COMPOSITIONS AND METHODS OF TREATING MUSCLE DYSTROPHY

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/001,211 filed March 27, 2020, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE DISCLOSURE

[0002] Gene suppression by RNA-induced gene silencing provides several levels of control: transcription inactivation, small interfering RNA (siRNA)-induced mRNA degradation, and siRNA-induced transcriptional attenuation. In some instances, RNA interference (RNAi) provides long lasting effect over multiple cell divisions. As such, RNAi represents a viable method useful for drug target validation, gene function analysis, pathway analysis, and disease therapeutics.

INCORPORATION BY REFERENCE

[0003] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

SUMMARY ~~OF THE DISCLOSURE~~

[0003a] Disclosed herein, in one aspect, is 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.

[0003b] Disclosed herein, in another aspect, is a pharmaceutical composition comprising: a small interfering RNA (siRNA) molecule conjugate disclosed herein; and a pharmaceutically acceptable excipient.

[0003c] Disclosed herein, in another aspect, is a use of the small interfering RNA (siRNA) molecule conjugate disclosed herein or the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a subject diagnosed with or suspected to have muscular dystrophy.

[0003d] Disclosed herein, in another aspect, is a siRNA molecule conjugate disclosed herein or the pharmaceutical composition disclosed herein for use in therapy.

[0004] Disclosed herein, in certain embodiments, are polynucleic acid molecules and pharmaceutical compositions for modulating a gene associated with muscle dystrophy (*e.g.,*

DM1). In some embodiments, also described herein are methods of treating muscle atrophy with a polynucleic acid molecule or a polynucleic acid molecule conjugate disclosed herein.

[0005] Disclosed herein, in certain embodiments, is a polynucleic acid 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.* The polynucleic acid molecule having a sense strand having a sequence at least 80% identical to SEQ ID NO: 1, and an antisense strand having a sequence at least 80% identical to SEQ ID NO: 2. The polynucleic acid molecule conjugate mediates RNA interference against the *DMPK*.

[0006] In some embodiments, the anti-transferrin receptor antibody or antigen binding fragment thereof comprises a variable heavy chain (VH) region and a variable light chain (VL) region, wherein the VH region comprises HCDR1 sequence comprising SEQ ID NO: 17; HCDR2 sequence EINPIX_1GRSNYAX_2KFQG, wherein X_1 is selected from N or Q and X_2 is selected from Q or E; and HCDR3 sequence comprising SEQ ID NO: 19. In some embodiments, the VH region comprises HCDR1 sequence comprising SEQ ID NO: 17, HCDR2 sequence comprising one of SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, and HCDR3 sequence