[0008] There are at least nineteen forms of LGMD, and the forms are classified by their associated genetic defects.

Type	Pattern of Inheritance	Gene or Chromosome
LGMD1A	Autosomal dominant	Myotilin gene
LGMD1B	Autosomal dominant	Lamin A/C gene
LGMD1C	Autosomal dominant	Caveolin gene
LGMD1D	Autosomal dominant	Chromosome 7
LGMD1E	Autosomal dominant	Desmin gene
LGMD1F	Autosomal dominant	Chromosome 7
LGMD1G	Autosomal dominant	Chromosome 4
LGMD2A	Autosomal recessive	Calpain-3 gene
LGMD2B	Autosomal recessive	Dysferlin gene
LGMD2C	Autosomal recessive	Gamma-sarcoglycan gene
LGMD2D	Autosomal recessive	Alpha-sarcoglycan gene
LGMD2E	Autosomal recessive	Beta-sarcoglycan gene
LGMD2F	Autosomal recessive	Delta-sarcoglycan gene
LGMD2G	Autosomal recessive	Telethonin gene
LGMD2H	Autosomal recessive	TRIM32
LGMD2I	Autosomal recessive	FKRP gene
LGMD2J	Autosomal recessive	Titin gene
LGMD2K	Autosomal recessive	POMT1 gene
LGMD2L	Autosomal recessive	Fukutin gene

[0009] Specialized tests for LGMD are now available through a national scheme for diagnosis, the National Commissioning Group (NCG).

[0010] As gene therapies for treating muscular dystrophy, such as DMD or LGMD, are developed, there is a need for optimizing these therapies and to evaluate the effects of immunosuppression on the expression of the micro-dystrophin transgene by the optimized gene therapy vectors.

SUMMARY

[0010a] In one aspect, the present disclosure relates to use a dose of recombinant adeno-virus associated (rAAV) AAVrh.74.MHCK7.microdystrophin for the preparation of a medicament for treating a muscular dystrophy in a human subject in need thereof, wherein

the rAAV is administered prior to subjecting the subject's plasma to at least one therapeutic plasma exchange (TPE) prior to administration of a second dose of the rAAV.

[0010b] In another aspect, the present disclosure relates to use of a dose of recombinant adeno-virus associated (rAAV) AAVrh.74.MHCK7.microdystrophin for the preparation of a medicament for treating a muscular dystrophy in a human subject in need thereof, wherein the rAAV is administered after a first dose of the rAAV and after subjecting the subject's plasma to at least one therapeutic plasma exchange (TPE).

[0010c] In another aspect, the present disclosure relates to use of a recombinant adeno-virus associated (rAAV) AAVrh.74.MHCK7.microdystrophin for the preparation of a medicament for treating muscular dystrophy in a human subject in need thereof, wherein the rAAV is administered after subjecting the subject's plasma to at least one therapeutic plasma exchange (TPE) prior to administering recombinant adeno-virus associated (rAAV).

[0011] The present disclosure is directed to gene therapy vectors, e.g. AAV, expressing a transgene of interest to skeletal muscles to treat a muscular dystrophy in combination with administration of immunosuppressants. In addition, the present disclosure includes methods

nucleic acid sequence of SEQ ID NO: 9 or nucleotides 1-4977 of SEQ ID NO: 8 or nucleotides 55-5021 of SEQ ID NO: 3, and rAAV particles comprising the nucleic acid sequence of SEQ ID NO: 9 or nucleotides 1-4977 of SEQ ID NO: 8 or nucleotides 55-5021 of SEQ ID NO: 3.

[0017] Another example of the disclosure provides for compositions comprising a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 3, 8 or 9, rAAV comprising the nucleic acid sequence of SEQ ID NO: 9 or nucleotides 1-4977 of SEQ ID NO: 8 or nucleotides 55-5021 of SEQ ID NO: 3, and rAAV particles comprising the nucleic acid sequence of SEQ ID NO: 9 or nucleotides 1-4977 of SEQ ID NO: 8 or nucleotides 55-5021 of SEQ ID NO: 3. Any of the methods disclosed herein may be carried out with these compositions.

[0018] In addition, the disclosure provide for a composition comprising a nucleic acid comprising the rAAV genome of one of the following AAVrh.74.tMCK.CAP N3, rAAVrh.74.MHCK7.DYSF, scAAVrh.74.MHCK7.hSGCG, AAVrh74.tMCK.hSCGA, scAAVrh74.MHCK7.HSGCB, and rAAVrh.74.MHCK7.huAN05.

[0019] The disclosure provides for methods of treating a muscular dystrophy in a human subject in need thereof comprising the step of comprising the step of administering a recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin and an anti-inflammatory steroid. In addition, the disclosure provides for use of a combination therapy comprising a recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin and an anti-inflammatory steroid for the preparation of a medicament for treating a muscular dystrophy in a human subject in need thereof, such that rAAV and the anti-inflammatory steroid of the medicament are co-administered separately, such as the rAAV and anti-inflammatory steroid are co-administered simultaneously or sequentially.. The disclosure also provides for a combination therapy for treating a muscular dystrophy wherein the therapy comprises a recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin and an anti-inflammatory steroid, wherein rAAV and the anti-inflammatory steroid are co-administered separately, such as the rAAV and anti-inflammatory steroid are co-administered simultaneously or sequentially. For example, the muscular dystrophy is DMD or Becker's muscular dystrophy. For example, the anti-inflammatory steroid is a glucocorticoid. In some examples, the anti-inflammatory steroid is prednisone, prednisolone, betamethasone, dexamethasone, hydrocortisone, methylprednisolone or deflazacort. In some examples, the anti-inflammatory steroid is

administered orally. The anti-inflammatory steroid may be administered both prior to and after administration of the rAAV. Alternatively, the anti-inflammatory steroid is administered only prior to or only after administration of the rAAV.

[0020] In addition, the disclosure provides for a method of treating a Limb Girdle Muscular Dystrophy in a human subject in need thereof comprising the step of administering a recombinant adeno-virus associated (rAAV) and an anti-inflammatory steroid, wherein the rAAV is selected from the group consisting of: AAVrh.74.tMCK.CAPN3, rAAVrh.74.MHCK7.DYSF, scAAVrh.74.MHCK7.hSGCG, AAVrh74.tMCK.hSCGA, scAAVrh74.MHCK7.HSGCB, and rAAVrh.74.MHCK7.huAN05. In addition, the disclosure provides for use of a combination therapy comprising a recombinant adeno-virus associated (rAAV) and an anti-inflammatory steroid for the preparation of a medicament for treating a Limb Girdle Muscular Dystrophy in a human subject in need thereof, wherein the rAAV is selected from the group consisting of: AAVrh.74.tMCK.CAPN3, rAAVrh.74.MHCK7.DYSF, scAAVrh.74.MHCK7.hSGCG, AAVrh74.tMCK.hSCGA, scAAVrh74.MHCK7.HSGCB, and rAAVrh.74.MHCK7.huAN05, such that rAAV and the anti-inflammatory steroid of the medicament are co-administered separately, such as the rAAV and anti-inflammatory steroid are co-administered simultaneously or sequentially. The disclosure also provides for a combination therapy for treating Limb Girdle Muscular Dystrophy wherein the combination therapy comprises a recombinant adeno-virus associated (rAAV) and an anti-inflammatory steroid, wherein the rAAV is selected from the group consisting of: AAVrh.74.tMCK.CAPN3, rAAVrh.74.MHCK7.DYSF, scAAVrh.74.MHCK7.hSGCG, AAVrh74.tMCK.hSCGA, scAAVrh74.MHCK7.HSGCB, and rAAVrh.74.MHCK7.huAN05, wherein rAAV and the anti-inflammatory steroid are co-administered separately, such as the rAAV and anti-inflammatory steroid are co-administered simultaneously or sequentially. For example, the anti-inflammatory steroid is a glucocorticoid. In some examples, the anti-inflammatory steroid is prednisone, prednisolone, betamethasone, dexamethasone, hydrocortisone, methylprednisolone or deflazacort. In some examples, the anti-inflammatory steroid is administered orally. The anti-inflammatory steroid may be administered both prior to and after administration of the rAAV. Alternatively, the anti-inflammatory steroid is administered only prior to or only after administration of the rAAV.

[0021] For example, in any of the methods, uses or combination therapies disclosed herein , the anti-inflammatory steroid is administered about 12 hour prior to administration of the

rAAV or about 24 hours prior to administration of the rAAV or about 36 hours prior to administration of the rAAV or about 48 hours prior to administration of the rAAV or about 60 hours prior to administration of the rAAV or about 72 hours prior to administration of the rAAV or about 96 hours prior to administration. In some examples, the inflammatory steroid is administered about 5 days hours prior to administration of the rAAV, about 6 days hours prior to administration of the rAAV, about 7 days hours prior to administration of the rAAV, or about 8 days prior to administration of the rAAV, or about 9 days prior to administration of the rAAV, or about 10 days prior to administration of the rAAV, or about 11 days prior to administration of the rAAV, or about 12 days prior to administration of the rAAV, or about 13 days prior to administration of the rAAV, or about 14 days prior to administration of the rAAV, or about 30 days prior to administration of the rAAV.

[0022] In addition, in any of the disclosed methods, uses or combination therapies, the anti-inflammatory steroid is administered at least once a day for about 7 days prior to administration of the rAAV, or administered at least once a day for about 14 days prior to administration of the rAAV, or administered at least once a day for 21 days, or administered at least once a day for about 28 days prior to administration of the rAAV, or administered at least once a day for about 30 days prior to administration of the rAAV, or administered at least once a day for about 45 days prior to administration of the rAAV, or administered at least once a day for about 60 days prior to administration of the rAAV. In some examples, the anti-inflammatory steroid is administered 30 to 60 days prior to administration of the rAAV.

[0023] For example, in any of the disclosed methods, uses or combination therapies, the anti-inflammatory steroid is administered prior to administration of the rAAV and the anti-inflammatory steroid is administered at least once a day from day 1 to 30 days after administration of the rAAV or at least once a day from 1 to 60 days after administration of the rAAV or at least once a day from 1 to 7 days after administration of the rAAV or at least once a day from 1 to 14 days after administration of the rAAV or at least once a day from 1 to 21 days after administration of the rAAV, or at least once a day from 1 to 24 days after administration of the rAAV, or at least once a day from 1 to 28 days after administration of the rAAV, or at least from 1 to 30 days after administration of the rAAV, or at least 30 to 60 days after administration of the rAAV.

[0024] In any of the methods, uses or combination therapies disclosed herein, an anti-CD20 specific antibody is administered prior to administration of the rAAV. In some

examples, the anti-CD20 specific antibody is administered at least 7 days prior to administration of the rAAV. The term anti-CD20 specific antibody refers to an antibody that specifically binds to or inhibits or reduces the expression or activity of CD20. Exemplary anti-CD20 antibodies include rituximab, ocrelizumab or ofatumumab.

[0025] In any of the disclosed methods, uses or combination therapies, an anti-CD20 specific antibody is administered about 60 days prior to administration of the rAAV, or about 45 days prior to administration the rAAV, or about 30 days prior to administration of the rAAV, about 14 days prior to administration of the rAAV, about 7 days prior to administration of the rAAV and within about 24 hours of the administration of the rAAV. In some examples, the anti-CD20 antibody is administered 30 to 60 days prior to administration of the rAAV. In some examples, the anti-CD20 specific antibody is administered after administration of the rAAV. For example, the anti-CD20 specific antibody is administered both prior to and after administration of the rAAV. Alternatively, the anti-CD20 specific antibody is administered prior to administration of the rAAV or the anti-CD20 specific antibody is administered after administration of the rAAV.

[0026] In addition, in any of the disclosed methods, uses or combination therapies may comprise administering an immunosuppressing macrolide. The term immunosuppressing macrolide refers to a macrolide agent suppresses or modulates the immune system of the subject. A macrolide is a classes of agents that comprise a large macrocyclic lactone ring to which one or more deoxy sugars, such as cladinose or desoamine, are attached. The lactone rings are usually 14-, 15-, or 16-membered. Macrolides belong to the polyketide class of agents and may be natural products. Examples of immunosuppressing macrolides include tacrolimus, pimecrolimus, and sirolimus. In some examples, the immunosuppressing macrolide is orally administered to the subject. In some examples, the immunosuppressing macrolide may be administered both prior to administration of the rAAV and after administration of the rAAV. Alternatively, the immunosuppressing macrolide is administered prior to administration or the rAAV or the immunosuppressing macrolide is administered after administration of the rAAV.

