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 example, the disclosure 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. In one aspect, the present invention refers to a recombinant AAVrh74 vector comprising in the 5' to 3´ direction an inverted terminal repeat (ITR), a muscle-specific control element, a chimeric intron sequence, the nucleotide sequence of SEQ ID NO: 7, a poly A tail, and an ITR.

[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.

[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 AAVrh74 vector as disclosed herein and a pharmaceutically acceptable carrier.

[0045b] In another aspect, the present invention provides for a composition comprising the recombinant AAV vector as disclosed herein for use in therapy.

[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 AAVrh74 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

What is claimed:

1. A recombinant AAVrh74 vector comprising in the 5’ to 3′ direction an inverted terminal repeat (ITR), a muscle-specific control element, a chimeric intron sequence, the nucleotide sequence of SEQ ID NO: 7, a poly A tail, and an ITR.

2. The recombinant AAVrh74 vector of claim 1 wherein the muscle-specific control element comprises the nucleotide sequence of SEQ ID NO: 10 or SEQ ID NO: 11.

3. The recombinant AAVrh74 vector of claim 1 or 2 further comprising a chimeric intron sequence between said nucleotide sequence and said muscle-specific control element, wherein the chimeric intron sequence is set forth as nucleotides 844-993 of SEQ ID NO: 9.

4. The recombinant AAVrh74 vector of claim 1 further comprising a poly A tail 3′ of said nucleotide sequence, wherein the sequence of said poly A tail is set forth as nucleotides 4585 to 4640 of SEQ ID NO: 9.

5. A composition comprising the recombinant AAVrh74 vector of any one of claims 1-4 and a pharmaceutically acceptable carrier.

6. A composition comprising the recombinant AAVrh74 vector of any one of claims 1-4 for use in therapy.

7. Use of the recombinant AAVrh74 vector of any one of claims 1-4 or the composition of claim 5 for the preparation of a medicament for treatment of muscular dystrophy.

8. Use of a recombinant AAVrh74 vector of any one of claims 1-4 or the composition of claim 5 for the preparation of a medicament for reducing or preventing fibrosis in a subject suffering from muscular dystrophy.

9. Use of the recombinant AAVrh74 vector of any one of claims 1-4 or the composition of claim 5 for the preparation of a medicament for the increasing muscular strength or muscle mass in a subject suffering from muscular dystrophy.

10. The use of any one of claims 7-9 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.

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

12. The composition for use or use of any one of claims 6-11 wherein the composition or medicament is formulated for intramuscular administration, intravenous injection, parental administration or systemic administration.

13. A method of producing a functional micro-dystrophin protein comprising infecting a host cell with a recombinant AAVrh74 vector of any one of claims 1-4 and expressing a functional micro-dystrophin protein in the host cell.

14. The recombinant AAVrh74 vector of any one of claims 1-4 for use in a method of producing a functional micro-dystrophin protein, the method comprising infecting a host cell with the recombinant AAV vector and expressing a functional micro-dystrophin protein in the host cell.