Silencing of Myotonic Dystrophy Protein Kinase (DMPK) Does Not Affect Cardiac or Muscle Function in Mice.

CARRELL, Samuel, University of Rochester
CARRELL, Ellie, University of Rochester
AUERBACH, David, University of Rochester
PANDEY, Sanjay, Ionis Pharmaceuticals
BENNETT, Frank, Ionis Pharmaceuticals
DIRKSEN, Robert T., University of Rochester
THORNTON, Charles, University of Rochester

OBJECTIVE: Assess cardiac and skeletal muscle requirements for DMPK.

BACKGROUND: Myotonic dystrophy type 1 (DM1) results from a CTG expansion in *DMPK*, triggering RNA toxicity. DMPK is expressed most highly in cardiac and skeletal muscle. DMPK levels are reduced by CTG expansion in DM1, perhaps contributing to cardiac conduction and muscle defects. Antisense oligonucleotides (ASOs) targeting *DMPK* are in clinical trials. These agents are designed to improve RNA toxicity, but potentially may aggravate DMPK deficiency.

DESIGN/METHODS: We used heterozygous *Dmpk* knockout (+/-) mice to model DMPK reductions in DM1. ISIS-486178 is an ASO directed against *DMPK.* This ASO was injected subcutaneously in +/- mice for up to 16 months. *In vivo* grip strength and *ex vivo* muscle specific force were determined. Cardiac conduction was assessed by surface ECG and radiotelemetry. Echocardiography was performed. Experimental groups were wild-type (WT), saline-treated +/-, ASO-treated +/-, and homozygous *Dmpk* knockout mice, with >10 mice per group.

RESULTS: DMPK protein levels in hearts and muscles of +/- mice were ~50% of WT at baseline, and further reduced to < 10% of WT with ASOs. DMPK knockdown was sustained for up to 16 months with twice monthly subcutaneous injections of ASO. Grip strength, muscle specific force, ECGs, cardiac chamber size, and ejection fraction showed no difference among experimental groups. Long-term DMPK knockdown did not affect survival or body weight.

CONCLUSIONS: Long-term ASO-mediated silencing of DMPK is feasible in muscle and heart in mice, and not associated with muscle or cardiac dysfunction.