[0027] In some examples, the immunosuppressing macrolide is administered at least once a day for at least three days prior to administration of the rAAV, or administered at least 4 days prior to administration of the rAAV, or administered at least 5 days prior to administration of the rAAV, or administered at least 6 days prior to administration of the rAAV, administered at least 7 days prior to administration of the rAAV, or administered at

least 10 days prior to administration of the rAAV, or administered at least 14 days prior to administration, or administered at least 30 days prior to administration of the rAAV, or administered at least 45 days prior to administration of the rAAV, or administered at least 60 days prior to administration of the rAAV. In some examples, the immunosuppressing macrolide is administered 30 to 60 days prior to administration of the rAAV.

[0028] The disclosure also provides for a method of treating muscular dystrophy in a human subject in need thereof comprising administering a recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin and an immunosuppressing regimen, wherein the immunosuppressing regimen comprises administering one or more of an anti-inflammatory steroid, an anti-CD20 antibody, and an immunosuppressing macrolide. The disclosure also provides for use of a combination therapy comprising a recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin and an immunosuppressing regimen for the preparation of a medicament for treating muscular dystrophy in a human subject in need, wherein the immunosuppressing regimen comprises administering one or more of an anti-inflammatory steroid, an anti-CD20 antibody, and an immunosuppressing macrolide, e.g. in the disclosed medicament the rAAV and one or more of the components of the immunosuppressing regimen are co-administered separately, such as the rAAV and one or more components to the immunosuppressing regiment are co-administered simultaneously or sequentially. The disclosure also provides for combination therapy for treating muscular dystrophy in a human subject in need, wherein the combination therapy comprises a recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin and an immunosuppressing regimen, wherein the rAAV and the immunosuppressing regimen are co-administered separately, such as the rAAV and one of more of the components of the immunosuppressing regimen co-administered simultaneously or sequentially. The term immunosuppressing regimen refers to a method of treatment or therapy which suppresses or modulates the immune system of the subject. The regimen comprises administration of one or more immune suppressing agents. In some examples, the immunosuppressing regimen comprises administering an anti-inflammatory steroid, an anti-CD20 antibody, and an immunosuppressing macrolide.

[0029] The disclosure also provides for a method of treating a Limb-Girdle muscular dystrophy in a human subject in need thereof comprising administering a recombinant adeno-virus associated (rAAV) selected from the group consisting of: AAVrh.74.tMCK.CAPN3, rAAVrh.74.MHCK7.DYSF, scAAVrh.74.MHCK7.hSGCG, AAVrh74.tMCK.hSCGA,

scAAVrh74.MHCK7.HSGCB, and rAAVrh.74.MHCK7.huAN05; and an immunosuppressing regimen, wherein the immunosuppressing regimen comprises administering one or more of an anti-inflammatory steroid, an anti-CD20 antibody, and an immunosuppressing macrolide. The disclosure also provides for use of a combination therapy comprising a rAAV and an immunosuppressing regimen for the preparation of a medicament for treating a Limb-Girdle muscular dystrophy in a human subject in need, wherein the rAAV comprises a rAAV recombinant adeno-virus associated (rAAV) is selected from the group consisting of: AAVrh.74.tMCK.CAPN3, rAAVrh.74.MHCK7.DYSF, scAAVrh.74.MHCK7.hSGCG, AAVrh74.tMCK.hSCGA, scAAVrh74.MHCK7.HSGCB, and rAAVrh.74.MHCK7.huAN05; and wherein the immunosuppressing regimen comprises administering one or more of an anti-inflammatory steroid, an anti-CD20 antibody, and an immunosuppressing macrolide, e.g. in the disclosed medicament the rAAV and one or more components of the immunosuppressing regimen are co-administered separately, such as the rAAV and one or more of components of the immunosuppressing regimen are co-administered simultaneously or sequentially. The disclosure also provides for a combination therapy for treating a Limb-Girdle muscular dystrophy in a human subject in need thereof, wherein the combination therapy comprises a recombinant adeno-virus associated (rAAV) selected from the group consisting of: AAVrh.74.tMCK.CAPN3, rAAVrh.74.MHCK7.DYSF, scAAVrh.74.MHCK7.hSGCG, AAVrh74.tMCK.hSCGA, scAAVrh74.MHCK7.HSGCB, and rAAVrh.74.MHCK7.huAN05; and wherein the immunosuppressing regimen comprises administering one or more of an anti-inflammatory steroid, an anti-CD20 antibody, and an immunosuppressing macrolide wherein the rAAV and one or more of the components of the immunosuppressing regimen are co-administered separately, such as the rAAV and one or more of the components of the immunosuppressing regimen are co-administered simultaneously or sequentially. In some examples, the immunosuppressing regimen comprises administering an anti-inflammatory steroid, an anti-CD20 antibody, and an immunosuppressing macrolide.

[0030] In one exemplary immunosuppressing regimen, an anti-inflammatory steroid is administered about 24 hours prior to administration of the rAAV. In another exemplary immunosuppressing regimen, an anti-inflammatory steroid is administered prior to administration of the rAAV and the anti-inflammatory steroid is administered at least once a

day from day 1 to 30 days after administration of the rAAV or the anti-inflammatory steroid is administered at least once a day from day 1 to 60 days after administration of the rAAV.

[0031] In any of the disclosed immunosuppressing regimens, the anti-inflammatory steroid is a glucocorticoid such as prednisone, prednisolone, betamethasone, dexamethasone, hydrocortisone, methylprednisolone or deflazacort. In some examples, the anti-inflammatory steroid is administered orally.

[0032] In additional exemplary immunosuppressing regimens, an anti-CD20 specific antibody prior to administration of the rAAV. For example, the anti-CD20 antibody is administered by intravascular infusion. Exemplary anti-CD20 specific antibody include rituximab, ocrelizumab or ofatumumab.

[0033] In one example, the anti-CD20 specific antibody is administered at least 14 days prior to administration of the rAAV. In another example, the anti-CD20 specific antibody is administered about 60 days prior to administration of the rAAV, about 45 days prior to administration of the rAAV, about 30 days prior to administration of the rAAV, 14 days prior to administration of the rAAV, about 7 days prior to administration of the rAAV and within about 24 hours of the administration of the rAAV. In addition, the anti-CD20 specific antibody administered for 30 to 60 days prior to administration of the rAAV. The disclosed immunosuppressing regimens also include administering an anti-CD20 specific antibody after administration of the rAAV.

[0034] In addition, the disclosed immunosuppressing regimens comprise administering an immunosuppressing macrolide at least once a day for at least three days prior to administration of the rAAV. The immunosuppressing regimens also may comprise administering an immunosuppressing macrolide after administration of the rAAV. In any of the disclosed immunosuppressing regimen, the immunosuppressing macrolide is administered orally. Exemplary immunosuppressing macrolides include tacrolimus, pinecrolimus or sirolimus.

[0035] In some examples, the disclosed immunosuppressing regimen is administered from 30 to 60 days prior to administration of the rAAV. In addition, the immunosuppressing regimen is administered about 60 days prior to administration of the rAAV, about 45 days prior to administration of the rAAV, about 30 days prior to administration the rAAV, about

14 days prior to administration of the rAAV, about 7 days prior to administration of the rAAV, about 24 hours prior to administration of the rAAV.

[0036] In a particular example, the disclosure provides for methods of treating muscular dystrophy in a human subject in need thereof comprising administering a recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin and an immunosuppressing regimen, wherein the immunosuppressing regimen comprises the steps of i) orally administering an anti-inflammatory steroid about 24 hours prior to administration of the rAAV, and administering an anti-inflammatory steroid at least once a day from day 1 to 30 days after administration of the rAAV or administering an the anti-inflammatory steroid at least once a day from day 1 to 60 days after administration of the rAAV, ii) intravenously administering an anti-CD20 antibody about 14 days prior to administration of the rAAV, about 7 days prior to administration of the rAAV and within about 24 hours of the administration of the rAAV, and optionally administering the anti-CD20 antibody after administration of the rAAV, iii) orally administering an immunosuppressing macrolide at least once a day for at least three days prior to administration of the rAAV, and optionally administering the an immunosuppressing macrolide after administration of the rAAV. For example, the anti-inflammatory steroid is prednisone, prednisolone, betamethasone, dexamethasone, hydrocortisone, methylprednisolone or deflazacort, the anti-CD20 specific antibody is rituximab, ocrelizumab or ofatumumabone or more of an anti-inflammatory steroid, an anti-CD20 antibody, and an immunosuppressing macrolide, the immunosuppressing macrolide is tacrolimus, pinecrolimus or sirolimus. In an exemplary example, the immunosuppressing regimen comprises the anti-inflammatory steroid prednisone or prednisolone, the anti-CD20 antibody rituximab, and the immunosuppressing macrolide sirolimus.

[0037] The also provides for use of a combination therapy comprising a rAAV and an immunosuppressing regimen for the preparation of a medicament for the treating muscular dystrophy in a human subject in need thereof, wherein the rAAV is a rAAV.MHCK7.microdystrophin and the immunosuppressing regimen comprises i) orally administering an anti-inflammatory steroid about 24 hours prior to administration of the rAAV, and administering an anti-inflammatory steroid at least once a day from day 1 to 30 days after administration of the rAAV or administering an the anti-inflammatory steroid at least once a day from day 1 to 60 days after administration of the rAAV, ii) intravenously administering an anti-CD20 antibody about 14 days prior to administration of the rAAV,

about 7 days prior to administration of the rAAV and within about 24 hours of the administration of the rAAV, and optionally administering the anti-CD20 antibody after administration of the rAAV, iii) orally administering an immunosuppressing macrolide at least once a day for at least three days prior to administration of the rAAV, and optionally administering the an immunosuppressing macrolide after administration of the rAAV. For example, the anti-inflammatory steroid is prednisone, prednisolone, betamethasone, dexamethasone, hydrocortisone, methylprednisolone or deflazacort, the anti-CD20 specific antibody is rituximab, ocrelizumab or ofatumumabone or more of an anti-inflammatory steroid, an anti-CD20 antibody, and an immunosuppressing macrolide, the immunosuppressing macrolide is tacrolimus, pinecrolimus or sirolimus. In an exemplary example, the immunosuppressing regimen comprises the anti-inflammatory steroid prednisone or prednisolone, the anti-CD20 antibody rituximab, and the immunosuppressing macrolide sirolimus.

[0038] The disclosure provides for a combination therapy comprising a rAAV and an immunosuppressing regimen for treating muscular dystrophy in a human subject in need thereof, wherein the rAAV is a rAAV.MHCK7.microdystrophin and the immunosuppressing regimen, comprises i) orally administering an anti-inflammatory steroid about 24 hours prior to administration of the rAAV, and administering an anti-inflammatory steroid at least once a day from day 1 to 30 days after administration of the rAAV or administering an the anti-inflammatory steroid at least once a day from day 1 to 60 days after administration of the rAAV, ii) intravenously administering an anti-CD20 antibody about 14 days prior to administration of the rAAV, about 7 days prior to administration of the rAAV and within about 24 hours of the administration of the rAAV, and optionally administering the anti-CD20 antibody after administration of the rAAV, iii) orally administering an immunosuppressing macrolide at least once a day for at least three days prior to administration of the rAAV, and optionally administering the an immunosuppressing macrolide after administration of the rAAV. For example, the anti-inflammatory steroid is prednisone, prednisolone, betamethasone, dexamethasone, hydrocortisone, methylprednisolone or deflazacort, the anti-CD20 specific antibody is rituximab, ocrelizumab or ofatumumabone or more of an anti-inflammatory steroid, an anti-CD20 antibody, and an immunosuppressing macrolide, the immunosuppressing macrolide is tacrolimus, pinecrolimus or sirolimus. In an exemplary example, the immunosuppressing regimen

comprises the anti-inflammatory steroid prednisone or prednisolone, the anti-CD20 antibody rituximab, and the immunosuppressing macrolide sirolimus.

[0039] In another particular example, the disclosure provides for a method of treating a Limb-Girdle muscular dystrophy in a human subject in need thereof comprising administering a recombinant adeno-virus associated (rAAV) selected from the group consisting of : AAVrh.74.tMCK.CAPN3, rAAVrh.74.MHCK7.DYSF, scAAVrh.74.MHCK7.hSGCG, AAVrh74.tMCK.hSCGA, scAAVrh74.MHCK7.HSGCB, and rAAVrh.74.MHCK7.huAN05; and an immunosuppressing regimen, wherein the immunosuppressing regimen comprises the steps of i) orally administering an anti-inflammatory steroid about 24 hours prior to administration of the rAAV, and administering an anti-inflammatory steroid at least once a day from day 1 to 30 days after administration of the rAAV or the anti-inflammatory steroid is administered at least once a day from day 1 to 60 days after administration of the rAAV, ii) intravenously administering an anti-CD20 antibody about 14 days prior to administration of the rAAV, about 7 days prior to administration of the rAAV and within about 24 hours of the administration of the rAAV, and optionally administering the anti-CD20 antibody after administration of the rAAV, iii) orally administering an immunosuppressing macrolide at least once a day for at least three days prior to administration of the rAAV, and optionally administering the an immunosuppressing macrolide after administration of the rAAV.

