several hours), making cold preservation of AAV less critical. AAV may even be lyophilized. Finally, AAV-infected cells are not resistant to superinfection.

[0009] Multiple studies have demonstrated long-term (> 1.5 years) recombinant AAV-mediated protein expression in muscle. See, Clark *et al., Hum Gene Ther, 8*: 659-669 (1997); Kessler *et al., Proc Nat. Acad Sc. USA, 93*: 14082-14087 (1996); and Xiao *et al., J Virol, 70*: 8098-8108 (1996). See also, Chao *et al*., *Mol Ther*, *2*:619-623 (2000) and Chao *et al*., *Mol Ther*, *4*:217-222 (2001). Moreover, because muscle is highly vascularized, recombinant AAV transduction has resulted in the appearance of transgene products in the systemic circulation following intramuscular injection as described in Herzog *et al., Proc Natl Acad Sci USA, 94*: 5804-5809 (1997) and Murphy *et al., Proc Natl Acad Sci USA, 94*: 13921-13926 (1997). Moreover, Lewis *et al., J Virol, 76*: 8769-8775 (2002) demonstrated that skeletal myofibers possess the necessary cellular factors for correct antibody glycosylation, folding, and secretion, indicating that muscle is capable of stable expression of secreted protein therapeutics.

[0010] Functional improvement in patients suffering from DMD and other muscular dystrophies require both gene restoration and reduction of fibrosis. There is a need for methods of reducing fibrosis that may be paired with gene restoration methods for more effective treatments of DMD and other muscular dystrophies. miR29 is a potential gene regulator and an ideal candidate for reducing muscle fibrosis.

SUMMARY

[0011] The present invention is directed to gene therapy methods that directly reduce the three primary components of connective tissue (collagen 1, collagen 3 and fibronectin) by delivering the microRNA miR29. In this system, the miR29 binds to the 3' UTR of the collagen and fibronectin gene to down regulate expression. The invention is directed to gene therapy vectors, e.g. AAV, expressing the guide strand of the microRNA miR29 and method of delivering miR29 to the muscle to reduce and/or prevent fibrosis.

[0012] In addition, the invention provides for combination therapies and approaches for reducing and preventing fibrosis using gene therapy vectors deliver miR-29 to suppress fibrosis along with micro-dystrophin to address the gene defect

observed in DMD. As shown in Examples 5-7, the combination treatment resulted in a greater reduction in fibrosis, increased muscle size and increased muscle force.

[0013] In one example, the disclosure provides for a rAAV vector expressing miR-29. For example, the rAAV vector comprises a polynucleotide sequence expressing miR29c such as a nucleotide sequence comprising the miR-29c target guide strand of SEQ ID NO: 3, the miR-29c guide strand of SEQ ID NO: 4 and the natural miR-30 back bone and stem loop (SEQ ID NO: 5). An exemplary polynucleotide sequence comprising the miR-29c cDNA in a miR-30 backbone is set out as SEQ ID NO: 2 (Figure 1).

[0014] An exemplary rAAV of the disclosure is the pAAV.CMV.Mir29C which comprises the nucleotide sequence of SEQ ID NO: 1; wherein the CMV promoter spans nucleotides 120-526, an EF1a intron spans nucleotides 927-1087 and nucleotides 1380-1854, the guide stand of miR-29c spans nucleotide 1257-1284 and the shRNA-miR29-c with primary seed sequence spans nucleotides 1088-1375, and the poly A sequence spans nucleotides 1896-2091. In one example, the rAAV vectors of the disclosure are AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAVrh.74, AAV8, AAV9, AAV10, AAV11, AAV12 or AAV13.

