CLAIMS

WHAT IS CLAIMED IS:

1. A ~~polynucleic acid molecule~~ small interfering RNA (siRNA)-antibody conjugate comprising~~:~~

an anti-transferrin receptor antibody or antigen binding fragment thereof conjugated to a siRNA~~polynucleic acid~~ molecule comprising a passenger strand and a guide strand, wherein the guide strand is from 19 to 30 nucleotides in length and comprises a sequence selected from a group consisting of SEQ ID NOs: 72, 76, 126, 131, 132, 134, 135, 136, 212, 216, 266, 271, 272, 274, 275, and 276, and wherein the siRNA molecule mediates RNA interference against ~~that hybridizes to a target sequence of~~ DUX4 mRNA~~;~~ and downregulation of DUX4 biomarker mRNA levels.

~~wherein the polynucleic acid molecule conjugate mediates RNA interference against the *DUX4*.~~

2. The siRNA-antibody~~polynucleic acid molecule~~ conjugate of claim 1, wherein the anti-transferrin receptor antibody or antigen binding fragment thereof binds to a transferrin receptor on a cell surface of a muscle cell~~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.~~3.The ~~polynucleic acid molecules~~siRNA-antibody conjugate of ~~any one of~~ claim~~s~~ 1 or 2 ~~-3~~, wherein the siRNA~~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.

4. The siRNA-antibody conjugate of any one of claims 1-3, wherein the passenger strand

and the guide 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 siRNA-antibody~~polynucleic acid molecule~~ conjugate of any one of claims 1-4, wherein the siRNA molecule~~polynucleotide~~ hybridizes to at least 8 contiguous bases of the target sequence of a human DUX4 *mRNA*.

6. The siRNA-antibody~~polynucleic acid molecule~~ conjugate of any one of claims 1-5, wherein the guide strand~~polynucleotide~~ is from ~~about 8 to about 50 nucleotides in length or from about~~ 19~~0~~ to ~~about~~ 25~~30~~ nucleotides in length.

7. The siRNA-antibody conjugate of any one of claims 1-6, wherein the siRNA-antibody conjugate comprises a linker connecting the anti-transferrin receptor antibody or antigen binding fragment thereof to the siRNA molecule.

~~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.~~8. The siRNA-antibody~~polynucleic acid molecule~~ conjugate of any one of claims 3~~1~~-7~~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.~~9. The siRNA-antibody~~polynucleic acid molecule~~ conjugate of any one of claims 31-~~89~~, wherein the at least one modified internucleotide linkage comprises a phosphorothioate linkage or a phosphorodithioate linkage.

~~11.~~10. The ~~polynucleic acid molecule~~siRNA-antibody conjugate of any one of claims 31-9~~10~~, wherein the siRNA~~polynucleic acid~~ molecule comprises 3 or more 2' modified nucleotides selected from 2'-O-methyl modified nucleotide and 2'-deoxy-2'-fluoro modifed nucleotide.

~~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.~~11. The siRNA-antibody~~polynucleic acid molecule~~ conjugate of any one of claims 1-10~~20~~, wherein the siRNA molecule conjugate has a siRNA to antibody ~~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~~from 1 to 4.

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

~~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.

30.13. The siRNA-antibody conjugate pharmaceutical composition of any one of claims 128-1229, wherein the siRNA molecule conjugatepharmaceutical composition is formulated for parenteral, oral, intranasal, buccal, rectal, transdermal, intravenous, subcutaneous, or intrathecal administration.

14. The siRNA-antibody conjugate of any one of claims 1-13, wherein the anti-transferrin receptor antibody or antigen binding fragment thereof is conjugated to the passenger strand of the siRNA molecule.

15. The siRNA-antibody conjugate of any one of claims 1-14, wherein the passenger strand of the siRNA molecule comprises a sequence selected from a group consisting of SEQ ID NOs: 2, 6, 56, 61, 62, 64, 65, 66, 142, 146, 196, 201, 202, 204, 205, and 206.

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.

33.16. The siRNA-antibody conjugatemethod of any one of claims 1-1532, wherein the downregulation of DUX4 biomarker mRNA levels is evaluated byinterference comprises affecting expression level of one or more DUX4 of a biomarker genes selected from a group consisting of MBD3L2, TRIM43, PRAMEF1, ZSCAN4, KHDC1L, and LEUTX in a cell affected by a muscle dystrophy.

17. The siRNA-antibody conjugate of any one of claims 1-16, wherein the anti-transferrin receptor antibody or antigen binding fragment thereof is conjugated to the guide strand of the siRNA molecule.

~~34.~~18. Use of the siRNA-antibody conjugate~~The method~~ of any one of claims 1~~31~~-17~~33,~~ in the manufacture of a medicament for treating ~~wherein the muscular dystrophy is f~~Facioscapulohumeral muscular dystrophy (FSHD) in a subject.

~~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.~~

19. The use of claim 18, wherein the RNA interference against the human DUX4. mRNA prevents or prevents progress of muscle atrophy in the subject.

20. The use of claim 18 or 19, the FSHD is caused by genetic and epigenetic changes in D4Z4 DNA region of long arm of chromosome 4 in muscle cells of the subject or associated with muscle atrophy of the subject.

21. The siRNA-antibody conjugate of any one of claims 1-17 for use in therapy.