[0040] In another particular example, the disclosure provides for a use of a combination therapy comprising a rAAV and an immunosuppressing regimen <u>for the preparation of a medicament</u> for treating a Limb-Girdle muscular dystrophy in a human subject in need thereof, wherein the rAAV is selected from the group consisting of : AAVrh.74.tMCK.CAPN3, rAAVrh.74.MHCK7.DYSF, scAAVrh.74.MHCK7.hSGCG, AAVrh74.tMCK.hSCGA, scAAVrh74.MHCK7.HSGCB, and rAAVrh.74.MHCK7.huAN05; and the immunosuppressing regimen comprises i) orally administering an anti-inflammatory steroid about 24 hours prior to administration of the rAAV, and administering an anti-inflammatory steroid at least once a day from day 1 to 30 days after administration of the rAAV or the anti-inflammatory steroid is administered at least once a day from day 1 to 60 days after administration of the rAAV, ii) intravenously administering an anti-CD20 antibody about 14 days prior to administration of the rAAV, about 7 days prior to administration of the rAAV and within about 24 hours of the administration of the rAAV, and optionally administering the anti-CD20 antibody after administration of the rAAV, iii) orally administering an immunosuppressing macrolide at least

once a day for at least three days prior to administration of the rAAV, and optionally administering the an immunosuppressing macrolide after administration of the rAAV.

[0041] In another particular example, the disclosure provides for a combination therapy comprising a rAAV and an immunosuppressing regimen for treating a Limb-Girdle muscular dystrophy in a human subject in need thereof, wherein the rAAV is selected from the group consisting of : AAVrh.74.tMCK.CAPN3, rAAVrh.74.MHCK7.DYSF, scAAVrh.74.MHCK7.hSGCG, AAVrh74.tMCK.hSCGA, scAAVrh74.MHCK7.HSGCB, and rAAVrh.74.MHCK7.huAN05; and the immunosuppressing regimen comprises i) orally administering an anti-inflammatory steroid about 24 hours prior to administration of the rAAV, and administering an anti-inflammatory steroid at least once a day from day 1 to 30 days after administration of the rAAV or the anti-inflammatory steroid is administered at least once a day from day 1 to 60 days after administration of the rAAV, ii) intravenously administering an anti-CD20 antibody about 14 days prior to administration of the rAAV, about 7 days prior to administration of the rAAV and within about 24 hours of the administration of the rAAV, and optionally administering the anti-CD20 antibody after administration of the rAAV, iii) orally administering an immunosuppressing macrolide at least once a day for at least three days prior to administration of the rAAV, and optionally administering the an immunosuppressing macrolide after administration of the rAAV.

[0042] In another example, the disclosure provides methods of treating muscular dystrophy in a human subject in need thereof comprising subjecting the subject's plasma to at least one therapeutic plasma exchange (TPE) prior to administration of a second dose of recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin, wherein the subject was administered a first dose of rAAV prior to being subjected to TPE.

[0043] In another example, the disclosure provides for use of a combination therapy for treating muscular dystrophy in a human subject in need thereof, wherein the combination therapy comprises subjecting the subject's plasma to at least one therapeutic plasma exchange (TPE) prior to administration of a second dose of recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin, wherein the subject was administered a first dose of rAAV prior to being subjected to TPE.

[0044] In another example, the disclosure provides for a combination therapy for treating muscular dystrophy in a human subject in need thereof, wherein the combination therapy comprises subjecting the subject's plasma to at least one therapeutic plasma exchange

(TPE) prior to administration of a second dose of recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin, wherein the subject was administered a first dose of rAAV prior to being subjected to TPE.

[0045] The disclosure provides for a method of treating a Limb-Girdle muscular dystrophy in a human subject in need thereof comprising subjecting the subject's plasma to at least one therapeutic plasma exchange (TPE) prior to administration of a second dose of recombinant adeno-virus associated (rAAV) selected from the group consisting of: AAVrh.74.tMCK.CAPN3, rAAVrh.74.MHCK7.DYSF, scAAVrh.74.MHCK7.hSGCG, AAVrh74.tMCK.hSCGA, scAAVrh74.MHCK7.HSGCB, and rAAVrh.74.MHCK7.huAN05; wherein the subject was administered a first dose of rAAV prior to being subjected to TPE.

[0046] In a further example, the disclosure provides methods of treating muscular dystrophy in a human subject in need thereof comprising the steps of a) administering a first dose of recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin, b) subjecting the subject's plasma to at least one therapeutic plasma exchange (TPE), and c) administering a second dose of rAAV. In any of the disclosed methods, the subject's plasmas is subject to at least two TPE or at least three TPE prior to administration of the 2nd dose or rAAV. In some examples, the subject's plasma is subject to at least four TPE prior to administration of the 2nd dose of rAAV, or the subject's plasma is subject five TPE prior to administration of the 2nd dose of rAAV, or the subject's plasma is subject six TPE prior to administration of the 2nd dose of rAAV, or the subject's plasma is subject seven TPE prior to administration of the 2nd dose of rAAV.

[0047] In another example, the disclosure provides for a method of treating a Limb Girdle muscular dystrophy in a human subject in need thereof comprising the steps of a) administering a first dose of recombinant adeno-virus associated selected from the group consisting of: AAVrh.74.tMCK.CAPN3, rAAVrh.74.MHCK7.DYSF, scAAVrh.74.MHCK7.hSGCG, AAVrh74.tMCK.hSCGA, scAAVrh74.MHCK7.HSGCB, and rAAVrh.74.MHCK7.huAN05; b) subjecting the subject's plasma to at least one therapeutic plasma exchange (TPE), and c) administering a second dose or rAAV. In any of the disclosed methods, the subject's plasmas is subject to at least two TPE or at least three TPE prior to administration of the 2nd dose or rAAV. In some examples, the subject's plasma is subject to at least four TPE prior to administration of the 2nd dose of rAAV, or the subject's plasma is subject five TPE prior to administration of the 2nd dose of rAAV, or the subject's

plasma is subject six TPE prior to administration of the 2nd dose of rAAV, or the subject's plasma is subject seven TPE prior to administration of the 2nd dose of rAAV.

[0048] In a further example, the disclosure provides for methods of treating muscular dystrophy in a human subject in need thereof comprising the steps of a) subjecting the subject's plasma to at least one therapeutic plasma exchange (TPE) prior to administering recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin, and b) administering rAAV. In any of the disclosed methods, the subject's plasma is subjected to at least two TPE prior to administering the rAAV, at least three TPE prior to administering the rAAV, at least four TPE prior to administering the rAAV, at least five TPE prior to administering the rAAV, at least six TPE prior to administering the rAAV or at least seven TPE prior to administering prior to administering the rAAV. In these disclosed methods, the subject is administered an anti-inflammatory steroid about 24 hours prior to administration of the rAAV. In addition, in some examples, the subject is administered an anti-inflammatory steroid at least once a day from day 1 to 60 days after administration of the rAAV. For example, the anti-inflammatory steroid is administered orally. In addition, the anti-inflammatory steroid is a glucocorticoid such as prednisone, prednisolone, betamethasone, dexamethasone, hydrocortisone, methylprednisolone or deflazacort.

[0049] In addition, the disclosure provides for methods of treating Limb Girdle muscular dystrophy in a human subject in need thereof comprising the steps of muscular dystrophy in a human subject in need thereof comprising the steps of a) subjecting the subject's plasma to at least one therapeutic plasma exchange (TPE) prior to administering recombinant adeno-virus associated (rAAV) selected from the group consisting of: AAVrh.74.tMCK.CAPN3, rAAVrh.74.MHCK7.DYSF, scAAVrh.74.MHCK7.hSGCG, AAVrh74.tMCK.hSCGA, scAAVrh74.MHCK7.HSGCB, and rAAVrh.74.MHCK7.huAN05; b administering rAAV. In any of the disclosed methods, the subject's plasma is subjected to at least two TPE prior to administering the rAAV, at least three TPE prior to administering the rAAV, at least four TPE prior to administering the rAAV, at least five TPE prior to administering the rAAV, at least six TPE prior to administering the rAAV or at least seven TPE prior to administering prior to administering the rAAV. In these disclosed methods, the subject is administered an anti-inflammatory steroid about 24 hours prior to administration of the rAAV. In addition, in some examples, the subject is administered an anti-inflammatory steroid at least once a day from day 1 to 60 days after administration of the rAAV. For example, the anti-inflammatory steroid is administered orally. In addition, the anti-inflammatory steroid is a

glucocorticoid such as prednisone, prednisolone, betamethasone, dexamethasone, hydrocortisone, methylprednisolone or deflazacort.

[0050] In any of the disclosed methods, the subject's plasma is subjected to TPE for at least 9 days prior to administration of the rAAV, at least 7 days prior to administration, 5 days prior to administration, or 2 days prior to administration. In addition, there is about 24 to about 48 hours between sessions of TPE carried out on the subject's plasma prior to administration of the rAAV. In a particular example, the subject's plasma is subjected to at least two TPE prior to administration of the rAAV, wherein there is about 48 hours between the TPE.

[0051] In any of the method described herein, the subject has a level of anti-AAVrh.74 antibodies of about 1:400 or less at the time of administration of the rAAV. For example, the subject has a level of anti-AAVrh.74 antibodies of about 1:100 to about 1:400 at the time of administration of the rAAV or a level of anti-AAVrh.74 antibodies of about 1:100 to 1:300, or a level of anti-AAVrh.74 antibodies of about 1:100 to 1:200, or a level of anti-AAVrh.74 antibodies of about 1:250 to 1:500, or a level of anti-AAVrh.74 antibodies of about 1:200 to 1:400. The antibody titer is determined as total antibody binding titer. In any of the disclosed methods of treating muscular dystrophy, these methods further comprise a step of determining the presence of anti-AAVrh.74 antibodies in serum or plasma of said subject. The step of determining the present of anti-AAVrh.74 antibodies may be carried out before administration of rAAV, after administration of rAAV, before an immune response or adverse event is observed or after an immune response or adverse event is observed. In addition, the determining step may be performed prior to the step of administering an immunosuppressing regimen or TPE. For example, the determining step is performed prior to any administration of any AAV to said subject or the determining step is performed prior to administration of any AAVrh.74 to said subject.

[0052] The disclosure also provides for methods further comprising a step of comparing the level of anti-AAVrh.74 antibodies in serum or plasma of said subject to a positive control. For example, the positive control utilizes an anti-AAVrh.74 monoclonal antibody.

[0053] In any of the disclosed methods, the determination of the presence of anti-AAVrh.74 may be determined utilizing an immunofluorescence assay, an immunohistochemical assay, a Western blot, a direct enzyme-linked immunosorbent assay

(ELISA), an indirect ELISA, a sandwich ELISA, a competitive ELISA, a reverse ELISA, a chemiluminescence assay, a radioimmunoassay, or an immunoprecipitation assay.

[0054] In any of the disclosed methods, the step of determining the presence of anti-AAVrh.74 antibodies comprises utilizing a monoclonal antibody comprising a VH CDR1 amino acid sequence selected from the group consisting of NYGMN (SEQ ID NO: 20), DYGMN (SEQ ID NO: 22), YTFTNYGMN (SEQ ID NO: 21), and YTFTKYGMN (SEQ ID NO: 23), or a monoclonal antibody comprising a VH CDR2 amino acid sequence selected from the group consisting of WINTYTGEPTYADDFKG (SEQ ID NO: 24), WINTNTGEPTYGDDFKG (SEQ ID NO:25), and WMGWINTYTGEPTY (SEQ ID NO: 26), or a monoclonal antibody comprising a VH CDR3 amino acid sequence selected from the group consisting of GVAHYSDSRFAFDY (SEQ ID NO: 27), GNAHPGGSAFVY (SEQ ID NO: 28), RGSYYYDSSPAWFAY (SEQ ID NO: 29), RGVDSSGYGAFAY (SEQ ID NO: 30), and TRGTSTMISTFAFVY (SEQ ID NO: 31), or a monoclonal antibody comprising VL CDR1 amino acid sequence selected from the group consisting of SVSSSVSYMH (SEQ ID NO: 32), SASSGVTYMH (SEQ ID NO: 33), SSVSYMH (SEQ ID NO: 34), and SSVRYMH (SEQ ID NO: 35), or a monoclonal antibody comprising a VL CDR2 amino acid sequence selected from the group consisting of YTSNLAS (SEQ ID NO: 36), RTSNLAS (SEQ ID NO: 37), LWIYSTSNLAS (SEQ ID NO: 38), and VWIYSTSNLAS (SEQ ID NO: 39), or a monoclonal antibody comprising a VH CDR3 amino acid sequence selected from the group consisting of QQRSSYPFT (SEQ ID NO: 40), QQRSTYPF (SEQ ID NO: 41), QQRSFYPF (SEQ ID NO: 42), and QQRTYYPF (SEQ ID NO: 43).

