Weill Cornell Medicine

Gene Therapy for Alpha 1-Antitrypsin (AAT) Deficiency

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Background & Unmet Need

- Alpha 1-antitrypsin (AAT) deficiency is a hereditary disorders characterized by low serum levels of functional AAT, and is associated with early development of panacinar emphysema
- AAT deficiency affects ~90 K patients in the U.S., and is caused by mutation in the *SERPINA1* gene
- AAT inhibits serine proteases, including neutrophil elastase, protecting the lung from proteolytic destruction
- The current SOC for AAT deficiency is weekly infusions of purified AAT from pooled human plasma
- While AAT augmentation therapy is safe and reduces the rate of lung destruction, it requires burdensome weekly parenteral infusions and carries risks of allergic reactions and viral contamination of human plasma-derived products
- **Unmet Need:** Therapeutic strategy to augment AAT levels in a safe and convenient format

Technology Overview

- **The Technology:** AAV8 gene transfer vector coding for an oxidant-resistant form of AAT for the treatment of AAT deficiency
- The oxidation-resistant AAT (A213/V351/L358) maintains antiprotease activity under oxidant stress compared to wild-type and other engineered variants
- **PoC Data:** A single dose of 8/AVL afforded sustained serum AAT levels, in both male and female mice, with similar absolute AAT levels for both IV and IPL delivery
- However, IPL delivery provided a significantly higher lung epithelial lining fluid (ELF) to serum ratio of AAT than IV delivery, suggesting IPL is the preferred delivery route
- Mice administered the 8/AVL vector retain anti-NE activity in the ELF 24 weeks after treatment, whereas mice receiving the WT 8/AMM vector display no anti-NE activity under oxidizing conditions

Inventors:
Ronald Crystal
Stephen Kaminsky
Jonathan Rosenberg
Katie Stiles
Dolan Sondhi
Meredith Sosulski

Patents:
US Application Filed
EP Application Filed

Publications:
Rosenberg et al. *Hum Gen Ther*. 2023.
Sosulski et al. *JCI Insight*. 2020.

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Technology Applications

- One-time treatment of AAT deficiency
- Provides a general strategy for optimizing gene therapy for other diseases associated with enzymatic deficiency

Technology Advantages

- The modified AAT protein is highly resistant to oxidant stress and less susceptible to potential anti-AAT immunity than the wild-type protein
- Single dose treatment significantly improves patient quality of life compared to weekly infusions

Supporting Data / Figures

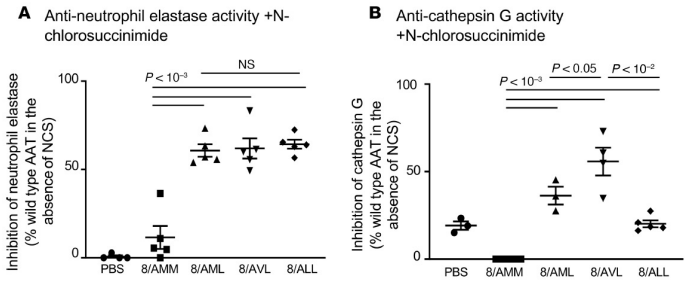

Figure 1: Comparison of in vivo-produced human AAT-modified variants' ability to inhibit neutrophil elastase (NE) and cathepsin G activity. 8/AMM expressed the WT enzyme. 8/AVL was selected for further characterization due to best performance under oxidizing conditions.

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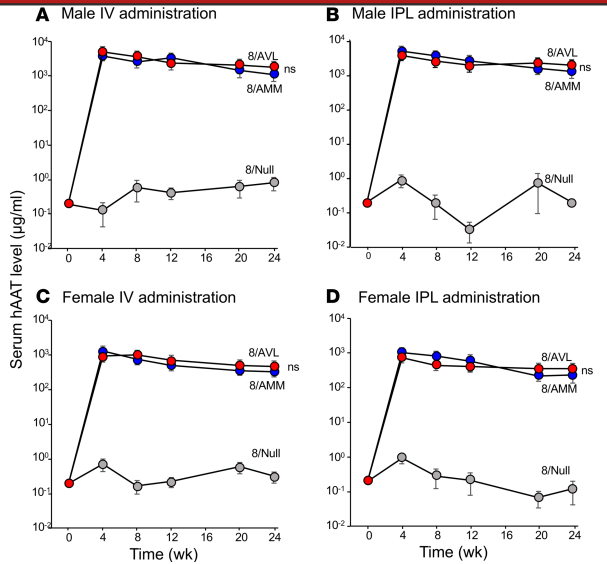

Figure 2: The 8/AVL gene therapy delivers durable hAAT levels equivalent to the 8/AMM WT vector in both male and female mice, with similar performance absolute levels of hAAT for both IV and IPL administration.

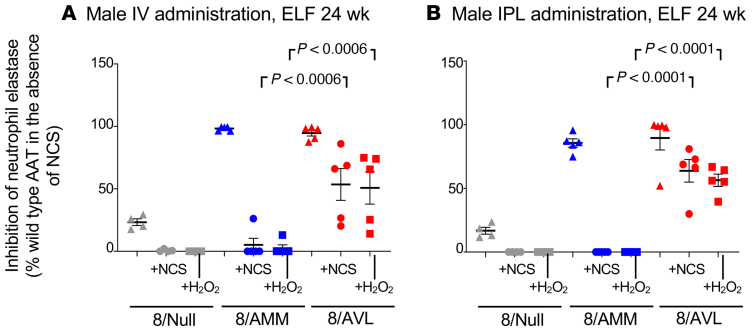

Figure 3: Mice administered the 8/AVL vector retain anti-NE activity in the lung epithelial lining fluid (ELF) 24 weeks after treatment, whereas mice receiving the WT 8/AMM vector display no anti-NE activity under oxidizing conditions.

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