CLAIMS

WHAT IS CLAIMED IS:

1. A polynucleic acid molecule conjugate comprising:
   an antibody or antigen binding fragment thereof conjugated to a polynucleic acid molecule that hybridizes to a target sequence of *DUX4*; and
   wherein the polynucleic acid molecule conjugate mediates RNA interference against the *DUX4*.

2. The polynucleic acid molecule conjugate of claim 1, wherein the antibody or binding fragment thereof comprises a non-human antibody or antigen binding fragment thereof, a human antibody or antigen binding fragment thereof, a humanized antibody or antigen binding fragment thereof, chimeric antibody or antigen binding fragment thereof, monoclonal antibody or antigen binding fragment thereof, monovalent Fab', divalent Fab2, single-chain variable fragment (scFv), diabody, minibody, nanobody, single-domain antibody (sdAb), or camelid antibody or antigen binding fragment thereof.

3. The polynucleic acid molecule conjugate of any one of claims 1-2, wherein the antibody or antigen binding fragment thereof is an anti-transferrin receptor antibody or antigen binding fragment thereof.

4. The polynucleic acid molecule conjugate of any one of claims 1-3, wherein the polynucleic acid molecule comprises a sense strand and/or an antisense strand, and wherein the sense strand and/or the antisense strand each independently comprises at least one 2' modified nucleotide, at least one modified internucleotide linkage, or at least one inverted abasic moiety.

5. The polynucleic acid molecule conjugate of any one of claims 1-4, wherein the polynucleotide hybridizes to at least 8 contiguous bases of the target sequence of *DUX4*.

6. The polynucleic acid molecule conjugate of any one of claims 1-5, wherein the polynucleotide is from about 8 to about 50 nucleotides in length or from about 10 to about 30 nucleotides in length.

7. The polynucleic acid molecule conjugate of any one of claims 1-6, wherein the polynucleic acid molecule comprises a sense strand and/or an antisense strand, and the sense strand comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%,

at least 98%, at least 99% identical to a sequence selected from SEQ ID NOS: 1-70 or SEQ ID NOS: 141-210.

8. The polynucleic acid molecule conjugate of any one of claims 1-7, wherein the polynucleic acid molecule comprises a sense strand and/or an antisense strand, and the antisense strand comprises at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to a sequence selected from SEQ ID NOS: 71-140 or SEQ ID NOS: 211-280.

9. The polynucleic acid molecule conjugate of any one of claims 1-8, wherein the polynucleotide comprises at least one 2' modified nucleotide, and further wherein the 2' modified nucleotide:

comprises 2'-O-methyl, 2'-O-methoxyethyl (2'-O-MOE), 2'-O-aminopropyl, 2'-deoxy, 2'-deoxy-2'-fluoro, 2'-O-aminopropyl (2'-O-AP), 2'-O-dimethylaminoethyl (2'-O-DMAOE), 2'-O-dimethylaminopropyl (2'-O-DMAP), 2'-O-dimethylaminoethyloxyethyl (2'-O-DMAEOE), or 2'-O-N-methylacetamido (2'-O-NMA) modified nucleotide;

comprises locked nucleic acid (LNA) or ethylene nucleic acid (ENA); or

comprises a combination thereof.

10. The polynucleic acid molecule conjugate of any one of claims 1-9, wherein the at least one modified internucleotide linkage comprises a phosphorothioate linkage or a phosphorodithioate linkage.

11. The polynucleic acid molecule conjugate of any one of claims 1-10, wherein the polynucleic acid molecule comprises 3 or more 2' modified nucleotides selected from 2'-O-methyl and 2'-deoxy-2'-fluoro.

12. The polynucleic acid molecule conjugate of any one of claims 1-11, wherein the polynucleic acid molecule comprises a 5'-terminal vinylphosphonate modified nucleotide.

13. The polynucleic acid molecule conjugate of any one of claims 1-12, wherein the 2' modified nucleotide is 2'-O-methyl modified nucleotide, and 2'-O-methyl modified nucleotide is at the 5'-end of the sense strand and/or the antisense strand.

14. The polynucleic acid molecule conjugate of claim 13, wherein the 2'-O-methyl modified nucleotide is a purine nucleotide.

15. The polynucleic acid molecule conjugate of claim 13, wherein the 2'-O-methyl modified nucleotide is a pyridine nucleotide.

16. The polynucleic acid molecule conjugate of any one of claims 13-15, wherein the sense and/or antisense strands comprise at least two, three, four consecutive the 2'-O-methyl modified nucleotides at the 5'-end.

