rAAV9 airway delivery results in effective knockdown of mutant alpha 1-antitrypsin in the liver while upregulating wildtype alpha 1-antitrypsin in the lung

Alisha Gruntman
University of Massachusetts Medical School

Let us know how access to this document benefits you.
Follow this and additional works at: https://escholarship.umassmed.edu/cts_retreat

Part of the Medical Genetics Commons, and the Respiratory Tract Diseases Commons

Repository Citation

Creative Commons License
This work is licensed under a Creative Commons Attribution-Noncommercial-Share Alike 3.0 License.

This material is brought to you by eScholarship@UMassChan. It has been accepted for inclusion in UMass Center for Clinical and Translational Science Research Retreat by an authorized administrator of eScholarship@UMassChan. For more information, please contact Lisa.Palmer@umassmed.edu.
rAAV9 AIRWAY DELIVERY RESULTS IN EFFECTIVE KNOCKDOWN OF MUTANT ALPHA 1-ANTITRYPSIN IN THE LIVER WHILE UPREGULATING WILDTYPE ALPHA 1-ANTITRYPSIN IN THE LUNG

Alisha Gruntman¹, Christian Mueller¹, Qiushi Tang¹, Lina Song¹, James M. Wilson², Terence Flotte¹, Maria P. Limberis²

1Pediatrics and Gene Therapy Center, UMass Medical School, Worcester, MA, United States, 01605 2Gene Therapy Program, Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA

Contact: Alisha.gruntman@umassmed.edu

Alpha 1-Antitrypsin (AAT) deficiency is a human genetic disease resulting in the production of mutant AAT, a hepatocyte produced serine protease inhibitor that functions to prevent alveolar epithelial damage by inhibiting neutrophil elastase. Patients with AAT deficiency have increased lung disease, due to decreased proteolytic protection, as well as sporadic severe liver disease secondary to accumulation of mutant AAT, especially a common mutant form termed PiZ, within hepatocytes. We previously showed, in a PiZ mutant mouse model, simultaneous knock-down of mutant PiZ-AAT and augmentation of wild-type AAT production through intravenous delivery of a recombinant adeno-associated viral (rAAV) vector encoding both a miRNA targeting PiZ-AAT and a miRNA-resistant wild-type AAT gene.

In this study we tested the hypothesis that rAAV2/9 vector administered intra-nasally or intra-tracheally can deliver a gene of interest to both the airways and liver.

Initially C57Bl/6 mice were administered intra-nasally 10¹¹ genome copies (GC) of rAAV2/9 vector expressing a firefly luciferase, which resulted in increased luminescence in the nasal passages, liver, and lung 21 days post delivery. Next, 10¹² GC of rAAV2/9 vector expressing GFP and miRNAs targeting PiZ-AAT were delivered via oro-tracheal intubation to PiZ mice. This resulted in decreased serum AAT levels in the PiZ mice and GFP expression in both the liver and lungs. Finally, 10¹² GC of rAAV2/9 vector encoding miRNA resistant wild-type AAT and miRNAs targeting PiZ-AAT were delivered via oro-tracheal intubation. This resulted in both systemic and local (liver and lung) elevations in wild-type AAT as well as decreased PiZ-AAT levels.

In conclusion, tracheal delivery of rAAV2/9 resulted in expression of AAT in the liver and lung of treated animals, with sufficient targeting of the liver to mediate knock-down of mutant AAT to a similar degree as intravenous delivery, representing a potential non-invasive delivery route for gene therapy in AAT deficient patients.