[0015] Another exemplary rAAV of the disclosure is the pAAV.MHC.Mir29C which comprises the nucleotide sequence of SEQ ID NO: 12; wherein the MCK enhancer spans nucleotides 190-395, the MHC promoter spans nucleotides 396-753, an EF1a intron spans nucleotides 1155-1315 and nucleotides 1609-2083, the guide stand of miR-29c spans nucleotide 1487-1512 and the shRNA-miR29-c with primary seed sequence spans nucleotides 1316-1608, and the poly A sequence spans nucleotides 2094-2146. In one example, the rAAV vectors of the disclosure are AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAVrh.74, AAV8, AAV9, AAV10, AAV11, AAV12 or AAV13.

[0016] In another example, the rAAV vectors of the disclosure may be operably linked to a muscle-specific control element. For example the muscle-specific control element is human skeletal actin gene element, cardiac actin gene element, myocyte-specific enhancer binding factor MEF, muscle creatine kinase (MCK), tMCK (truncated MCK), myosin heavy chain (MHC), C5-12 (synthetic promoter), murine creatine kinase enhancer element, skeletal fast-twitch troponin C gene element, slow-

twitch cardiac troponin C gene element, the slow-twitch troponin I gene element, hypozia-inducible nuclear factors, steroid-inducible element or glucocorticoid response element (GRE).

[0017] For example, any of the rAAV vectors of the disclosure are operably linked to the muscle-specific control element comprising the MCK enhancer nucleotide sequence of SEQ ID NO: 10 and/or the MCK promoter sequence of SEQ ID NO: 11.

[0018] The disclosure also provides for pharmaceutical compositions (or sometimes referred to herein as simply "compositions") comprising any of the rAAV vectors of the disclosure.

[0019] In another example, the disclosure provides for methods of producing a rAAV vector particle comprising culturing a cell that has been transfected with any rAAV vector of the invention and recovering rAAV particles from the supernatant of the transfected cells. The disclosure also provides for viral particles comprising any of the recombinant AAV vectors of the disclosure.

[0020] In another example, the disclosure provides for methods of reducing fibrosis in a subject in need comprising administering a therapeutically effective amount of any rAAV vector of the disclosure expressing miR-29. For example, any of the rAAV of the disclosure are administered to subjects suffering from muscular dystrophy to reduce fibrosis, and in particular reduces fibrosis in skeletal muscle or in cardiac muscle of the subject. These methods may further comprise the step of administering a rAAV expressing micro-dystrophin.

[0021] "Fibrosis" refers to the excessive or unregulated deposition of extracellular matrix (ECM) components and abnormal repair processes in tissues upon injury including skeletal muscle, cardiac muscle, liver, lung, kidney, and pancreas. The ECM components that are deposited include fibronectin and collagen, e.g. collagen 1, collagen 2 or collagen 3.

[0022] In another example, the disclosure provides for methods of preventing fibrosis in a subject in need comprising administering a therapeutically effective amount of the any recombinant AAV vector of the disclosure expressing miR-29. For example, any of the rAAV of the disclosure are administered to subjects suffering from muscular dystrophy to prevent fibrosis, e.g. the rAAV of the disclosure expressing miR-29 are administered before fibrosis is observed in the subject. In

addition, the rAAV of the disclosure expressing miR-29 are administered to a subject at risk of developing fibrosis, such as those suffering or diagnosed with muscular dystrophy, e.g. DMD. The rAAV of the disclosure are administered to the subject suffering from muscular dystrophy in order to prevent new fibrosis in these subjects. These methods may further comprise the step of administering a rAAV expressing micro-dystrophin.

[0023] The disclosure also provides for methods of increasing muscular force and/or muscle mass in a subject suffering from muscular dystrophy comprising administering a therapeutically effective amount of any of the rAAV vector of the disclosure expressing miR-29. These methods may further comprise the step of administering a rAAV expressing micro-dystrophin.

The terms "combination therapy" and "combination treatment" refer to administration of a rAAV vector of the disclosure expressing miR-29 and a rAAV vector expressing micro-dystrophin.

[0024] In any of the methods of the disclosure, the subject may be suffering from muscular dystrophy such as DMD, Becker muscular dystrophy or any other dystrophin-associated muscular dystrophy. In addition, in any of the methods of the disclosure, the subject may be suffering from dystrophinopathy.

