WE CLAIM:

1. An adeno-associated virus (AAV) comprising:

(a) a viral capsid protein from AAV9 comprising a modified subunit 1 (VP1) sequence comprising a serine at position 1, a glutamic acid at position 26, an arginine at position 40, an aspartic acid at position 43, and a serine at position 44, wherein the amino acids at positions 1, 26, 40, 43, and 44 are definedmodified relative to a corresponding wildtype AAV9 VP1 sequence set forth in SEQ ID NO: 87, and wherein no additional amino acids other than those at positions 1, 26, 40, 43, and 44 are modified relative to a corresponding wildtype AAV9 VP1 sequence; and

(b) a polynucleotide sequence comprising (i) a DNA-directed RNAi (ddRNAi) construct comprising a nucleic acid comprising a sequence which encodes a short hairpin micro-RNA (shmiR); and (ii) a PABPN1 construct comprising a nucleic acid comprising a sequence encoding a functional PABPN1 protein having a mRNA transcript which is not targeted by the shmiR(s) encoded by the ddRNAi construct.

2. The AAV of claim 1, wherein the modified VP1 sequence comprises a serine at position 1, a glutamic acid at position 26, an arginine at position 40, an aspartic acid at position 43, and a serine at position 44 relative to the wildtype AAV9 VP1 sequence set forth in SEQ ID NO: 87.

23. The AAV of claim 1 or 2, wherein the modified AAV9 VP1 sequence comprises the sequence set forth in SEQ ID NO: 88.

34. The AAV of claim 1 or 2any one of claim 1-3, wherein the polynucleotide sequence at (b) comprises, in a 5' to 3' direction, the ddRNAi construct and the PABPN1 construct.

45. The AAV of claim 1 or 2any one of claim 1-3, wherein the polynucleotide sequence at (b) comprises, in a 5' to 3' direction, the PABPN1 construct and the ddRNAi construct.

5~~6~~. The AAV of any one of claim 1 to 4~~1-5~~, wherein the polynucleotide sequence at (b) comprises inverted terminal repeats (ITRs) from an AAV serotype and wherein the ITRs flank the sequence comprising the ddRNAi construct and PABPN1 construct.

6~~7~~. The AAV of claim 5~~6~~, wherein the ITRs are from an AAV2 serotype.

7~~8~~. The AAV of any one of claims 1 to 6~~1-7~~, wherein the sequence encoding the functional PABPN1 protein is codon optimised such that its mRNA transcript is not targeted by the shmiRs of the ddRNAi construct.

8~~9~~. The AAV of any one of claims 1 to 7~~1-8~~, wherein the sequence encoding the functional PABPN1 protein is set forth in SEQ ID NO: 73.

9~~10~~. The AAV of any of claims 1 to 8~~1-9~~, wherein the ddRNAi construct and the sequence encoding the functional PABPN1 protein are operably-linked to a promoter positioned upstream of the ddRNAi construct and the sequence encoding the functional PABPN1 protein.

10~~11~~. The AAV of claim 9~~10~~, wherein the promoter is a muscle-specific promoter.

11~~12~~. The AAV of any one of claims 1 to 10~~1-11~~, wherein the shmiR comprises:

an effector sequence of at least 17 nucleotides in length;

an effector complement sequence;

a stemloop sequence; and

a primary micro RNA (pri-miRNA) backbone;

wherein the effector sequence is substantially complementary to a region of corresponding length in an RNA transcript set forth in any one of SEQ ID NOs: 1-13.

12~~13~~. The AAV of any one of claims 1 to 11~~1-12~~, wherein the shmiR is selected from the group consisting of:

a shmiR comprising an effector sequence set forth in SEQ ID NO: 15 and an effector complement sequence set forth in SEQ ID NO: 14;

a shmiR comprising an effector sequence set forth in SEQ ID NO: 17 and an effector complement sequence set forth in SEQ ID NO: 16;

a shmiR comprising an effector sequence set forth in SEQ ID NO: 19 and an effector complement sequence set forth in SEQ ID NO: 18;

a shmiR comprising an effector sequence set forth in SEQ ID NO: 21 and an effector complement sequence set forth in SEQ ID NO: 20;

a shmiR comprising an effector sequence set forth in SEQ ID NO: 23 and an effector complement sequence set forth in SEQ ID NO: 22;

