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

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rAAV9 AIRWAY DELIVERY RESULTS IN EFFECTIVE KNOCKDOWN OF MUTANT ALPHA 1-ANTITRYPSIN IN THE LIVER WHILE UPREGULATING WILDTYPE ALPHA 1-ANTITRYPSIN IN THE LUNG

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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 10^{11} 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, 10^{12} 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, 10^{12} 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.