[0025] In one example, the disclosure provides for recombinant AAV vectors comprising a nucleotide sequence encoding a micro-dystrophin protein. In one aspect, the invention provides for a rAAV comprising a) a nucleotide sequence having at least 85% identity to the nucleotide sequence SEQ ID NO: 7 and encodes a functional micro-dystrophin protein, b) the nucleotide sequence of SEQ ID NO: 7, or c) the nucleotide sequence of SEQ ID NO: 9.

[0026] An exemplary rAAV expressing micro-dystrophin of the disclosure is the pAAV.mck.micro-dystrophin which comprises the nucleotide sequence of SEQ ID NO: 9 and shown in Figure 10 and 11. This rAAV vector comprises the MCK promoter, a chimeric intron sequence, the coding sequence for the micro-dystrophin gene, polyA, ampicillin resistance and the pGEX plasmid backbone with pBR322 origin or replication. In one example, the recombinant AAV vectors of the disclosure are AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAVrh.74, AAV8, AAV9, AAV10, AAV11, AAV12 or AAV13.

[0027] The disclosure provides for rAAV vectors encoding a micro-dystrophin protein that is, e.g., at least at least 65%, at least 70%, at least 75%, at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, or 89%, more typically at least 90%, 91%, 92%, 93%, or 94% and even more typically at least 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 8, wherein the protein retains micro-dystrophin activity. The micro-dystrophin protein provides stability to the muscle membrane during muscle contraction, e.g. micro-dystrophin acts as a shock absorber during muscle contraction.

[0028] The disclosure provides for rAAV vectors expressing micro-dystrophin comprising a nucleotide sequence that has at least 65%, at least 70%, at least 75%, at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, or 89%, more typically at least 90%, 91%, 92%, 93%, or 94% and even more typically at least 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO: 7, and encodes a functional micro-dystrophin protein.

[0029] The disclosure provides for rAAV vectors expressing micro-dystrophin comprising a nucleotide sequence that hybridizes under stringent conditions to the nucleic acid sequence of SEQ ID NOS: 7, or compliments thereof, and encodes a functional micro-dystrophin protein.

[0030] The term “stringent” is used to refer to conditions that are commonly understood in the art as stringent. Hybridization stringency is principally determined by temperature, ionic strength, and the concentration of denaturing agents such as formamide. Examples of stringent conditions for hybridization and washing are 0.015 M sodium chloride, 0.0015 M sodium citrate at 65-68^{o}C or 0.015 M sodium chloride, 0.0015M sodium citrate, and 50% formamide at 42^{o}C. See Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory, (Cold Spring Harbor, N.Y. 1989). More stringent conditions (such as higher temperature, lower ionic strength, higher formamide, or other denaturing agent) may also be used, however, the rate of hybridization will be affected. In instances wherein hybridization of deoxyoligonucleotides is concerned, additional exemplary stringent hybridization conditions include washing in 6x SSC 0.05% sodium pyrophosphate at 37°C (for 14-base oligos), 48°C (for 17-base oligos), 55°C (for 20-base oligos), and 60°C (for 23-base oligos).

[0031] Other agents may be included in the hybridization and washing buffers for the purpose of reducing non-specific and/or background hybridization. Examples are 0.1% bovine serum albumin, 0.1% polyvinyl-pyrrolidone, 0.1% sodium pyrophosphate, 0.1% sodium dodecylsulfate, NaDodSO4, (SDS), ficoll, Denhardt's solution, sonicated salmon sperm DNA (or other non-complementary DNA), and dextran sulfate, although other suitable agents can also be used. The concentration and types of these additives can be changed without substantially affecting the stringency of the hybridization conditions. Hybridization experiments are usually carried out at pH 6.8-7.4, however, at typical ionic strength conditions, the rate of hybridization is nearly independent of pH. See Anderson et al., Nucleic Acid Hybridisation: A Practical Approach, Ch. 4, IRL Press Limited (Oxford, England). Hybridization conditions can be adjusted by one skilled in the art in order to accommodate these variables and allow DNAs of different sequence relatedness to form hybrids.

