich's Ataxia.

99. The polypeptide or the particle of any one of claims 78-98, wherein the polypeptide, the particle, or both have increased muscle cell potency, muscle cell specificity, reduced immunogenicity, or any combination thereof.
100. A cell comprising:
- a composition as in any of claims 1-43;
 - a vector system as in any one of claims 44-77 and 85-98;
 - a polypeptide as in any one of claims 81-84 and 85-99;
 - a particle as in any one of claims 81-99; or
 - a combination thereof.
101. The cell of claim 100, wherein the cell is prokaryotic.
102. The cell of claim 100, wherein the cell is eukaryotic.
103. A pharmaceutical formulation comprising:
- a composition as in any of claims 1-43;
 - a vector system as in any one of claims 44-77 and 85-98;
 - a polypeptide as in any one of claims 81-84 and 85-99;
 - a particle as in any one of claims 81-99;
 - a cell as in any one of claims 100-102; or
 - a combination thereof; and
- a pharmaceutically acceptable carrier.
104. A composition as in any of claims 1-43; a vector system as in any one of claims 44-77 and 85-98; a polypeptide as in any one of claims 81-84 and 85-99; a particle as in any one of claims 81-99; a cell as in any one of claims 100-102; a pharmaceutical formulation as in claim 103; or combination thereof for use in therapy.
105. Use of composition as in any of claims 1-43; a vector system as in any one of claims 44-77 and 85-98; a particle as in any one of claims 81-99; a cell as in any one

of claims 100-102; a pharmaceutical formulation as in claim 103; or combination thereof in the manufacture of a medicament for treating muscle disease or disorder.

106. The use of claim 105, wherein the muscle disease or disorder is
- a. an auto immune disease;
 - b. a cancer;
 - c. a muscular dystrophy;
 - d. a neuro-muscular disease;
 - e. a sugar or glycogen storage disease;
 - f. an expanded repeat disease;
 - g. a dominant negative disease;
 - h. a cardiomyopathy;
 - i. a viral disease;
 - j. a progeroid disease; or
 - k. any combination thereof.
107. The use of claim 106, wherein the expanded repeat disease is Huntington's disease, a Myotonic Dystrophy, or Facioscapulohumeral muscular dystrophy (FSHD).
108. The use of any one of claims 105-106, wherein the muscular dystrophy is Duchene muscular dystrophy, Becker Muscular dystrophy, a Limb-Girdle muscular dystrophy, an Emery Dreifuss muscular dystrophy, a myotonic dystrophy, or FSHD.
109. The use of claim 107, wherein the myotonic dystrophy is Type 1 or Type 2.
110. The use of any of claims 105-109, wherein the cardiomyopathy is dilated cardiomyopathy, hypertrophic cardiomyopathy, DMD-associated cardiomyopathy, or Dannon disease.
111. The use of any of claims 105-106, wherein the sugar or glycogen storage disease is a MPS type III disease or Pompe disease.

112. The use of claim 111, wherein the MPS type III disease, is MPS Type IIIA, IIIB, IIIC, or IIID.
113. The use of any of claims 105-112, wherein the neuro-muscular disease is Charcot-Marie-Tooth disease or Friedreich's Ataxia.