a shmiR comprising an effector sequence set forth in SEQ ID NO: 25 and an effector complement sequence set forth in SEQ ID NO: 24;

a shmiR comprising an effector sequence set forth in SEQ ID NO: 27 and an effector complement sequence set forth in SEQ ID NO: 26;

a shmiR comprising an effector sequence set forth in SEQ ID NO: 29 and an effector complement sequence set forth in SEQ ID NO: 28;

a shmiR comprising an effector sequence set forth in SEQ ID NO: 31 and an effector complement sequence set forth in SEQ ID NO: 30;

a shmiR comprising an effector sequence set forth in SEQ ID NO: 33 and an effector complement sequence set forth in SEQ ID NO: 32;

a shmiR comprising an effector sequence set forth in SEQ ID NO: 35 and an effector complement sequence set forth in SEQ ID NO: 34;

a shmiR comprising an effector sequence set forth in SEQ ID NO: 37 and an effector complement sequence set forth in SEQ ID NO: 36; and

a shmiR comprising an effector sequence set forth in SEQ ID NO: 39 and an effector complement sequence set forth in SEQ ID NO: 38.

13~~14~~. The AAV of any one of claims 1 to 12~~1-13~~, wherein the shmiR comprises, in a 5' to 3' direction:

a 5' flanking sequence of the pri-miRNA backbone;

the effector complement sequence;

the stemloop sequence;

the effector sequence; and

a 3’ flanking sequence of the pri-miRNA backbone.

14~~15~~. The AAV of claim 13~~14~~, wherein the stemloop sequence is the sequence set forth in SEQ ID NO: 40.

15~~16~~. The AAV of claim 13 or 14 ~~or 15~~, wherein the pri-miRNA backbone is a pri-miR-30a backbone.

16~~17~~. The AAV of any one of claims 13 to 15~~14-16~~, wherein the 5’ flanking sequence of the pri-miRNA backbone is set forth in SEQ ID NO: 41 and the 3’ flanking sequence of the pri-miRNA backbone is set forth in SEQ ID NO: 42.

17~~18~~. The AAV of any one of claims 1 to 16~~1-17~~, wherein the ddRNAi construct comprises at least two nucleic acids each encoding a shmiR, wherein each shmiR comprises an effector sequence which is substantially complementary to a RNA transcript corresponding to a PABPN1 protein which is causative of oculopharyngeal muscular dystrophy (OPMD), and wherein each shmiR comprises a different effector sequence.

18~~19~~. The AAV of any one of claims 1 to 17~~1-18~~, wherein each of the at least two nucleic acids encode a shmiR comprising an effector sequence which is substantially complementary to a region of corresponding length in an RNA transcript set forth in one of SEQ ID NOs: 1, 2, 4, 7, 9, 10 and 13.

19~~20~~. The AAV of claim 18~~19~~, wherein the at least two nucleic acids are selected from the group consisting of:

a nucleic acid comprising or consisting of a DNA sequence encoding a shmiR comprising an effector sequence set forth in SEQ ID NO: 15 and an effector complement sequence set forth in SEQ ID NO: 14 (shmiR2);

a nucleic acid comprising or consisting of a DNA sequence encoding a shmiR comprising an effector sequence set forth in SEQ ID NO: 17 and an effector complement sequence set forth in SEQ ID NO: 16 (shmiR3);

a nucleic acid comprising or consisting of a DNA sequence encoding a shmiR comprising an effector sequence set forth in SEQ ID NO: 21 and an effector complement sequence set forth in SEQ ID NO: 20 (shmiR5);

a nucleic acid comprising or consisting of a DNA sequence encoding a shmiR comprising an effector sequence set forth in SEQ ID NO: 27 and an effector complement sequence set forth in SEQ ID NO: 26 (shmiR9);

a nucleic acid comprising or consisting of a DNA sequence encoding a shmiR comprising an effector sequence set forth in SEQ ID NO: 31 and an effector complement sequence set forth in SEQ ID NO: 30 (shmiR13);

a nucleic acid comprising or consisting of a DNA sequence encoding a shmiR comprising an effector sequence set forth in SEQ ID NO: 33 and an effector complement sequence set forth in SEQ ID NO: 32 (shmiR14); and

a nucleic acid comprising or consisting of a DNA sequence encoding a shmiR comprising an effector sequence set forth in SEQ ID NO: 39 and an effector complement sequence set forth in SEQ ID NO: 38 (shmiR17).