[0055] In an exemplary example, the disclosed methods comprise a step of determining the presence of anti-AAVrh.74 antibodies utilizing an anti-AAVrh.74 monoclonal antibody such as a monoclonal antibody comprising a variable heavy chain (VH) sequence set forth in SEQ ID NO: 10, 12, 14, 16, or 18, or a monoclonal antibody comprising a variable light chain (VL) sequence set forth in SEQ ID NO: 11, 13, 15, 17, or 19.

[0056] In a further example, the disclosed methods comprise a step of determining the presence of anti-AAVrh.74 antibodies utilizing an anti-AAVrh.74 monoclonal antibody

$1.5x10^{14}$ vg/kg to about $2.75x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $2.5x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $2.0x10^{14}$ vg/kg, or $1.75x10^{14}$ vg/kg to about $1.0x10^{15}$ vg/kg, or about $1.75x10^{14}$ vg/kg to $6.0x10^{14}$, or about $1.75x10^{14}$ vg/kg to $5.0x10^{14}$, or about $1.75x10^{14}$ vg/kg to $4.0x10^{14}$, or about $1.75x10^{14}$ vg/kg to about $3.75x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $3.5x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $3.25x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $3.0x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $2.75x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $2.5x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $2.25x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $2.0x10^{14}$ vg/kg, or about $2.0x10^{14}$ vg/kg to $1.0x10^{15}$, or about $2.0x10^{14}$ vg/kg to $6.0x10^{14}$, or about $2.0x10^{14}$ vg/kg to $5.0x10^{14}$, or about $2.0x10^{14}$ vg/kg to about $4.0x10^{14}$ vg/kg, or about $2.0x10^{14}$ vg/kg to about $3.75x10^{14}$ vg/kg, or about $2.0x10^{14}$ vg/kg to about $3.5x10^{14}$ vg/kg, or about $2.0x10^{14}$ vg/kg to about $3.25x10^{14}$ vg/kg.

[0059] In one example, the methods of the disclosure comprise systemically administering rAAV wherein the systemic route of administration is an intravenous route and the dose of the rAAV administered is about 2.0 $x10^{14}$ vg/kg. In another example, the methods of the disclosure comprise systemically administering rAAV wherein the systemic route of administration is an intravenous route and the dose of the rAAV administered is about $5.0x10^{12}$ vg/kg, or about $6.0x10^{12}$ vg/kg, or about $7.0x10^{12}$ vg/kg, or about $8.0x10^{12}$ vg/kg, or about $9.0x10^{12}$ vg/kg, or about $1.0x10^{13}$ vg/kg, or about $1.25x10^{13}$ vg/kg, or about $1.5x10^{13}$ vg/kg, or about $1.75x10^{13}$ vg/kg, or about $2.25x10^{13}$ vg/kg, or about $2.5x10^{13}$ vg/kg, or about $2.75x10^{13}$ vg/kg, or about $3.0x10^{13}$ vg/kg, or about $3.25x10^{13}$ vg/kg, or about $3.5x10^{13}$ vg/kg, or about $3.75x10^{13}$ vg/kg, or about $4.0x10^{13}$ vg/kg, or about $5.0x10^{13}$ vg/kg, or about $6.0x10^{13}$ vg/kg, or about $7.0x10^{13}$ vg/kg, or about $8.0x10^{13}$ vg/kg, or about $9.0x10^{13}$ vg/kg, or about $1.0x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg, or about $2.25x10^{14}$ vg/kg, or about $2.5x10^{14}$ vg/kg, or about $2.75x10^{14}$ vg/kg, or about $3.0x10^{14}$ vg/kg, or about $3.25x10^{14}$ vg/kg, or about $3.5x10^{14}$ vg/kg, or about $3.75x10^{14}$ vg/kg, or about $4.0x10^{14}$ vg/kg, or about $5.0x10^{14}$ vg/kg, or about $6.0x10^{14}$ vg/kg, or about $1x10^{15}$ vg/kg. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin or AAVrh74.MCK.microdystrophin. In one example, the rAAV is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO

3, nucleotides 1-4977 of SEQ ID NO: 8 or nucleotides 56-5022 of SEQ ID NO: 6. In one example, the rAAV is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[0060] In any of the methods, combination therapies or uses of the disclosure, the dose of rAAV can be administered at about 5 mL/kg to about 15 mL/kg, or about 8 mL/kg to about 12 mL/kg, or 8 mL/kg to about 10 mL/kg, or 5 mL/kg to about 10 mL/kg or about 10 mL/kg to 12 mL/k, or about 10 mL/kg to 15 mL/kg or 10 mL/kg to about 20 mL/kg. In a particular example, the dose or the rAAV is administered in about 10 mL/kg. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin or AAVrh74.MCK.microdystrophin. In one example, the rAAV is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8 or nucleotides 56-5022 of SEQ ID NO: 6. In one example, the rAAV is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[0061] In any of the methods, combination therapies or medicaments of the disclosure, the dose of rAAV can be administered by injection, infusion or implantation. For example, the dose of rAAV is administered by infusion over approximately one hour. In addition, the dose of rAAV is administered by an intravenous route through a peripheral limb vein, such as a peripheral arm vein or a peripheral leg vein. Alternatively, the infusion may be administered over approximately 30 minutes, or approximately 1.5 hours, or approximately 2 hours, or approximately 2.5 hours or approximately 3 hours. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin. In one example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8 or nucleotides 56-5022 of SEQ ID NO: 6. In one example, the rAAV is AAVrh74.MCK.microdystrophin. In one example, the AAVrh74.MCK.microdystrophin is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[0062] The rAAV administered by any of the methods, combination therapies or uses of the disclosure can comprise the human micro-dystrophin nucleotide sequence of SEQ ID NO: 1, the MHCK7 promoter sequence of SEQ ID NO: 2 or SEQ ID NO: 7. In addition, the rAAV administered by any of the methods of the disclosure comprises the human micro-dystrophin nucleotide sequence of SEQ ID NO: 1 and the MHCK7 promoter sequence of SEQ ID NO: 2 or SEQ ID NO: 7. For example, the rAAV can comprise the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9,

nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin. In one example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6.

[0063] In one example, the rAAV is AAVrh74.MCK.microdystrophin. In one example, the AAVrh74.MCK.microdystrophin is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[0064] In any of the methods, combination therapies or uses of the disclosure, the rAAV administered is of the serotype for AAVrh.74 antibodies.

[0065] In some examples, the methods, combination therapies or use of the disclosure treat Duchenne muscular dystrophy or Becker's muscular dystrophy. An exemplary example is a method, combination therapy or medicament for treating Duchenne muscular dystrophy or Becker's muscular dystrophy in a human subject in need thereof comprising the step of administering a dose recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin, wherein the route of administration is intravenous infusion and the dose of the rAAV administered is about $2x10^{14}$ vg/kg over approximately one hour, and wherein the rAAV vector comprises the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9 or of nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin. In one example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9 or of nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. in one example, the rAAV is AAVrh74.MCK.microdystrophin. In one example, the AAVrh74.MCK.microdystrophin is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[0066] In one example, the disclosure provides for a rAAV comprising a muscle specific control element nucleotide sequence, and a nucleotide sequence encoding the micro-dystrophin protein. For example, the nucleotide sequence encodes a functional micro-dystrophin protein, wherein the nucleotide has, e.g., 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%, 99%, or 100% sequence identity to SEQ ID NO: 1, 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. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin. In one example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9 or of nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. In one example, the rAAV is AAVrh74.MCK.microdystrophin. In one example, the AAVrh74.MCK.microdystrophin is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[0067] The disclosure also provides for rAAV wherein the nucleotide sequence comprises a nucleotide sequence that hybridizes under stringent conditions to the nucleic acid sequence of SEQ ID NO: 1, or compliments thereof, and encodes a functional micro-dystrophin protein.

[0068] In one example, the rAAV is a non-replicating, recombinant adeno-associated virus (AAV) termed AAVrh74.MHCK7.micro-dystrophin of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. This vector genome contains minimal elements required for gene expression, including AAV2 inverted terminal repeats (ITR), the micro-dystrophin, SV40 intron (SD/SA), and synthetic polyadenylation (Poly A) signal, all under the control of the MHCK7 promoter/enhancer. The schematic of the genome and expression cassette is shown Figure 1. The AAVrh.74 serotype can be employed to achieve efficient gene transfer in skeletal and cardiac muscle following IV administration.

[0069] In another example, the disclosure provides for a method of treating a Limb Girdle muscular dystrophy in a human subject in need thereof comprising administering a rAAV comprising the nucleotide sequence of SEQ ID NO: 44.

[0070] In another example, this disclosure provides a method, combination therapy or use for treating a limb-girdle muscular dystrophy in a subject in need, comprising administering to the subject an rAAV intravenous infusion over approximately 1 to 2 hours at a dose of about 5.0×10^{13} vg/kg or about 2.0×10^{14} vg/kg based on a supercoiled plasmid as the quantitation standard, or about 1.85×10^{13} vg/kg or 7.41×10^{13} vg/kg based on a linearized plasmid as the quantitation standard, and wherein the rAAV comprises a nucleotide sequence of SEQ ID

NO: 44. In another example, the disclosure describes a method of expressing beta-sarcoglycan gene in a subject's cell comprising administering to the subject the scAAVrh74.MHCK7.hSGCB construct that comprises a nucleotide sequence that is at least 90%, 95%, or 99% identical to SEQ ID NO: 19. In one example, the disclosure provides a method of increasing beta-sarcoglycan positive fibers and/or decreasing CK level in a subject's muscle tissue comprising administering to the subject the scAAVrh74.MHCK7.hSGCB construct nucleotide sequence that is at least 90%, 95%, or 99% identical to SEQ ID NO: 44.

[0071] In another example, described here in a recombinant AAV vector comprising a polynucleotide sequence encoding β-sarcoglycan. In some examples, the polynucleotide sequence encoding β-sarcoglycan comprises a sequence e.g. at least 65%, at least 70%, at least 75%, at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, or 89%, more typically 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the nucleotide sequence set forth in SEQ ID NO: 45 and encodes protein that retains β-sarcoglycan activity. In some examples, the polynucleotide sequence encoding β-sarcoglycan comprises the nucleotide sequence set forth in SEQ ID NO: 45. In some examples, the polynucleotide sequence encoding β-sarcoglycan consists of the nucleotide sequence set forth in SEQ ID NO: 45.

[0072] In another example, a recombinant AAV vector described herein comprises a polynucleotide sequence encoding β-sarcoglycan that is 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 the amino acid sequence of SEQ ID NO: 46, and the protein retains β-sarcoglycan activity.

[0073] In another example, a recombinant AAV vector described herein comprises a polynucleotide sequence encoding β-sarcoglycan that has the amino acid sequence of SEQ ID NO: 46.

[0074] In another example, described herein is a recombinant AAV vector comprising a polynucleotide sequence encoding functional β-sarcoglycan that comprises a nucleotide sequence that hybridizes under stringent conditions to the nucleic acid sequence of SEQ ID NO: 45, or a complement thereof.

[0075] In a particular example, the disclosure provides for methods, combination therapies or uses for treating LGMD2E in a human subject in need thereof comprising administering the rAAV scAAVrh74.MHCK7.HSGCB. For example, in any of the methods of treating LGMD2E, scAAVrh74.MHCK7.HSGCB is administered by intravenous infusion at a dose of about 0.5x 10^{14} vg/kg or about 2x 10^{14} vg/kg. The dosages stated herein in reference to scAAVrh74.MHCK7.HSGCB including in the immediate forgoing to are based on utilizing supercoiled qPCR standards. Respectively, 0.5x 10^{14} vg/kg and 2x 10^{14} vg/kg correspond to 1.85 X 10^{13} and 7.41X 10^{13} vg/kg as measured by utilizing linear qPCR standards.

[0076] In a particular example, in any of the methods, combination therapies or uses for treating a Limb Girdle muscular dystrophy in a human subject, the human subject is suffering from LGMD2E, and the rAAV is administered by intravenous infusion at a dose of about 2x 10^{14} vg/kg, and wherein the rAAV comprises the rAAV is scAAVrh74.MHCK7.HSGCB comprising the nucleotide sequence of SEQ ID NO: 44.

[0077] In a related example, the human subject is suffering from the muscular dystrophy LGMD2E and the rAAV is scAAVrh74.MHCK7.HSGCB administered by intravenous infusion at a dose of about 2x 10^{14} vg/kg, the method further comprising administering to the subject 1mg/kg/ day of prednisone beginning one day (12 to 24 hours) prior to the administration of the rAAV and continuing with or without tapering for sixty day.