[0032] In another example, the rAAV vectors expressing micro-dystrophin comprises the coding sequence of the micro-dystrophin gene operably linked to a muscle-specific control element. For example, the muscle-specific control element is human skeletal actin gene element, cardiac actin gene element, myocyte-specific enhancer binding factor MEF, muscle creatine kinase (MCK), tMCK (truncated MCK), myosin heavy chain (MHC), C5-12 (synthetic promoter), murine creatine kinase enhancer element, skeletal fast-twitch troponin C gene element, slow-twitch cardiac troponin C gene element, the slow-twitch troponin I gene element, hypozia-inducible nuclear factors, steroid-inducible element or glucocorticoid response element (GRE).

[0033] In addition, the disclosure provides for rAAV vectors expressing micro-dystrophin comprising a muscle-specific control element comprising the nucleotide sequence of SEQ ID NO: 10 or SEQ ID NO: 11.

[0034] The disclosure also provides for pharmaceutical compositions (or sometimes referred to herein as simply "compositions") comprising any of the rAAV vectors of the disclosure.

[0035] In another example, the disclosure provides for methods of producing a rAAV vector particle comprising culturing a cell that has been transfected with any rAAV vector of the disclosure and recovering rAAV particles from the supernatant of

the transfected cells. The disclosure also provides for viral particles comprising any of the recombinant AAV vectors of the disclosure.

[0036] In another aspect, the present invention also provides for methods of producing a functional micro-dystrophin protein comprising infecting a host cell with a recombinant AAV vector expressing micro-dystrophin as disclosed herein and expressing a functional micro-dystrophin protein in the host cell.

[0037] In another example, the disclosure provides for methods of reducing fibrosis in a subject in need comprising administering a therapeutically effective amount of any rAAV vector of the disclosure expressing micro-dystrophin. For example, any of the rAAV of the disclosure are administered to subjects suffering from muscular dystrophy or dystrophinopathy to reduce fibrosis, and in particular reduces fibrosis in skeletal muscle or in cardiac muscle of the subject.

[0038] In another example, the disclosure provides for methods of preventing fibrosis in a subject in need comprising administering a therapeutically effective amount of the any recombinant AAV vector of the disclosure expressing micro-dystrophin. For example, any of the rAAV of the disclosure are administered to subjects suffering from muscular dystrophy or dystrophinopathy to prevent fibrosis, e.g. the rAAV of the disclosure expressing micro-dystrophin are administered before fibrosis is observed in the subject. In addition, the rAAV of the disclosure expressing micro-dystrophin are administered to a subject at risk of developing fibrosis, such as those suffering or diagnosed with dystrophinopathy or muscular dystrophy, e.g. DMD or Becker muscular dystrophy. The rAAV of the disclosure are administered to the subject suffering from dystrophinopathy or dystrophinopathy muscular dystrophy in order to prevent new fibrosis in these subjects.

[0039] The disclosure also provides for methods of increasing muscular force and/or muscle mass in a subject suffering from muscular dystrophy or dystrophinopathy comprising administering a therapeutically effective amount of any of the rAAV vector of the disclosure expressing miR-29.

[0040] Any of the foregoing methods comprising the step of administering the rAAV expressing miR-29c of the disclosure may comprise a further step of administering any of the rAAV expressing the micro-dystrophin described herein. The terms “combination therapy” and “combination treatment” refer to administration

of a rAAV vector of the disclosure expressing miR-29 and an rAAV vector expressing micro-dystrophin.

