AAV MEDIATED GENE TRANSFER TO SKELETAL MUSCLE RESULTS IN SUSTAINED REDUCTION OF HYPERBILIRUBINEMIA IN AN ANIMAL MODEL OF CRIGLER-NAJJAR SYNDROME TYPE 1

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Crigler-Najjar syndrome is an autosomal recessive disorder characterized by severe unconjugated hyperbilirubinemia due to deficiency of the liver-specific uridine diphosphogluconosyl transferase 1A1 (UGT1A1). Current therapy relies on phototherapy to prevent life-threatening elevations of serum bilirubin levels but liver transplantation is the only permanent treatment. Given the mortality and morbidity related to the transplant procedures, there is high motivation at developing gene therapy for this disorder. Although correction of the deficient enzymatic activity in the affected organ, i.e. the liver, would be most straightforward, expression within an ectopic tissue to clear toxic metabolites from the circulation is very attractive. The muscle is the preferred tissue for this goal because of its simple and safe access through intramuscular (IM) injections. Moreover, the IM route has been investigated extensively for gene therapy of various diseases and in human clinical trials as well. In this study, we have investigated the efficacy of muscle-directed gene therapy for Crigler-Najjar syndrome type 1 using Adeno Associated Viral (AAV) vectors. A serotype 1 AAV vector expressing the UGT1A1 under the control of the muscle-specific creatine kinase (MCK) promoter was injected at the dose of 3x10e12 genome copies/kg into the muscles of one month-old Gunn rats, the animal model of Crigler-Najjar syndrome type 1. IM injections of AAV vectors resulted in the expression of functionally active UGT1A1 enzyme in the muscle as demonstrated by Western blot analysis and enzyme assay on muscle tissues. AAV-injected Gunn rats showed an approximately 50% reduction of baseline serum bilirubin levels by 3 weeks post-injection which were sustained for at least 1 year post-injection. Taken together, these data show that clinically relevant and sustained reduction of serum bilirubin levels can be achieved by simple and safe IM injections in the Gunn rats. AAV-mediated muscle directed gene therapy has potential for the treatment of patients with Crigler-Najjar syndrome type 1.