[0078] In another related example, the human subject is suffering from the muscular dystrophy LGMD2E and the rAAV is scAAVrh74.MHCK7.HSGCB administered by intravenous infusion at a dose of about 0.5x 10^{14} vg/kg, the method further comprising administering to the subject 1mg/kg/ day of prednisone beginning one day (12 to 24 hours) prior to the administration of the rAAV and continuing with or without tapering for thirty days.

[0079] It is recognized that the thirty day and the sixty day administrations of prednisone can be tapered, by those skilled in the art according to the particular clinical exhibits of the subject and as otherwise further described herein the methods of the invention.

[0080] 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 65-68ºC or 0.015 M sodium chloride, 0.0015M sodium citrate, and 50% formamide at 42ºC. 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).

[0081] 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.

[0082] The term "muscle specific control element" refers to a nucleotide sequence that regulates expression of a coding sequence that is specific for expression in muscle tissue. These control elements include enhancers and promoters. The disclosure provides for constructs comprising the muscle specific control elements MCKH7 promoter, the MCK promoter and the MCK enhancer.

[0083] In one example, the disclosure provides for a rAAV wherein the muscle specific control element is a 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), hybrid α-myosin heavy chain enhancer-/MCK enhancer-promoter (MHCK7), 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).

[0084] For example, the muscle specific control element is the MHCK7 promoter nucleotide sequence SEQ ID NO: 2 or SEQ ID NO: 7, or the muscle specific control element is MCK nucleotide sequence SEQ ID NO: 4. In addition, in any of the rAAV vectors of the disclosure, the muscle specific control element nucleotide sequence, e.g. MHCK7 or MCK nucleotide sequence, is operably linked to the nucleotide sequence encoding the micro-dystrophin protein. For example, the MHCK7 promoter nucleotide sequence (SEQ ID NO: 2 or SEQ ID NO: 7) is operably linked to the human micro-dystrophin coding sequence (SEQ ID NO: 1) as set out in the construct provided in Figure 1 or Figure 2 (SEQ ID NO: 3) or Figure 13 (SEQ ID NO: 9). In another example, the MCK promoter (SEQ ID NO: 4) is operably linked to the human micro-dystrophin coding sequence (SEQ ID NO: 1) as set out in the construct provided in Figure 5 or Figure 6 (SEQ ID NO: 5). In another example, the disclosure provides for a rAAV vector comprising the nucleotide sequence of SEQ ID NO: 1 and SEQ ID NO: 2, or SEQ ID NO: 1 and SEQ ID NO: 7. The disclosure also provides for a rAAV vector comprising the nucleotide sequence of SEQ ID NO: 1 and SEQ ID NO: 4.

[0085] In a further example, the disclosure provides for an rAAV construct contained in the plasmid comprising the nucleotide sequence of SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 8. For example, the AAVrh74.MHCK7.microdystrophin vector comprises the nucleotide sequence within and inclusive of the ITR's of SEQ ID NO: 3 and shown in Figure 2. The rAAV vector comprises the 5' ITR, MHCK7 promoter, a chimeric intron sequence, the coding sequence for the human micro-dystrophin gene, polyA, and 3' ITR. In one example, the vector comprises nucleotides 55-5021 of SEQ ID NO: 3. The plasmid set forth in SEQ ID NO: 3 further comprises ampicillin resistance and the pGEX plasmid backbone with pBR322 origin of replication.

[0086] In another example, the disclosure provides for a rAAV comprising the nucleotide sequence of SEQ ID NO: 9. for example, the AAVrh74.MHCK7.microdystrophin vector construct comprises the nucleotide sequence of SEQ ID NO: 9 and shown in Figure 7. This rAAV vector construct comprises the MHCK7 promoter, a chimeric intron sequence, the coding sequence for the human micro-dystrophin gene, and polyA. In one example, the rAAV vector construct further comprises an ITR 5' to the promoter, and an ITR 3' to the polyA. In one example, the rAAV is AAVrh.74

[0087] In another example, the AAVrh74.MHCK7.microdystrophin vector comprises the nucleotide sequence within and inclusive of the ITR's of SEQ ID NO: 8 and shown in Figure 9. The rAAV vector comprises the 5' ITR, MHCK7 promoter, a chimeric intron sequence, the coding sequence for the human micro-dystrophin gene, polyA, and 3' ITR. In one example, the vector comprises nucleotides 1-4977 of SEQ ID NO: 9. The plasmid set forth in SEQ ID NO: 3 further comprises kanamycin resistance and the pGEX plasmid backbone with pBR322 origin of replication.

[0088] In another example, the disclosure provides for a plasmid comprising the AAVrh74.MHCK7.microdystrophin vector construct. In one example, the plasmid comprises the 5' ITR, MHCK7 promoter, a chimeric intron sequence, the coding sequence for the human micro-dystrophin gene, polyA, and 3' ITR. In one example, the plasmid comprises kanamycin resistance and optionally comprises the pGEX plasmid backbone with pBR322 origin of replication. In a particular example, the plasmid is set forth in SEQ ID NO: 8, and shown in Figures 8 and 9.

[0089] The disclosure provides for a recombinant AAV vector comprising the human micro-dystrophin nucleotide sequence of SEQ ID NO: 1 and the MHCK7 promoter nucleotide sequence of SEQ ID NO: 2 or SEQ ID NO: 7. This rAAV vector is the AAV serotype AAVrh.74.

[0090] The disclosure also provides for a rAAV comprising the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence within and inclusive of the ITR's in SEQ ID NO: 3, the nucleotide sequence within and inclusive of the ITR's in SEQ ID NO: 8 or the nucleotide sequence as set forth in SEQ ID NO: 9. This rAAV vector is the AAV serotype AAVrh.74.

[0091] The rAAV vectors of the disclosure may be any AAV serotype, such as the serotype AAVrh.74, AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12 or AAV13.

[0092] The disclosure also provides for pharmaceutical compositions (or sometimes referred to herein as simply "compositions") comprising any of the rAAV vectors of the disclosure.

[0093] 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

by Western blot or immunohistochemistry on muscle biopsies before and after administration of the rAAV.

[0098] In any of the methods, combination therapies or uses for treating a muscular dystrophy, disease progression in the subject is delayed after administration of the rAAV as measured by any of: the six minute walk test, time to rise, ascend 4 steps, ascend and descend 4 steps, North Star Ambulatory Assessment (NSAA), 10 meter timed test, 100 meter timed test, hand held dynamometry (HHD), Timed Up and Go, and/or Gross Motor Subtest Scaled (Bayley-III) score.

[0099] For example, in any of the methods, combination therapies or uses, the subject has at least a 6-point improvement in NSAA score at least 270 days after administration of the rAAV as compared to NSAA score before administration of the rAAV. Further, in any of the methods, combination therapies or uses, the subject has at least about 0.8 second improvement in time to rise at least 270 days after administration of the rAAV as compared to time to rise before administration of the rAAV. In addition, in any of the methods, combination therapies or uses, the subject has at least about 1.2 second improvement in time to ascend 4 steps test at least 270 days after administration of the rAAV as compared to time to ascend 4 steps test before administration of the rAAV. In addition, in any of the methods, combination therapies or uses, the subject has at least about 7 second improvement in the 100 m timed test at least 270 days after administration of the rAAV as compared to the 100 m timed test before administration of the rAAV.

[00100] In another example, the disclosure provides for methods, compositions, combination therapies or uses for expressing micro-dystrophin gene in a patient cell comprising administering to the patient the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8 or nucleotides 56-5022 of SEQ ID NO: 6. For example, expression of the micro-dystrophin gene in the patient cell is detected by measuring the micro-dystrophin protein level by Western blot or immunohistochemistry in muscle biopsies before and after administration of the rAAV.MHCK7.micro-dystrophin construct. In addition, the expression of the micro-dystrophin gene is measured in the patient by detecting greater the number of vector genomes per nucleus, wherein 1vector genome per nucleus is about 50% micro-dystrophin expression and great than 1 copy per nucleus is consistent with micro-dystrophin expression level. For example, the cells have 1.2 vector copies per nucleus, or 1.3 vector copies per nucleus, or 1.4 vector copies per nucleus, or 1.5 vector copies per nucleus, or 1.6

vector copies per nucleus, or 1.7 vector copies per nucleus, or 1.8 vector copies per nucleus, or 1.9 vector copies per nucleus.

[00101] In a further example, the disclosure provides for methods, compositions, combination therapies or uses for decreasing serum CK levels in a patient in need thereof, the method comprising administering to the patient the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. For example, the serum CK level in the patient is decreased by at least about 65% to about 90% or about 65% to about 95% or about 75% to about 90% or about 80% to about 90% or about 85% to about 95% or about 87% to about 95% or about 87% to about 90% by 60 days after administration of the rAAV as compared to the serum CK level before administration of the rAAV. In particular, the serum CK level in the subject is decreased by about 87% by 60 days after administration of the rAAV as compared to the serum CK level before administration of the rAAV or in any of the methods, compositions, combination therapies or uses for treating a muscular dystrophy of the disclosure, the serum CK level in the subject is decreased by about 72% by 60 days after administration of the rAAV as compared to the serum CK level before administration of the rAAV, or in any of the methods, compositions, combination therapies or uses for treating a muscular dystrophy of the disclosure, the serum CK level in the subject is decreased by about 73% by 60 days after administration of the rAAV as compared to the serum CK level before administration of the rAAV, or in any of the methods, compositions, combination therapies or uses for treating a muscular dystrophy of the disclosure, the serum CK level in the subject is decreased by about 78% by 60 days after administration of the rAAV as compared to the serum CK level before administration of the rAAV, or in any of the methods, compositions, combination therapies or uses for treating a muscular dystrophy of the disclosure, the serum CK level in the subject is decreased by about 95% by 60 days after administration of the rAAV as compared to the serum CK level before administration of the rAAV.

[00102] The disclosure also provides for methods, compositions, combination therapies or uses for increasing micro-dystrophin positive fibers in a patient muscle tissue comprising administering to the patient the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. For example, the number of micro-dystrophin positive fibers is detected by measuring the dystrophin protein level by Western

blot or immunohistochemistry on muscle biopsies before and after administration of the rAAV. In addition, the expression of the micro-dystrophin gene is measured in the patient by detecting greater the number of vector genomes per nucleus, wherein 1vector genome per nucleus is about 50% micro-dystrophin expression and great than 1 copy per nucleus is consistent with micro-dystrophin expression level. For example, the cells have 1.2 vector copies per nucleus, or 1.3 vector copies per nucleus, or 1.4 vector copies per nucleus, or 1.5 vector copies per nucleus, or 1.6 vector copies per nucleus, or 1.7 vector copies per nucleus, or 1.8 vector copies per nucleus, or 1.9 vector copies per nucleus.

[00103] In another example, the disclosure provides for methods, compositions, combination therapies or uses for increasing the expression of alpha-sarcoglycan in a patient in need thereof comprising administering to the patient the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. For example, the level of alpha-sarcoglycan is detected by measuring the alpha-sarcoglycan protein level by Western blot or immunohistochemistry on muscle biopsies before and after administration of the rAAV.

[00104] In addition, the disclosure provides for methods, compositions, combination therapies or uses for increasing the expression of beta-sarcoglycan in a patient in need thereof comprising administering to the patient the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. For example, the level of beta-sarcoglycan is detected by measuring the beta-sarcoglycan protein level by Western blot or immunohistochemistry on muscle biopsies before and after administration of the rAAV.

[00105] The disclosure also provides for methods, compositions, combination therapies or uses for treating a patient with Duchenne muscular dystrophy or Becker muscular dystrophy comprising administering to the patient the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6, such that disease progression in the patient is delayed as measured by any of: the six minute walk test, time to rise, ascend 4 steps, ascend and descend 4 steps, North Star Ambulatory Assessment (NSAA), 10 meter timed test, 100 meter timed test, hand held dynamometry (HHD), Timed Up and Go, and/or Gross Motor Subtest Scaled (Bayley-III) score.

[00106] For example, in any of the methods, compositions, combination therapies or uses, the subject has at least a 6-point improvement in NSAA score at least 270 days after administration of the rAAV as compared to NSAA score before administration of the rAAV. Further, in any of the methods, the subject has at least about 0.8 second improvement in time to rise at least 270 days after administration of the rAAV as compared to time to rise before administration of the rAAV. In addition, in any of the methods, the subject has at least about 1.2 second improvement in time to ascend 4 steps test at least 270 days after administration of the rAAV as compared to time to ascend 4 steps test before administration of the rAAV. In addition, in any of the methods, the subject has at least about 7 second improvement in the 100 m timed test at least 270 days after administration of the rAAV as compared to the 100 m timed test before administration of the rAAV.

[00107] "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.

