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Gene Therapy Improves Lifespan and Cardiorespiratory Function in a Rat Model of Pompe Disease

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Pompe disease is characterized by systemic depletion of acid-alpha glucosidase (GAA) resulting in ubiquitous lysosome glycogen accumulation. Cardiac and respiratory dysfunction are hallmarks of the disease. We have created a novel knockout model of Pompe disease that is more reflective of the phenotypic presentation. Zinc finger nucleases were designed to disrupt the rat Gaa gene, causing a deletion that results in global knockout of GAA (KO). Male Sprague-Dawley rats were divided into the following groups: wild-type (WT), KO, and KO+AAV9-hGAA (KO+AAV). Animal body weight was recorded monthly and gross heart weight was collected at 6 months of age following euthanasia. Animals were subjected to in vivo physiological measures including cardiac MRI and plethysmography. Biodistribution of transgene expression and lysosomal glycogen following vector administration was assessed at study endpoint. Compared to WT, KO and KO+AAV animals displayed a marked reduction in developmental weight gain between 1-5 months of age. All KO+AAV receiving treatment survived to 6 months, whereas KO rats had a median survival of 5 months and near 100% mortality at 6 months. Heart/Body weight ratio was increased by ~70% in KO animals compared to WT and KO+AAV. Cardiac MR revealed significant differences in KO and KO+AAV when compared to WT animals (483.1±31.7 WT, 359.6±35.5 KO, 547.5±29.5 KO+AAV end diastolic volume-EDV (ul); 196.8±13.3 WT, 121.1±7.6 KO, 199.0±15.8 KO+AAV end systolic volume-ESV (ul); with normalization in animals following AAV administration. Absence of GAA and lysosomal glycogen accumulation was observed in KO animals alone, demonstrating AAV-mediated resolution of disease phenotype. Gene replacement via AAV9 results in widespread GAA expression. Cardiac and respiratory functional measures show significant improvement in KO animals receiving AAV9-hGAA when compared to age matched KO rats. Our results give the opportunity to optimize and evaluate therapeutic potential of existing and next-generation therapies for Pompe disease in this model.