WE CLAIM:

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

(a) a viral capsid protein from AAV9 comprising a modified subunit 1 (VP1) sequence wherein the amino acids at positions 1, 26, 40, 43, and 44 are modified relative to a corresponding wildtype AAV9 VP1 sequence set forth in SEQ ID NO: 87; 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.

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

4. The AAV of any one of claim 1-3, wherein the polynucleotide sequence comprises, in a 5’ to 3’ direction, the ddRNAi construct and the PABPN1 construct.

5. The AAV of any one of claim 1-3, wherein the polynucleotide sequence comprises,, in a 5’ to 3’ direction, the PABPN1 construct and the ddRNAi construct.

6. The AAV of any one of claim 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.

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

8. The AAV of any one of claims 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.

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

10. The AAV of any of claims 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.

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

12. The AAV of any one of claims 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.

13. The AAV of any one of claims 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.

14. The AAV of any one of claims 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.

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

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

17. The AAV of any one of claims 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.

18. The AAV of any one of claims 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 OPMD, and wherein each shmiR comprises a different effector sequence.

19. The AAV of any one of claims 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.

20. The AAV of claim 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).

21. The AAV of claim 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).

22. The AAV of claim 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.

23. The AAV of claim 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).

24. The AAV of claim 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).

25. The AAV of any one of claims 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).

26. The AAV of claim 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).

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

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