[0041] In the methods of administering an rAAV vector expressing miR-29 and an rAAV vector expressing the micro-dystrophin protein, these rAAV vectors may be administered concurrently, or administered consecutively with the rAAV vector expressing miR29 administered immediately before the rAAV expressing the micro-dystrophin protein, or administered consecutively with the rAAV vector expressing miR29 is administered immediately after the rAAV expressing the micro-dystrophin protein. Alternatively, the methods of the disclosure are carried out wherein the AAV vector expressing the micro-dystrophin protein is administered within about 1-5 hours or 5-12 hours or 12 to 15 hours or 15 to 24 hours after administering the rAAV expressing miR-29 or the methods of the disclosure are carried out wherein the AAV vector expressing the micro-dystrophin protein is administered within about 1-5 hours or 5-12 hours or 12 to 15 hours or 15 to 24 hours before administering the rAAV expressing miR-29. Alternatively, the methods of the disclosure are carried out wherein the AAV vector expressing the micro-dystrophin protein is administered within about 1 or 6 or 12 or 24 hours after administering the rAAV expressing miR-29 or the methods of the disclosure are carried out wherein the AAV vector expressing the micro-dystrophin protein is administered within about 1 or 6 or 12 or 24 hours before administering the rAAV expressing miR-29.

[0042] The disclosure contemplates administering any of the AAV vectors of the disclosure to patients diagnosed with dystrophinopathy or muscular dystrophy, such as DMD or Becker Muscular dystrophy, before fibrosis is observed in the subject or before the muscle force has been reduced in the subject or before the muscle mass has been reduced in the subject.

[0043] The disclosure also contemplates administering any of the rAAV of the disclosure to a subject suffering from dystrophinopathy or muscular dystrophy, such as DMD or Becker Muscular dystrophy, who already has developed fibrosis, in order to prevent new fibrosis in these subjects. The disclosure also provides for administering any of the rAAV of the disclosure to the patient suffering from muscular dystrophy who already has reduced muscle force or has reduced muscle mass in order to protect the muscle from further injury.

[0044] In any of the methods of the disclosure, the rAAV vector are administered by intramuscular injection or intravenous injection.

[0045] In addition, in any of the methods of the disclosure, the rAAV vector or composition is administered systemically. For examples, the rAAV vector or composition is parentally administration by injection, infusion or implantation.

[0045a] In one aspect, the present invention provides for a composition comprising the recombinant AAV vector as disclosed herein.

[0045b] In another aspect, the present invention provides for a composition comprising the recombinant AAV vector as disclosed herein for use in treatment of muscular dystrophy, for use in reducing or preventing fibrosis in a subject suffering from muscular dystrophy, or for use in increasing muscular force in a subject suffering from muscular dystrophy.

[0046] In one example, the disclosure provides for composition comprising any of the rAAV vectors expressing miR29 or any of the rAAV vectors expressing micro-dystrophin or comprising both a rAAV vector expressing miR-29 and a rAAV vector expressing micro-dystrophin for reducing fibrosis in a subject in need. In addition, the disclosure provides for compositions comprising any of the recombinant AAV vectors expressing miR29 or any of the rAAV vectors expressing micro-dystrophin or comprising both a rAAV vector expressing miR-29 and a rAAV vector expressing micro-dystrophin for preventing fibrosis in a patient suffering from dystrophinopathy or muscular dystrophy, such as DMD or Becker Muscular dystrophy.

[0047] The disclosure also provides for compositions comprising any of the rAAV vectors of the disclosure expressing miR29 or any of the rAAV vectors expressing micro-dystrophin protein or comprising both a rAAV vector expressing miR-29 and a rAAV vector expressing micro-dystrophin protein for increasing muscular force and/or muscle mass in a subject suffering from dystrophinopathy or muscular dystrophy, such as DMD or Becker Muscular dystrophy.

[0048] In a further example, the disclosure provides for compositions comprising any of the rAAV vectors of the disclosure expressing miR29 or any of the rAAV vectors expressing micro-dystrophin protein or comprising both a rAAV vector expressing miR-29 and a rAAV vector expressing micro-dystrophin protein for

treatment of dystrophinopathy or muscular dystrophy, such as DMD or Becker Muscular dystrophy.