[00108] The disclosure also provides for methods of reducing or preventing fibrosis in a subject suffering from muscular dystrophy comprising administering a therapeutically effective amount of a rAAV comprising the human micro-dystrophin nucleotide sequence of SEQ ID NO: 1 and the MHCK7 promoter nucleotide sequence of SEQ ID NO: 2 or SEQ ID NO: 7; or a rAAV vector comprising the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin. In one example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of nucleotides 55-5021 of SEQ ID NO: 3. In another example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9. In another example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of nucleotides 1-4977 of SEQ ID NO: 8 or nucleotides 56-5066 of SEQ ID NO: 6. In a further example, the rAAV is AAVrh74.MCK.microdystrophin. In one example, the AAVrh74.MCK.microdystrophin is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[00109] In another example, the disclosure provides for methods of preventing fibrosis in a subject in need thereof, comprising administering a therapeutically effective amount of

subject suffering from a muscular dystrophy who already has developed fibrosis, in order to prevent new fibrosis in these subjects or to reduce fibrosis in these subjects. The disclosure also provides for administering the human micro-dystrophin nucleotide sequence of SEQ ID NO: 1 and the MHCK7 promoter nucleotide sequence of SEQ ID NO: 2 or SEQ ID NO:7; or a rAAV vector comprising the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6 to the subject suffering from a muscular dystrophy who already has reduced muscle force or has reduced muscle mass in order to protect the muscle from further injury.

[00114] In any of the methods of the disclosure, the subject may be suffering from a muscular dystrophy such as DMD or any other dystrophin-associated muscular dystrophy.

[00115] In other examples of any of the methods of the disclosure described herein, the serum CK level in the subject is decreased after administration of the rAAV as compared to the serum CK level before administration of the rAAV by a percentage level selected from the group consisting of:

a) at least 78% by 90, 180, or 270 days after the administration;

b) at least 46, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70 or 85% by 270 days after the administration;

c) at least 72, 73, 74, or 95% by 180 days after the administration;

d) at least 87, 88, 93 or 95% by 90 days after the administration;

e) at least 70 % by 270 days after the administration;

f) 70 to 95% by 90, 180, or 270 days after the administration;

g) at least 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, or 95 % by 90, 180, or 270 days after the administration; and

h) at least 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, or 95 % by 90, 180, or 270 days after the administration.

[00116] In another example, the disclosure provides for compositions for treating a muscular dystrophy in a human subject in need, wherein the composition comprises a dose of

recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin, wherein composition is formulated for a systemic route of administration and the dose of the rAAV is about $1x10^{14}$ vg/kg to about $4x10^{14}$ vg/kg. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin. In one example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. In one example, the rAAV is AAVrh74.MCK.microdystrophin. In one example, the AAVrh74.MCK.microdystrophin is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[00117] For example, the composition of the disclosure comprises a dose of rAAV of about $5.0x10^{12}$ vg/kg to about $1.0x10^{14}$ vg/kg, or about $5.0x10^{12}$ vg/kg to$1.0x10^{14}$ vg/kg, or about $5.0x10^{12}$ vg/kg to about $2.0x10^{14}$ vg/kg, or about $5.0x10^{12}$ vg/kg to about $1.0x10^{14}$ vg/kg, or about $5.0x10^{12}$ vg/kg to about $5.0x10^{13}$ vg/kg, or about $5.0x10^{12}$ vg/kg to about $2.0x10^{13}$ vg/kg, or about $5.0x10^{12}$ vg/kg to about $1.0x10^{13}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $1.0x10^{15}$ vg/kg, or $1.0x10^{13}$ vg/kg to about $1.0x10^{14}$ vg/kg, or about $1.0x10^{13}$ vg/kg to$1.0x10^{14}$ vg/kg, or about $1.0x10^{13}$ vg/kg to about $2.0x10^{14}$ vg/kg, or about $1.0x10^{13}$ vg/kg to about $1.0x10^{14}$ vg/kg, or about $1.0x10^{13}$ vg/kg to about $5.0x10^{13}$ vg/kg, or about $1.0x10^{13}$ vg/kg to about $3.0x10^{14}$ vg/kg, or about $1.0x10^{13}$ vg/kg to about $5.0x10^{14}$ vg/kg, or about $1.0x10^{13}$ vg/kg to about $6.0x10^{14}$ vg/kg, or $1.0x10^{13}$ vg/kg to about $1.0x10^{15}$ vg/kg, or $5.0x10^{13}$ vg/kg to about $1.0x10^{14}$ vg/kg, or about $5.0x10^{13}$ vg/kg to$1.0x10^{14}$ vg/kg, or about $5.0x10^{13}$ vg/kg to about $2.0x10^{14}$ vg/kg, or about $5.0x10^{13}$ vg/kg to about $1.0x10^{14}$ vg/kg, or about $5.0x10^{13}$ vg/kg to about $3.0x10^{14}$ vg/kg, or about $5.0x10^{13}$ vg/kg to about $5.0x10^{14}$ vg/kg, or about $5.0x10^{13}$ vg/kg to about $6.0x10^{14}$ vg/kg, or $5.0x10^{13}$ vg/kg to about $1.0x10^{15}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $6.0x10^{14}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $5.0x10^{14}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $4.0x10^{14}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $1.0x10^{15}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $3.0x10^{14}$ vg/kg, or about $1.0x10^{14}$ vg/kg to about $2.5x10^{14}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $2.0x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg to about $3.75x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg to $6.0x10^{14}$, or about $1.25x10^{14}$ vg/kg to $5.0x10^{14}$, or about $1.25x10^{14}$ vg/kg to $4.0x10^{14}$, or about $1.25x10^{14}$ vg/kg to $1.0x10^{15}$, or about $1.25x10^{14}$ vg/kg to about $3.5\ x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg to about $3.0x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg to about $2.75x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg to about $2.5x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg to about $2.0x10^{14}$ vg/kg, or $1.25x10^{14}$ vg/kg to about $3.75x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg to about $3.5\ x10^{14}$ vg/kg, or $1.5x10^{14}$ vg/kg to about $1.0x10^{15}$

vg/kg, or about $1.5x10^{14}$ vg/kg to $6.0x10^{14}$, or about $1.5x10^{14}$ vg/kg to $5.0x10^{14}$, or about $1.5x10^{14}$ vg/kg to $4.0x10^{14}$, or about $1.5x10^{14}$ vg/kg to about $3.75x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $3.5x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $3.25x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $3.0x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $2.75x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $2.5x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $2.0x10^{14}$ vg/kg, or $1.75x10^{14}$ vg/kg to about $1.0x10^{15}$ vg/kg, or about $1.75x10^{14}$ vg/kg to $6.0x10^{14}$, or about $1.75x10^{14}$ vg/kg to $5.0x10^{14}$, or about $1.75x10^{14}$ vg/kg to $4.0x10^{14}$, or about $1.75x10^{14}$ vg/kg to about $3.75x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $3.5x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $3.25x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $3.0x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $2.75x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $2.5x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $2.25x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $2.0x10^{14}$ vg/kg, or about $2.0x10^{14}$ vg/kg to $1.0x10^{15}$, or about $2.0x10^{14}$ vg/kg to $6.0x10^{14}$, or about $2.0x10^{14}$ vg/kg to $5.0x10^{14}$, or about $2.0x10^{14}$ vg/kg to about $4.0x10^{14}$ vg/kg, or about $2.0x10^{14}$ vg/kg to about $3.75x10^{14}$ vg/kg, or about $2.0x10^{14}$ vg/kg to about $3.5x10^{14}$ vg/kg, or about $2.0x10^{14}$ vg/kg to about $3.25x10^{14}$ vg/kg. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin. In one example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. In one example, the rAAV is AAVrh74.MCK.microdystrophin. In one example, the AAVrh74.MCK.microdystrophin is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[00118] In one example, the compositions of the disclosure are formulated for intravenous administration and comprise a dose of rAAV that is about 2.0 $x10^{14}$ vg/kg. In another example, the compositions of the disclosure are formulated for intravenous administration and comprise a dose of rAAV that is about $5.0x10^{12}$ vg/kg, or about $6.0x10^{12}$ vg/kg, or about $7.0x10^{12}$ vg/kg, or about $8.0x10^{12}$ vg/kg, or about $9.0x10^{12}$ vg/kg, or about $1.0x10^{13}$ vg/kg, or about $1.25x10^{13}$ vg/kg, or about $1.5x10^{13}$ vg/kg, or about $1.75x10^{13}$ vg/kg, or about $2.25x10^{13}$ vg/kg, or about $2.5x10^{13}$ vg/kg, or about $2.75x10^{13}$ vg/kg, or about $3.0x10^{13}$ vg/kg, or about $3.25x10^{13}$ vg/kg, or about $3.5x10^{13}$ vg/kg, or about $3.75x10^{13}$ vg/kg, or about $4.0x10^{13}$ vg/kg, or about $5.0x10^{13}$ vg/kg, or about $6.0x10^{13}$ vg/kg, or about $7.0x10^{13}$ vg/kg, or about $8.0x10^{13}$ vg/kg, or about $9.0x10^{13}$ vg/kg, or about $1.0x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg, or about $2.25x10^{14}$ vg/kg, or about $2.5x10^{14}$ vg/kg, or about $2.75x10^{14}$ vg/kg, or about $3.0x10^{14}$ vg/kg, or about

$3.25x10^{14}$ vg/kg, or about $3.5x10^{14}$ vg/kg, or about $3.75x10^{14}$ vg/kg, or about $4.0x10^{14}$ vg/kg, or about $5.0x10^{14}$ vg/kg, or about $6.0x10^{14}$ vg/kg, or about $1x10^{15}$ vg/kg. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin. In one example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. In another example, the rAAV is AAVrh74.MCK.microdystrophin. In one example, the AAVrh74.MCK.microdystrophin is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[00119] In any of the compositions of the disclosure, the dose of rAAV is delivered in about 5mL/kg to about 15 mL/kg, or about 8 mL/kg to about 12 mL/kg, or 8 mL/kg to about 10 mL/kg, or 5 mL/kg to about 10 mL/kg or about 10 mL/kg to 12 mL/kg, or about 10 mL/kg to 15 mL/kg or 10 mL/kg to about 20 mL/kg. In a particular example, the composition comprises a dose of the rAAV delivered in about 10 mL/kg. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin. In one example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. In another example, the rAAV is AAVrh74.MCK.microdystrophin. In one example, the AAVrh74.MCK.microdystrophin is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[00120] The compositions of the disclosure are formulated for administration by injection, infusion or implantation. For example, the compositions are formulated for administration by infusion over approximately one hour. In addition, the compositions of the disclosure are formulated for intravenous administration through a peripheral limb vein such as a peripheral arm vein or a peripheral leg vein. Alternatively, the infusion may be administered over approximately 30 minutes, or approximately 1.5 hours, or approximately 2 hours, or approximately 2.5 hours or approximately 3 hours.

[00121] Any of the compositions of the disclosure comprise a rAAV comprising the human micro-dystrophin nucleotide sequence of SEQ ID NO: 1 and the MHCK7 promoter sequence of SEQ ID NO: 2 or SEQ ID NO:7 or a rAAV vector comprising the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6.

[00122] In particular, the compositions of the disclosure are for treating Duchenne muscular dystrophy or Becker's muscular dystrophy. For example, the disclosure provides for compositions for treating Duchenne muscular dystrophy or Becker's muscular dystrophy in a human subject in need thereof wherein the composition comprises a dose of recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin, wherein the composition is formulated for administration by intravenous infusion over approximately one hour and the dose of the rAAV administered is about 2x 10^{14} vg/kg, and wherein the rAAV comprises the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6.

[00123] In another example, the disclosure also provides a composition comprising rAAV for reducing fibrosis in a subject in need thereof. In addition, the disclosure provides a composition comprising a rAAV vectors for preventing fibrosis in a subject suffering from a muscular dystrophy.

[00124] The disclosure also provides for compositions comprising rAAV for increasing muscular force and/or muscle mass in a subject suffering from a muscular dystrophy. In a further example, the disclosure provides for compositions comprising any of the rAAV of the disclosure for treatment of muscular dystrophy.

[00125] In other examples of any of the compositions of the disclosure, after administration of said composition to a human subject in need of treatment for muscular dystrophy, the serum CK level in the subject is decreased as compared to the serum CK level before administration of the composition by a percentage level selected from the group consisting of:

a) at least 78% by 90, 180, or 270 days after the administration;

b) at least 46, 55, 70, or 85 % by 270 days after the administration;

c) at least 72, 73, 74, or 95 % by 180 days after the administration;

d) at least 87, 99, 93 or 95% by 90 days after the administration;

e) at least 70 % by 270 days after the administration;

f) 70 to 95% by 90, 180, or 270 days after the administration;

g) at least 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, or 95 % by 90, 180, or 270 days after the administration; and

h) 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, or 95 % by 90, 180, or 270 days after the administration.

