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Antisense oligonucleotide targeting glycogen synthase (GYS1) in a Pompe disease mouse model

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Background: Pompe disease is a progressive myopathy resulting from the deficiency of acid α-glucosidase (GAA). ERT with recombinant human (rh) GAA works well in alleviating the cardiomyopathy; however, many patients continue to have progressive muscle weakness from muscle glycogen accumulation produced by muscle glycogen synthase (GYS1). Antisense Oligonucleotides (ASO) technology has emerged as a powerful therapeutic alternative for the treatment of genetic disorders by targeting RNA. Objectives: In order to impart specificity for the muscle GYS1, we propose the use of ASO-mediated gene silencing through the RNaseH1 dependent degradation mechanism. Most recently therapy for spinal muscular atrophy has been successful using ASOs, and our hope is that ASO technology will be successful in Pompe disease. Results: Over 150 ASOs were designed and screened in vitro to identify the most efficacious ASO for testing in wild type mice. The lead from the screen were validated and screened in vivo. Eight-dose treatment of wild type mice with selected GYS1 ASOs resulted in a significant reduction in GYS1 mRNA levels with a maximal knockdown of 80% in the liver and 44% in muscle. We performed a pilot study of the efficacy of three GYS1 ASOs (ASO#1, ASO#2 and ASO#3) in Pompe mice as monotherapy and have reduced by approximately 24% muscle GYS1 mRNA levels versus PBS and a mismatch ASO after 16 doses of treatment. Significant reduction of glycogen was seen on PAS staining of muscle and glycogen measurements (22–43%). Specially ASO#3 treatment could decrease autophagy markers while increase mTOR to WT level. Thus, our preclinical studies in Pompe mice have indicated that GYS1 ASO has been effective in knocking down GYS1 in muscle. Conclusions: These preliminary studies provide proof of principle that GYS ASOs might be a potentially promising adjunct treatment for Pompe disease.

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