[0049] The compositions of the disclosure are formulated for intramuscular injection or intravenous injection. The composition of the disclosure is also formulated for systemic administration, such as parentally administration by injection, infusion or implantation. In addition, any of the compositions are formulated for administration to a subject suffering from dystrophinopathy or muscular dystrophy,such as DMD, Becker muscular dystrophy or any other dystrophin associated muscular dystrophy.

[0049a] In one aspect, the present invention provides for the use of a recombinant AAV vector of the present disclosure or the composition of the present disclosure for the preparation of a medicament for treatment of muscular dystrophy, for reducing or preventing fibrosis in a subject suffering from muscular dystrophy, or for the increasing muscular strength or muscle mass in a subject suffering from muscular dystrophy.

[0050] In a further example, the disclosure provides for use of any of the rAAV vectors of the disclosure expressing miR29 or any of the rAAV vectors expressing micro-dystrophin or comprising both a rAAV vector expressing miR-29 and a rAAV vector expressing micro-dystrophin for preparation of a medicament for reducing fibrosis in a subject in need. For example, the subject is in need suffering from dystrophinopathy or muscular dystrophy, such as DMD, Becker muscular dystrophy or any other dystrophin associated muscular dystrophy.

[0051] In another example, the disclosure provides for provides for use of any of the rAAV vectors of the disclosure expressing miR29 or any of the rAAV vectors expressing micro-dystrophin or comprising both a rAAV vector expressing miR-29 and a rAAV vector expressing micro-dystrophin for the preparation of a medicament for preventing fibrosis in a subject suffering from muscular dystrophy. In addition, the disclosure provides for use of the recombinant AAV vectors of the disclosure expressing miR29 or any of the rAAV vectors expressing micro-dystrophin or comprising both a rAAV vector expressing miR-29 and a rAAV vector expressing micro-dystrophin for the preparation of a medicament for the increasing muscular

strength and/or muscle mass in a subject suffering from dystrophinopathy or muscular dystrophy, such as DMD or Becker Muscular dystrophy.

[0052] The disclosure contemplates use of the any of the AAV vectors of the disclosure for the preparation of a medicament for administration to a patient diagnosed with DMD before fibrosis is observed in the subject or before the muscle force has been reduced in the subject or before the muscle mass has been reduced in the subject.

[0053] The disclosure also contemplates use of any of the AAV vectors of the disclosure for the preparation of a medicament for administration to administering any of the rAAV of the disclosure to a subject suffering from muscular dystrophy who already has developed fibrosis, in order to prevent new fibrosis in these subjects. The disclosure also provides for administering any of the rAAV of the disclosure to the

patient suffering from muscular dystrophy who already has reduced muscle force or has reduced muscle mass in order to protect the muscle from further injury.

[0054] The disclosure also provides for use of the rAAV vectors of the disclosure expressing miR296 or any of the rAAV vectors expressing micro-dystrophin or comprising both a rAAV vector expressing miR-29 and a rAAV vector expressing micro-dystrophin for the preparation of a medicament for treatment of muscular dystrophy.

[0055] In any of the uses of the disclosure, the medicament is formulated for intramuscular injection. In addition, any of the medicaments may be prepared for administration to a subject suffering from muscular dystrophy such as DMD or any other dystrophin associated muscular dystrophy.

[0056] In addition, any of the medicaments of the disclosure may be a combination therapy in which the rAAV vectors expressing miR-29 and rAAV vectors expressing micro-dystrophin are administered concurrently, or administered consecutively with the rAAV vector expressing miR29 administered immediately before the rAAV expressing micro-dystrophin, or administered consecutively with the rAAV vector expressing miR29 administered immediately after the rAAV expressing micro-dystrophin. Alternatively, the medicament comprises administration of the AAV vector expressing micro-dystrophin administered within about 1-5 hours after administering the rAAV expressing miR-29 or the medicament comprises the AAV vector expressing micro-dystrophin administered within about 1-5 hours before administering the rAAV expressing miR-29.