[00126] In another example, the disclosure provides for use of a dose of recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin for the preparation of a medicament for the treatment of muscular dystrophy in a human subject in need thereof, wherein the medicament is formulated for a systemic route of administration and the dose of the rAAV is about $1x10^{14}$ vg/kg to about $4x\ 10^{14}$ vg/kg. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin. In one example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ ID NO: 6. In one example, the rAAV is AAVrh74.MCK.microdystrophin. In one example, the AAVrh74.MCK.microdystrophin is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[00127] For example, the medicament comprises a dose of rAAV of about $5.0x10^{12}$ vg/kg to about $1.0x10^{14}$ vg/kg, or about $5.0x10^{12}$ vg/kg to$1.0x10^{14}$ vg/kg, or about $5.0x10^{12}$ vg/kg to about $2.0x10^{14}$ vg/kg, or about $5.0x10^{12}$ vg/kg to about $1.0x10^{14}$ vg/kg, or about $5.0x10^{12}$ vg/kg to about $5.0x10^{13}$ vg/kg, or about $5.0x10^{12}$ vg/kg to about $2.0x10^{13}$ vg/kg, or about $5.0x10^{12}$ vg/kg to about $1.0x10^{13}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $1.0x10^{15}$ vg/kg, or $1.0x10^{13}$ vg/kg to about $1.0x10^{14}$ vg/kg, or about $1.0x10^{13}$ vg/kg to$1.0x10^{14}$ vg/kg, or about $1.0x10^{13}$ vg/kg to about $2.0x10^{14}$ vg/kg, or about $1.0x10^{13}$ vg/kg to about $1.0x10^{14}$ vg/kg, or about $1.0x10^{13}$ vg/kg to about $5.0x10^{13}$ vg/kg, or about $1.0x10^{13}$ vg/kg to about $3.0x10^{14}$ vg/kg, or about $1.0x10^{13}$ vg/kg to about $5.0x10^{14}$ vg/kg, or about $1.0x10^{13}$ vg/kg to about $6.0x10^{14}$ vg/kg, or $1.0x10^{13}$ vg/kg to about $1.0x10^{15}$ vg/kg, or $5.0x10^{13}$ vg/kg to about $1.0x10^{14}$ vg/kg, or about $5.0x10^{13}$ vg/kg to$1.0x10^{14}$ vg/kg, or about $5.0x10^{13}$ vg/kg to about $2.0x10^{14}$ vg/kg, or about $5.0x10^{13}$ vg/kg to about $1.0x10^{14}$ vg/kg, or about $5.0x10^{13}$ vg/kg to about $3.0x10^{14}$ vg/kg, or about $5.0x10^{13}$ vg/kg to about $5.0x10^{14}$ vg/kg, or about $5.0x10^{13}$ vg/kg to about $6.0x10^{14}$ vg/kg, or $5.0x10^{13}$ vg/kg to about $1.0x10^{15}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $6.0x10^{14}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $5.0x10^{14}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $4.0x10^{14}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $1.0x10^{15}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $3.0x10^{14}$ vg/kg, or about $1.0x10^{14}$ vg/kg to about $2.5x10^{14}$ vg/kg, or $1.0x10^{14}$ vg/kg to about $2.0x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg to about $3.75x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg

to $6.0x10^{14}$, or about $1.25x10^{14}$ vg/kg to $5.0x10^{14}$, or about $1.25x10^{14}$ vg/kg to $4.0x10^{14}$, or about $1.25x10^{14}$ vg/kg to $1.0x10^{15}$, or about $1.25x10^{14}$ vg/kg to about $3.5 x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg to about $3.0x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg to about $2.75x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg to about $2.5x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg to about $2.0x10^{14}$ vg/kg, or $1.25x10^{14}$ vg/kg to about $3.75x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg to about $3.5 x10^{14}$ vg/kg, or $1.5x10^{14}$ vg/kg to about $1.0x10^{15}$ vg/kg, or about $1.5x10^{14}$ vg/kg to $6.0x10^{14}$, or about $1.5x10^{14}$ vg/kg to $5.0x10^{14}$, or about $1.5x10^{14}$ vg/kg to $4.0x10^{14}$, or about $1.5x10^{14}$ vg/kg to about $3.75x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $3.5x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $3.25x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $3.0x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $2.75x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $2.5x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg to about $2.0x10^{14}$ vg/kg, or $1.75x10^{14}$ vg/kg to about $1.0x10^{15}$ vg/kg, or about $1.75x10^{14}$ vg/kg to $6.0x10^{14}$, or about $1.75x10^{14}$ vg/kg to $5.0x10^{14}$, or about $1.75x10^{14}$ vg/kg to $4.0x10^{14}$, or about $1.75x10^{14}$ vg/kg to about $3.75x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $3.5x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $3.25x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $3.0x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $2.75x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $2.5x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $2.25x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg to about $2.0x10^{14}$ vg/kg, or about $2.0x10^{14}$ vg/kg to $1.0x10^{15}$, or about $2.0x10^{14}$ vg/kg to $6.0x10^{14}$, or about $2.0x10^{14}$ vg/kg to $5.0x10^{14}$, or about $2.0x10^{14}$ vg/kg to about $4.0x10^{14}$ vg/kg, or about $2.0x10^{14}$ vg/kg to about $3.75x10^{14}$ vg/kg, or about $2.0x10^{14}$ vg/kg to about $3.5x10^{14}$ vg/kg, or about $2.0x10^{14}$ vg/kg to about $3.25x10^{14}$ vg/kg. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin. In one example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ ID NO: 6. In one example, the rAAV is AAVrh74.MCK.microdystrophin. In one example, the AAVrh74.MCK.microdystrophin is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[00128] In one example, the medicaments of the disclosure are formulated for systemic administration of a dose of rAAV wherein the systemic route of administration is an intravenous route and the dose of the rAAV administered is about $2.0 x10^{14}$ vg/kg. In another example, the medicament of the disclosure is formulated for systemic administration of a dose of rAAV wherein the systemic route of administration is an intravenous route and the dose of the rAAV is about $5.0x10^{12}$ vg/kg, or about $6.0x10^{12}$ vg/kg, or about $7.0x10^{12}$ vg/kg,

or about $8.0x10^{12}$ vg/kg, or about $9.0x10^{12}$ vg/kg, or about $1.0x10^{13}$ vg/kg, or about $1.25x10^{13}$ vg/kg, or about $1.5x10^{13}$ vg/kg, or about $1.75x10^{13}$ vg/kg, or about $2.25x10^{13}$ vg/kg, or about $2.5x10^{13}$ vg/kg, or about $2.75x10^{13}$ vg/kg, or about $3.0x10^{13}$ vg/kg, or about $3.25x10^{13}$ vg/kg, or about $3.5x10^{13}$ vg/kg, or about $3.75x10^{13}$ vg/kg, or about $4.0x10^{13}$ vg/kg, or about $5.0x10^{13}$ vg/kg, or about $6.0x10^{13}$ vg/kg, or about $7.0x10^{13}$ vg/kg, or about $8.0x10^{13}$ vg/kg, or about $9.0x10^{13}$ vg/kg, or about $1.0x10^{14}$ vg/kg, or about $1.25x10^{14}$ vg/kg, or about $1.5x10^{14}$ vg/kg, or about $1.75x10^{14}$ vg/kg, or about $2.25x10^{14}$ vg/kg, or about $2.5x10^{14}$ vg/kg, or about $2.75x10^{14}$ vg/kg, or about $3.0x10^{14}$ vg/kg, or about $3.25x10^{14}$ vg/kg, or about $3.5x10^{14}$ vg/kg, or about $3.75x10^{14}$ vg/kg, or about $4.0x10^{14}$ vg/kg, or about $5.0x10^{14}$ vg/kg, or about $6.0x10^{14}$ vg/kg, or about $1x10^{15}$ vg/kg. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin. In one example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ ID NO: 6. In one example, the rAAV is AAVrh74.MCK.microdystrophin. In one example, the AAVrh74.MCK.microdystrophin is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[00129] In any of the uses of the disclosure, the medicament comprises a dose of rAAV in about 5mL/kg to about 15 mL/kg, or about 8 mL/kg to about 12 mL/kg, or 8 mL/kg to about 10 mL/kg, or 5 mL/kg to about 10 mL/kg or about 10 mL/kg to 12 mL/k, or about 10 mL/kg to 15 mL/kg or 10 mL/kg to about 20 mL/kg. In a particular example, the dose or the rAAV is in about 10 mL/kg. In one example, the rAAV is AAVrh74.MHCK7.microdystrophin. In one example, the AAVrh74.MHCK7.microdystrophin is the AAVrh74.MHCK7.microdystrophin of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ ID NO: 6. In one example, the rAAV is AAVrh74.MCK.microdystrophin. In one example, the AAVrh74.MCK.microdystrophin is the AAVrh74.MCK.microdystrophin of nucleotides 56-4820 of SEQ ID NO: 5.

[00130] In any of the uses of the disclosure, the medicament is formulated for administration by injection, infusion or implantation. For example, the medicament is formulated for administration by infusion over approximately one hour. In addition, the medicament is formulated for intravenous administration through a peripheral limb vein, such as a peripheral arm vein or a peripheral leg vein. Alternatively, the infusion may be

administered over approximately 30 minutes, or approximately 1.5 hours, or approximately 2 hours, or approximately 2.5 hours or approximately 3 hours.

[00131] In any of the uses of the disclosure, the medicament comprises an rAAV comprising the human micro-dystrophin nucleotide sequence of SEQ ID NO: 1 and the MHCK7 promoter sequence of SEQ ID NO: 2 or SEQ ID NO:7 or the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ ID NO: 6.

[00132] A particular use of the disclosure is for preparation of a medicament for the treatment of Duchenne muscular dystrophy or Becker's muscular dystrophy. For example, the disclosure provides for use of a dose of recombinant adeno-virus associated (rAAV) rAAV.MHCK7.microdystrophin for the preparation of a medicament for treating Duchenne muscular dystrophy in a or Becker's muscular dystrophy human subject in need thereof, wherein the medicament is formulated for administration by intravenous infusion over approximately one hour and the dose of the rAAV administered is about $2x\ 10^{14}$ vg/kg, and wherein the rAAV comprises the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ ID NO: 6.

[00133] In a further example, the disclosure provides for use of a rAAV for preparation of a medicament for reducing fibrosis in a subject in need thereof. For example, the subject in need can be suffering from a muscular dystrophy, such as DMD or any other dystrophin associated muscular dystrophy.

[00134] In another example, the disclosure provides for use of a rAAV for the preparation of a medicament to prevent fibrosis in a subject suffering from a muscular dystrophy.

[00135] In addition, the disclosure provides for use of a rAAV for the preparation of a medicament to increase muscular strength and/or muscle mass in a subject suffering from muscular dystrophy.

[00136] The disclosure also provides for use of the rAAV for the preparation of a medicament for treatment of muscular dystrophy.

[00137] The disclosure provides for use of a rAAV vector comprising the human micro-dystrophin nucleotide sequence of SEQ ID NO: 1 and the MHCK7 promoter nucleotide sequence of SEQ ID NO: 2 or SEQ ID NO:7 for preparation of a medicament for the treatment of a muscular dystrophy or a rAAV vector comprising the AAVrf74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ ID NO: 6 for treatment of muscular dystrophy.

[00138] In other examples of any of the uses of the disclosure, the serum CK level in the subject is decreased after administration of the rAAV to the subject as compared to the serum CK level before administration of the rAAV by a percentage level selected from the group consisting of:

a) at least 78% by 90, 180, or 270 days after the administration;

b) at least 46, 55, 70, or 95 % by 270 days after the administration;

c) at least 72, 73, 74, or 95 % by 180 days after the administration;

d) at least 87, 88, 93 or 95% by 90 days after the administration;

e) at least 70 % by 270 days after the administration;

f) 70 to 95% by 90, 180, or 270 days after the administration;

g) at least 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, or 95 % by 90, 180, or 270 days after the administration; and

h) 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, or 95 % by 90, 180, or 270 days after the administration.

[00139] In any of the combination therapies, compositions for treating a muscular dystrophy or the uses of a medicament for treating a muscular dystrophy, the level of micro-dystrophin gene expression in a cell of the subject is increased after administration of the composition or medicament. Expression of the micro-dystrophin gene in the cell is detected by measuring the micro-dystrophin protein level by Western blot in muscle biopsied before and after administration of the composition or medicament. In particular, the level of micro-dystrophin protein is increased by at least about 70% to at least about 80%, or at least about 70% to at least about 90%, or at least about 80% to at least about 90% after administration of the composition or medicament compared to the level of micro-dystrophin before

[00143] In any of the combination therapies, compositions for treating a muscular dystrophy or the uses of a medicament for treating a muscular dystrophy, disease progression in the subject is delayed after administration of the rAAV as measured by any of: the six minute walk test, time to rise, ascend 4 steps, ascend and descend 4 steps, North Star Ambulatory Assessment (NSAA), 10 meter timed test, 100 meter timed test, hand held dynamometry (HHD), Timed Up and Go, and/or Gross Motor Subtest Scaled (Bayley-III) score.

