CLAIMS

1. A composition comprising:

a first nucleic acid molecule comprising:

a sequence encoding a first portion of the dysferlin protein; and

a first portion of a split intein;

a second nucleic acid molecule comprising:

a sequence encoding a second portion of the dysferlin protein; and

a second portion of a split intein,

wherein the first nucleic acid molecule and second nucleic acid molecule encode different portions of the dysferlin protein.

2. The composition of claim 1, wherein the first and second portion of the dysferlin protein together provide a functional dysferlin protein.

3. The composition of claim 2, wherein the first nucleic acid molecule is packaged is in a first vector and the second nucleic acid molecule is packaged in a second vector.

4. The composition of claim 3, wherein each vector is an adeno-associated viral (AAV) vector.

5. The composition of claim 4, wherein the first portion of the dysferlin protein is between 1100-1150 amino acids in length.

6. The composition of claim 5, wherein the sequence encoding the first portion of the dysferlin protein comprises the C2A-C2C, Fer domains, and dysF domains of the dysferlin protein and the second portion of the dysferlin protein comprises the C2D-C2G domains and transmembrane domain of the dysferlin protein.

7. The composition of claim 4, wherein the first nucleic acid molecule comprises in order:

an inverted terminal repeats (ITR) region;

a promoter;

the sequence encoding a first portion of the dysferlin protein;

the first portion of a split intein;

an ITR region, and

the second nucleic acid molecule comprises in order:

an ITR region;

a promoter;

the second portion of a split intein intein;

the sequence encoding a second portion of the dysferlin protein;

an ITR region.

8. The composition of claim 4, wherein each AAV vector comprises a capsid protein having at least one modification that results in reduced liver-tropism of the AAV vector and/or preferential targeting of the AAV vector to muscle tissue.

9. The composition of claim 8, wherein when the composition is provided to a subject, the first nucleic acid molecule and second nucleic acid molecule are each expressed in different nuclei in muscle tissue.

10. The composition of claim 9, wherein once expressed, the two portions of the dysferlin protein are joined by splicing of the respective inteins within the cytoplasm of the muscle cells.

11. A composition for use in the treatment of a dysferlinopathy, wherein the composition comprises:

a first nucleic acid molecule comprising:

a sequence encoding a first portion of the dysferlin protein; and

a first portion of a split intein; and

a second nucleic acid molecule comprising a sequence encoding:

a second portion of the dysferlin protein; and

a second portion of a split intein,

wherein the first nucleic acid molecule and second nucleic acid molecule encode different portions of the dysferlin protein.

12. The composition for use of claim 11, wherein the first nucleic acid molecule is packaged is in a first vector and the second nucleic acid molecule is packaged in a second vector.

13. The composition for use of claim 12, wherein each vector is an adeno-associated viral (AAV) vector.

14. The composition for use of claim 13, wherein the first portion of the dysferlin protein is between 1100-1150 amino acids in length.

15. The composition for use of claim 14, wherein the sequence encoding the first portion of the dysferlin protein comprises the C2A-C2C, Fer domains, and dysF domains of the dysferlin protein and the second portion of the dysferlin protein comprises the C2D-C2G domains and the transmembrane domain of the dysferlin protein.

16. The composition for use of claim 13, wherein the first nucleic acid molecule comprises in order:

an inverted terminal repeats (ITR) region;

a promoter;

the sequence encoding a first portion of the dysferlin protein;

the first portion of a split intein;

an ITR region, and

the second nucleic acid molecule comprises in order:

an ITR region;

a promoter;

the second portion of a split intein;

the sequence encoding a second portion of the dysferlin protein;

an ITR region.

17. The composition for use of claim 13, wherein each AAV vector comprises a capsid protein having at least one modification that results in reduced liver-tropism of the AAV vector and/or preferential targeting of the AAV vector to muscle tissue.

18. The composition for use of claim 17, wherein when the composition is provided to a subject, the first nucleic acid molecule and second nucleic acid molecule are each expressed in different nuclei in multi-nucleated muscle cells.

19. The composition for use of claim 11, wherein once expressed, the two portions of the dysferlin protein are joined by splicing of the respective inteins within the cytoplasm of the muscle cells.

20. The composition for use of claim 19, wherein splicing of the respective inteins results in formation of a functional dysferlin protein.