

COMPOSITIONS AND METHODS OF TREATING FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/992,071 filed March 19, 2020, and U.S. Provisional Application No. 63/066,655 filed August 17, 2020, each of 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] In one aspect, provided herein is a small interfering RNA (siRNA)-antibody conjugate comprising an anti-transferrin receptor antibody or antigen binding fragment thereof conjugated to a siRNA 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 DUX4 mRNA and downregulation of DUX4 biomarker mRNA levels.

[0003b] In another aspect, provided herein is use of the siRNA-antibody conjugate as described herein in the manufacture of a medicament for treating facioscapulohumeral muscular dystrophy (FSHD) in a subject.

[0003c] In yet another aspect, provided herein is the siRNA-antibody conjugate as described 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 atrophy, especially Facioscapulohumeral muscular dystrophy (FSHD). In some embodiments, also described herein are methods of treating muscle atrophy, especially FSHD, 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 antibody or antigen binding fragment thereof conjugated to a polynucleic acid molecule that hybridizes to a target sequence of *DUX4*, and the polynucleic acid molecule conjugate mediates RNA interference against the *DUX4*. In certain embodiments, the antibody or antigen binding fragment thereof comprises a non-human antibody or 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