20~~21~~. The AAV of claim 18~~19~~, wherein the at least two nucleic acids are selected from the group consisting of:

a nucleic acid comprising or consisting of a DNA sequence set forth in SEQ ID NO: 56 (shmiR2);

a nucleic acid comprising or consisting of a DNA sequence set forth in SEQ ID NO: 57 (shmiR3);

a nucleic acid comprising or consisting of a DNA sequence set forth in SEQ ID NO: 59 (shmiR5);

a nucleic acid comprising or consisting of a DNA sequence set forth in SEQ ID NO: 62 (shmiR9);

a nucleic acid comprising or consisting of a DNA sequence set forth in SEQ ID NO: 64 (shmiR13);

a nucleic acid comprising or consisting of a DNA sequence set forth in SEQ ID NO: 65 (shmiR14); and

a nucleic acid comprising or consisting of a DNA sequence set forth in SEQ ID NO: 68 (shmiR17).

21~~22~~. The AAV of claim 18~~19~~, wherein each of the at least two nucleic acids encode a shmiR comprising an effector sequence which is substantially complementary to a region of corresponding length in an RNA transcript set forth in one of SEQ ID NOs: 2, 9, 10 and 13.

22~~23~~. The AAV of claim 18~~19~~, wherein the at least two nucleic acids are selected from the group consisting of:

a nucleic acid comprising or consisting of a DNA sequence encoding a shmiR comprising an effector sequence set forth in SEQ ID NO: 17 and an effector complement sequence set forth in SEQ ID NO: 16 (shmiR3);

a nucleic acid comprising or consisting of a DNA sequence encoding a shmiR comprising an effector sequence set forth in SEQ ID NO: 31 and an effector complement sequence set forth in SEQ ID NO: 30 (shmiR13);

a nucleic acid comprising or consisting of a DNA sequence encoding a shmiR comprising an effector sequence set forth in SEQ ID NO: 33 and an effector complement sequence set forth in SEQ ID NO: 32 (shmiR14); and

a nucleic acid comprising or consisting of a DNA sequence encoding a shmiR comprising an effector sequence set forth in SEQ ID NO: 39 and an effector complement sequence set forth in SEQ ID NO: 38 (shmiR17).

23~~24~~. The AAV of claim 18~~19~~, wherein the at least two nucleic acids are selected from the group consisting of:

a nucleic acid comprising or consisting of a DNA sequence set forth in SEQ ID NO: 57 (shmiR3);

a nucleic acid comprising or consisting of a DNA sequence set forth in SEQ ID NO: 64 (shmiR13);

a nucleic acid comprising or consisting of a DNA sequence set forth in SEQ ID NO: 65 (shmiR14); and

a nucleic acid comprising or consisting of a DNA sequence set forth in SEQ ID NO: 68 (shmiR17).

24~~25~~. The AAV of any one of claims 1 to 23~~1 24~~, wherein said ddRNAi construct comprises:

(a) a nucleic acid comprising or consisting of a DNA sequence encoding a shmiR comprising an effector sequence set forth in SEQ ID NO: 31 and an effector complement sequence set forth in SEQ ID NO: 30 (shmiR13); and

(b) a nucleic acid comprising or consisting of a DNA sequence encoding a shmiR comprising an effector sequence set forth in SEQ ID NO: 39 and an effector complement sequence set forth in SEQ ID NO: 38 (shmiR17).

25~~26~~. The AAV of claim 24~~25~~, wherein said ddRNAi construct comprising:

(a) a nucleic acid comprising or consisting of the DNA sequence set forth in SEQ ID NO: 64 (shmiR13); and

(b) a nucleic acid comprising or consisting of the DNA sequence set forth in SEQ ID NO: 68 (shmiR17).

26~~27~~. A pharmaceutical composition comprising AAV of any one of claims 1 to 25~~1 26~~ and one or more pharmaceutically acceptable carriers.

27~~28~~. Use of the AAV of any one of claims 1 to 25~~1 26~~ or the pharmaceutical composition of claim 26~~27~~ in the preparation of a medicament for treating a subject suffering from oculopharyngeal muscular dystrophy (OPMD).