

CLAIMS

WHAT IS CLAIMED IS:

1. A small interfering RNA (siRNA) molecule conjugate comprising:
an anti-transferrin receptor antibody or antigen binding fragment thereof conjugated to a polynucleic acid molecule that hybridizes to a target sequence of *DMPK* mRNA; wherein an antisense strand of the siRNA molecule comprises a sequence selected from the group consisting of SEQ ID NOs: 4, 6, 8, 10, 12, 14, and 16; and wherein the siRNA molecule conjugate mediates RNA interference against the *DMPK* mRNA.
2. The siRNA molecule conjugate of claim 1, wherein the sense strand of the siRNA molecule comprises a sequence selected from the group consisting of SEQ ID Nos: 3, 5, 7, 9, 11, 13, and 15.
3. The siRNA molecule conjugate of claim 1 or 2, wherein the VH region comprises HCDR1 sequence comprising SEQ ID NO: 17, HCDR2 sequence comprising one of SEQ ID NO: 20, SEQ ID NO: 18, SEQ ID NO: 21, and HCDR3 sequence comprising SEQ ID NO: 19.
4. The siRNA molecule conjugate of claim 3, wherein the VL region comprises LCDR1 sequence comprising SEQ ID NO: 22 or SEQ ID NO:27, LCDR2 sequence comprising SEQ ID NO: 23, SEQ ID NO: 25, or SEQ ID NO: 28, and LCDR3 sequence comprising SEQ ID NO: 24 or SEQ ID NO:26.
5. The siRNA molecule conjugate of any one of claims 3-4, wherein the VH region comprises HCDR1 sequence comprising SEQ ID NO: 17, HCDR2 sequence comprising SEQ ID NO: 20, and HCDR3 sequence comprising SEQ ID NO: 19; and the VL region comprises LCDR1 sequence comprising SEQ ID NO: 22, LCDR2 sequence comprising SEQ ID NO: 23, and LCDR3 sequence comprising SEQ ID NO: 24.
6. The siRNA molecule conjugate of any one of claims 3-5, wherein the VH region comprises at least 80%, 85%, 90%, 95%, 99%, or 100% sequence identity to SEQ ID NO: 30, and

wherein the VL region comprises at least 80%, 85%, 90%, 95%, 99%, or 100% sequence identity to SEQ ID NO: 34.

7. The siRNA molecule conjugate of any one of claims 1-6, wherein the anti-transferrin receptor antibody comprises a humanized antibody, or antigen binding fragment thereof or a chimeric antibody or antigen binding fragment thereof, or a multi-specific antibody or antigen binding fragment thereof.
8. The siRNA molecule conjugate of any one of claims 1-7, wherein the anti-transferrin receptor antibody comprises an IgG-scFv, nanobody, BiTE, diabody, DART, TandAb, scDiabody, scDiabody-CH3, triple body, mini-antibody, minibody, TriBi minibody, scFv-CH3 KIH, Fab-scFv-Fc KIH, Fab-scFv, scFv-CH-CL-scFv, F(ab')₂, F(ab')₂-scFv₂, scFv-KIH, Fab-scFv-Fc, tetravalent HCAb, scDiabody-Fc, diabody-Fc, tandem scFv-Fc, or intrabody.
9. The siRNA molecule conjugate of any one of claims 1-8, wherein the anti-transferrin receptor antibody further comprises at least one mutation in the Fc region, and wherein the at least one mutation is at residue position D265, N297, K322, L328, or P329, wherein the residue position is in reference to IgG1.
10. The siRNA molecule conjugate of any one of claims 1-9, wherein the anti-transferrin receptor antibody specifically binds to human transferrin receptor (TfR).
11. The siRNA molecule conjugate of any one of claims 1-10, wherein the polynucleic acid molecule conjugate comprises a linker connecting anti-transferrin receptor antibody or antigen binding fragment thereof to the polynucleic acid molecule.
12. The siRNA molecule conjugate of claim 11, wherein the C6 linker is a 6-Amino-1-hexanol linker.
13. The siRNA molecule conjugate of claim 11, wherein the linker comprises 4-(N-maleimidomethyl) cyclohexane -1-amidate (SMCC).
14. The siRNA molecule conjugate of any one of claims 11-13, wherein the linker is coupled to the 5'-end of the sense strand.

15. The siRNA molecule conjugate of any one of claims 11-14, wherein the siRNA molecule is conjugated to a cysteine residue of the anti-transferrin receptor antibody or antigen binding fragment thereof.
16. The siRNA molecule conjugate of any one of claims 1-15, wherein a ratio between the siRNA molecule and the anti-transferrin receptor antibody or antigen binding fragment thereof is about 1:1, 2:1, 3:1, or 4:1.
17. A pharmaceutical composition comprising:
 - a small interfering RNA (siRNA) molecule conjugate of any one of claims 1-16; and
 - a pharmaceutically acceptable excipient.
18. The pharmaceutical composition of claim 17, wherein the pharmaceutical composition is formulated for intravenous, parenteral, oral, intranasal, buccal, rectal, or transdermal administration.
19. Use of the small interfering RNA (siRNA) molecule conjugate of any one of claims 1-16 or the pharmaceutical composition of any one of claims 17-18 in the manufacture of a medicament for treating a subject diagnosed with or suspected to have muscular dystrophy.
20. The use of the siRNA molecule conjugate of claim 19, wherein the muscular dystrophy is myotonic dystrophy type 1 (DM1).
21. The siRNA molecule conjugate of any one of claims 1-16 or the pharmaceutical composition of any one of claims 17-18 for use in therapy.