17. The polynucleic acid molecule conjugate of any one of claims 1-16, wherein the polynucleic acid molecule conjugate comprises a linker connecting the antibody or antigen binding fragment thereof to the polynucleic acid molecule.

18. The polynucleic acid molecule conjugate of claim 17, wherein the linker is C1-C6 alkyl linker.

19. The polynucleic acid molecule conjugate of claim 17, wherein the linker is a homobifunctional linker or heterobifunctional linker, and comprises a maleimide group, a dipeptide moiety, a benzoic acid group, or its derivative thereof.

20. The polynucleic acid molecule conjugate of claim 17, wherein the linker is a cleavable or non-cleavable linker.

21. The polynucleic acid molecule conjugate of any one of claims 1-20, wherein a ratio between the polynucleic acid molecule and the antibody or antigen binding fragment thereof is about 1:1, 2:1, 3:1, or 4:1.

22. The polynucleic acid molecule conjugate of any one of claims 1-21, wherein the polynucleic acid molecule mediates RNA interference against the human *DUX4* and modulates muscle atrophy in a subject.

23. The polynucleic acid molecule conjugate of claim 22, wherein the RNA interference comprises reducing expression of the mRNA transcript of DUX4 gene at least 50%, at least 60%, or at least 70% or more compared to a quantity of the mRNA transcript of DUX4 gene in an untreated cell.

24. The polynucleic acid molecule conjugate of any one of claims 22-23, wherein the RNA interference comprises affecting expression of a marker gene selected from a group consisting of MBD3L2, TRIM43, PRAMEF1, ZSCAN4, KHDC1L, and LEUTX in a cell.

25. The polynucleic acid molecule conjugate of claim 24, wherein the affecting expression of the marker gene is reducing expression of the marker gene at least 20%, at least 30%, at least 40%, at least 50%, at least 60% or more.

26. The polynucleic acid molecule conjugate of any one of claims 22-25, wherein the muscle dystrophy is Facioscapulohumeral muscular dystrophy (FSHD).

27. The polynucleic acid molecule conjugate of any one of claims 1-26, wherein the polynucleic acid molecule conjugate comprises a molecule of Formula (I):

A-X-B

Formula I

wherein,

A is the antibody or antigen binding fragment thereof;

B is the polynucleic acid molecule that hybridizes to a target sequence of *DUX4*;

X is a bond or a non-polymeric linker; and

wherein X is conjugated to a cysteine residue of A.

28. A pharmaceutical composition comprising:

a polynucleic acid molecule conjugate of claims 1-27; and

a pharmaceutically acceptable excipient.

29. The pharmaceutical composition of claim 28, wherein the pharmaceutical composition is formulated as a nanoparticle formulation.

30. The pharmaceutical composition of any one of claims 28-29, wherein the pharmaceutical composition is formulated for parenteral, oral, intranasal, buccal, rectal, transdermal, intravenous, subcutaneous, or intrathecal administration.

31. A method for treating muscular dystrophy in a subject in need thereof, comprising:

providing a polynucleic acid conjugate of any one of claims 1-30; and

administering the polynucleic acid conjugate to the subject in need thereof to treat the muscular dystrophy, wherein the polynucleic acid conjugate reduces a quantity of the mRNA transcript of human *DUX4*.

32. The method of claim 31, wherein the polynucleic acid moiety mediates RNA interference against the human *DUX4* and modulates muscle atrophy in a subject.

33. The method of claim 32, wherein the RNA interference comprises affecting expression of a marker gene selected from a group consisting of MBD3L2, TRIM43, PRAMEF1, ZSCAN4, KHDC1L, and LEUTX in a cell affected by a muscle dystrophy.

34. The method of any one of claims 31-33, wherein the muscular dystrophy is Facioscapulohumeral muscular dystrophy (FSHD).

35. Use of the polynucleic acid molecule conjugate of any one of claims 1-27 or the pharmaceutical composition of any one of claims 28-30 for treating in a subject diagnosed with or suspected to have Facioscapulohumeral muscular dystrophy (FSHD).

36. Use of the polynucleic acid molecule conjugate of any one of claims 1-27 or the pharmaceutical composition of any one of claims 28-30 for manufacturing a medicament for treating in a subject diagnosed with or suspected to have Facioscapulohumeral muscular dystrophy (FSHD).

37. A kit comprising a polynucleic acid molecule conjugate of claims 1-27 or the pharmaceutical composition of any one of claims 28-30.