BRIEF DESCRIPTION OF DRAWING

[0057] **Figure 1** provide a schematic of rAAV vector scAAVCrh.74.CMV.miR29c and the nucleotide sequence of the miR-29c in a natural miR-30 backbone and the nucleotide sequence of the predicted hairpin structure.

[0058] **Figure 2A-CD** illustrates that injection of miR-29c into muscle reduces collagen throughout the muscle and restores miR-29c expression.

[0059] **Figure 3A-3C** demonstrates that injection of miR-29c improves absolute muscle force (panel A) and specific muscle force (panel B) but does not protect against contraction-induced damage (panel C).

What is claimed:

1. A recombinant AAV vector comprising

a) a nucleotide sequence having at least 85% identity to the nucleotide sequence SEQ ID NO: 7 and encodes a functional micro-dystrophin protein,

b) the nucleotide sequence of SEQ ID NO: 7, or

c) the nucleotide sequence of SEQ ID NO: 9.

2. The recombinant AAV vector of claim 1 wherein the vector is the serotype AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAVrh74, AAV8, AAV9, AAV10, AAV11, AAV12 or AAV13.

3. The recombinant AAV vector of claim 1 or 2 wherein the polynucleotide sequence is operably linked to a muscle-specific control element.

4. The recombinant AAV vector of claim 3 wherein the muscle-specific control element is human skeletal actin gene element, cardiac actin gene element, myocyte-specific enhancer binding factor mef, muscle creatine kinase (MCK), truncated MCK (tMCK), myosin heavy chain (MHC), C5-12, murine creatine kinase enhancer element, skeletal fast-twitch troponin c gene element, slow-twitch cardiac troponin c gene element, the slow-twitch troponin i gene element, hypoxia-inducible nuclear factors, steroid-inducible element or glucocorticoid response element (gre).

5. The recombinant AAV vector of claim 3 or 4 wherein the muscle-specific control element comprises the nucleotide sequence of SEQ ID NO: 10 or SEQ ID NO: 11.

6. A composition comprising the recombinant AAV vector of any one of claims 1-5.

7. A composition comprising the recombinant AAV vector of any one of claims 1-5 for use in treatment of muscular dystrophy.

8. A composition comprising the recombinant AAV vector of any one of claims 1-5 for use in reducing or preventing fibrosis in a subject suffering from muscular dystrophy.

9. A composition comprising the recombinant AAV vector of any one of claims 1-5 for use in increasing muscular force in a subject suffering from muscular dystrophy.

10. The composition of any one of claims 7-9 wherein the composition is to be administered before fibrosis is observed in the subject or before muscle force is reduced in the subject or before muscle mass is reduced in the subject.

11. The composition of any one of claims 7-10 wherein the subject is suffering from Duchenne muscular dystrophy or Becker muscular dystrophy.

12. Use of the recombinant AAV vector of any one of claims 1-5 or the composition of claim 6 for the preparation of a medicament for treatment of muscular dystrophy.

13. Use of a recombinant AAV vector of any one of claims 1-5 or the composition of claim 6 for the preparation of a medicament for reducing or preventing fibrosis in a subject suffering from muscular dystrophy.

14. Use of the recombinant AAV vector of any one of claims 1-5 or the composition of claim 6 for the preparation of a medicament for the increasing muscular strength or muscle mass in a subject suffering from muscular dystrophy.

15. The use of any one of claims 12-14 wherein the medicament is to be administered before fibrosis is observed in the subject or before muscle force is reduced in the subject or before muscle mass is reduced in the subject.

16. The use of any one of claims 12-15 wherein the subject is suffering from Duchenne muscular dystrophy or Becker muscular dystrophy.

17. The composition for use or use of any one of claims 7-16 wherein the composition or medicament is formulated for intramuscular administration, intravenous injection, parental administration or systemic administration.

18. A method of producing a functional micro-dystrophin protein comprising infecting a host cell with a recombinant AAV vector of any one of claims 1-5 and expressing a functional micro-dystrophin protein in the host cell.