[00144] For example, after administration of any of the combination therapies, compositions for treating a muscular dystrophy or the uses of a medicament for treating a muscular dystrophy, the subject has at least a 6-point improvement in NSAA score at least 270 days after administration of the composition or medicament as compared to NSAA score before administration of the rAAV. Further, in any of the methods, combination therapies, compositions for treating a muscular dystrophy or the uses of a medicament for treating a muscular dystrophy, the subject has at least about 0.8 second improvement in time to rise at least 270 days after administration of the rAAV as compared to time to rise before administration of the combination therapy, composition or medicament. In addition, in any of the methods, combination therapies, compositions or uses of the disclosure, the subject has at least about 1.2 second improvement in time to ascend 4 steps test at least 270 days after administration of the rAAV as compared to time to ascend 4 steps test before administration of the combination therapy, composition or medicament. In addition, in any of the methods, combination therapy, compositions or uses of the disclosure, the subject has at least about 7 second improvement in the 100 m timed test at least 270 days after administration of the rAAV as compared to the 100 m timed test before administration of the rAAV.

[00145] In another example, the disclosure provides for compositions for expressing micro-dystrophin gene in a patient cell comprising the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8 or nucleotides 56-5022 of SEQ ID NO: 6. In a further example, the disclosure provides for use of a dose of a AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8 or nucleotides 56-5022 of SEQ ID NO: 6 for the preparation of a medicament for expressing micro-dystrophin gene in a patient cell. For example, expression of the micro-dystrophin gene in the patient cell is detected by measuring the micro-dystrophin protein level by Western blot or immunohistochemistry in muscle

biopsies before and after administration of the rAAV.MHCK7.micro-dystrophin construct. In addition, the expression of the micro-dystrophin gene is measured in the patient by detecting greater the number of vector genomes per nucleus, wherein 1 vector genome per nucleus is about 50% micro-dystrophin expression and great than 1 copy per nucleus is consistent with micro-dystrophin expression level. For example, the cells have 1.2 vector copies per nucleus, or 1.3 vector copies per nucleus, or 1.4 vector copies per nucleus, or 1.5 vector copies per nucleus, or 1.6 vector copies per nucleus, or 1.7 vector copies per nucleus, or 1.8 vector copies per nucleus, or 1.9 vector copies per nucleus.

[00146] In a further example, the disclosure provides for compositions for decreasing serum CK levels in a patient in need thereof, the composition comprising the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. In addition, the disclosure provides for use of a dose of AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6 for the preparation of a medicament for decreasing serum CK levels in a patient in need thereof. For example, the serum CK level in the patient is decreased by at least about 65% to about 90% or about 65% to about 95% or about 75% to about 90% or about 80% to about 90% or about 85% to about 95% or about 87% to about 95% or about 87% to about 90% by 60 days after administration of the composition or medicament as compared to the serum CK level before administration of the composition or medicament. In particular, the serum CK level in the subject is decreased by about 87% by 60 days after administration of the composition or medicament as compared to the serum CK level before administration of the composition or medicament, or decreased by about 72% by 60 days after administration of the composition or medicament as compared to the serum CK level before administration of the composition or medicament, or decreased by about 73% by 60 days after administration of the composition or medicament as compared to the serum CK level before administration of the composition or medicament, or decreased by about 78% by 60 days after administration of the composition or medicament as compared to the serum CK level before administration of the composition or medicament, or decreased by about 95% by 60 days after administration of the composition or medicament as compared to the serum CK level before administration of the composition or medicament.

[00147] The disclosure also provides for compositions for increasing micro-dystrophin positive fibers in a patient muscle tissue comprising the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. In addition, the disclosure provides for use of a dose of AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6 for the preparation of a medicament for increasing micro-dystrophin positive fibers in a patient muscle tissue. For example, the number of micro-dystrophin positive fibers is detected by measuring the dystrophin protein level by Western blot or immunohistochemistry on muscle biopsies before and after administration of the composition or medicament. In addition, the expression of the micro-dystrophin gene is measured in the patient by detecting greater the number of vector genomes per nucleus, wherein 1 vector genome per nucleus is about 50% micro-dystrophin expression and great than 1 copy per nucleus is consistent with micro-dystrophin expression level. For example, the cells have 1.2 vector copies per nucleus, or 1.3 vector copies per nucleus, or 1.4 vector copies per nucleus, or 1.5 vector copies per nucleus, or 1.6 vector copies per nucleus, or 1.7 vector copies per nucleus, or 1.8 vector copies per nucleus, or 1.9 vector copies per nucleus.

[00148] In another example, the disclosure provides for compositions for increasing the expression of alpha-sarcoglycan in a patient in need thereof comprising the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6. The disclosure also provides for use of a dose of AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID NO: 3, nucleotides 1-4977 of SEQ ID NO: 8, or nucleotides 56-5022 of SEQ IDNO: 6 for the preparation of a medicament for increasing the expression of alpha-sarcoglycan in a patient in need thereof. For example, the level of alpha-sarcoglycan is detected by measuring the alpha-sarcoglycan protein level by Western blot or immunohistochemistry on muscle biopsies before and after administration of the composition or medicament.

[00149] In addition, the disclosure provides for compositions for increasing the expression of beta-sarcoglycan in a patient in need thereof comprising the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, nucleotides 55-5021 of SEQ ID

CLAIMS

What is claimed:

1. Use of a dose of recombinant adeno-virus associated (rAAV) AAVrh.74.MHCK7.microdystrophin for the preparation of a medicament for treating a muscular dystrophy in a human subject in need thereof, wherein the rAAV is administered prior to subjecting the subject's plasma to at least one therapeutic plasma exchange (TPE) prior to administration of a second dose of the rAAV.

2. Use of a dose of recombinant adeno-virus associated (rAAV) AAVrh.74.MHCK7.microdystrophin for the preparation of a medicament for treating a muscular dystrophy in a human subject in need thereof, wherein the rAAV is administered after a first dose of the rAAV and after subjecting the subject's plasma to at least one therapeutic plasma exchange (TPE).

3. The use of claim 1 or 2, wherein the muscular dystrophy is Duchenne muscular dystrophy.

4. The use of any one of claim 1-3, wherein the subject's plasma is subject to at least two TPE or at least three TPE prior to administration of the dose of rAAV.

5. Use of a recombinant adeno-virus associated (rAAV) AAVrh.74.MHCK7.microdystrophin for the preparation of a medicament for treating muscular dystrophy in a human subject in need thereof, wherein the rAAV is administered after subjecting the subject's plasma to at least one therapeutic plasma exchange (TPE) prior to administering recombinant adeno-virus associated (rAAV).

6. The use of any one of claims 1-5 wherein the subject's plasma is subjected to at least two TPE, at least three TPE, at least four TPE, at least five TPE rAAV, at least six TPE or at least seven TPE prior to administering.

7. The use of any one of claims 1-6 wherein the subject's plasma is subjected to TPE for at least 9 days prior to administration of the rAAV, at least 7 days prior to administration, 5 days prior to administration, or 2 days prior to administration or the subject plasma is subjected to TPE on the day the rAAV is administered.

8. The use of claim 6 or 7, wherein the subject's plasma is subjected to at least two TPE, wherein there is about 48 hours in between the TPE.

9. The use of any one of claims 6-8, wherein the subject is administered an anti-inflammatory steroid about 24 hours prior to administration of the rAAV or wherein the subject is administered an anti-inflammatory steroid at least once a day from day 1 to 60 days after administration of the rAAV.

10. The use of any one of claims 1-9 wherein the rAAV is formulated for systemic route of administration.

11. The use of claim 10 wherein the systemic route of administration is an intravenous route and the dose of the rAAV administered is about 2x 10^{14} vg/kg.

12. The use of any one of claims 1-11 wherein the rAAV comprises
    a) the human micro-dystrophin nucleotide sequence of SEQ ID NO: 1,
    b) the MHCK7 promoter sequence of SEQ ID NO: 2 or SEQ ID NO:7,
    c) the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9, or
    d) nucleotides 55-5021 of SEQ ID NO: 3.

13. The use of any one of claim 1-12 wherein the human subject is suffering from Duchenne muscular dystrophy, and the rAAV is administered by intravenous infusion over approximately one hour at a dose of about 2x 10^{14} vg/kg, and wherein the rAAV comprises the AAVrh74.MHCK7.micro-dystrophin construct nucleotide sequence of SEQ ID NO: 9 or of nucleotides 55-5021 of SEQ ID NO: 3.

14. The use of any one of claims 1-13 wherein the level of micro-dystrophin gene expression in a cell of the subject is increased after administration of the rAAV as compared to the level of micro-dystrophin gene expression before administration of the rAAV.

15. The use of any one of claims 1-14, wherein the presence of anti-AAVrh.74 antibodies is determined in serum or plasma of said subject.

16. The use of claim 15, wherein the presence of anti-AAVrh7.4 antibodies is determined

a) prior to the step of administering said administering of an immunosuppressing regimen or TPE, and/or

b) prior to any administration of an AAV to said subject.

17. The use of claim 16, wherein said determination is quantitative and the level of anti-AAVrh.74 antibodies in serum or plasma of said subject is compared to a positive control.

18. The use of claim 17 wherein said positive control utilizes an anti-AAVrh.74 monoclonal antibody.

19. The use of any one of claims 16-18, wherein an anti-AAVrh.74 monoclonal antibody is used to determine the level of anti-AAVrh.74 antibodies.

20. The use of claims 16-19, wherein said determination step comprises utilizing an immunofluorescence assay, an immunohistochemical assay, a Western blot, a direct enzyme-linked immunosorbent assay (ELISA), an indirect ELISA, a sandwich ELISA, a competitive ELISA, a reverse ELISA, a chemiluminescence assay, a radioimmunoassay, or an immunoprecipitation assay.

21. The use of any one of claims 18-20, wherein said monoclonal antibody comprises

a) a VH CDR1 amino acid sequence selected from the group consisting of NYGMN (SEQ ID NO: 20), DYGMN (SEQ ID NO: 22), YTFTNYGMN (SEQ ID NO: 21), and YTFTKYGMN (SEQ ID NO: 23),

b) VH CDR2 amino acid sequence selected from the group consisting of WINTYTGEPTYADDFKG (SEQ ID NO: 24), WINTNTGEPTYGDDFKG (SEQ ID NO: 25), and WMGWINTYTGEPTY (SEQ ID NO: 26),

c) VH CDR3 amino acid sequence selected from the group consisting of GVAHYSDSRFAFDY (SEQ ID NO: 27), GNAHPGGSAFVY (SEQ ID NO: 28), RGSYYYDSSPAWFAY (SEQ ID NO: 29), RGVDSSGYGAFAY (SEQ ID NO: 30), and TRGTSTMISTFAFVY (SEQ ID NO: 31),

d) VL CDR1 amino acid sequence selected from the group consisting of SVSSSVSYMH (SEQ ID NO: 32), SASSGVTYMH (SEQ ID NO: 33), SSVSYMH (SEQ ID NO: 34), and SSVRYMH (SEQ ID NO: 35),

e) VL CDR2 amino acid sequence selected from the group consisting of YTSNLAS (SEQ ID NO: 36), RTSNLAS (SEQ ID NO: 37), LWIYSTSNLAS (SEQ ID NO: 38), and VWIYSTSNLAS (SEQ ID NO: 39),and/or

f) VH CDR3 amino acid sequence selected from the group consisting of QQRSSYPFT (SEQ ID NO: 40), QQRSTYPF (SEQ ID NO: 41), QQRSFYPF (SEQ ID NO: 42), and QQRTYYPF (SEQ ID NO: 43).

22. The use of any one of claim 18-21, wherein said monoclonal antibody comprises

a) a variable heavy chain (VH) sequence set forth in SEQ ID NO: 10, 12, 14, 16, or 18

b) a variable light chain (VL) sequence set forth in SEQ ID NO: 11, 13, 15, 17, or 19, or

c) a variable heavy chain (VH) sequence set forth in SEQ ID NO: 10, 12, 14, 16, or 18, and a variable light chain (VL) sequence set forth in SEQ ID NO: 11, 13, 15, 17, or 19.

23. The use of any one of claims 18-22, wherein said determination is quantitative, wherein said subject is identified as seropositive for anti-AAVrh.74 antibodies based said quantitation, and wherein said immunosuppressing regimen or TPE is selectively administered to the seropositive subject.