Gene Therapy for α1-antitrypsin Deficiency with AAV Intrapleural Administration
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Emphysema Associated with α1-Antitrypsin Deficiency
- Common autosomal recessive disorder characterized by a marked reduction in serum α1AT levels
- α1AT normally protects the lung from the destructive potential of neutrophil elastase; if α1AT levels are low, neutrophil elastase slowly destroys the lung parenchyma
- Onset of emphysema ages 35-40 in cigarette smokers
- Current therapy requires weekly intravenous infusions of 4 gm of human α1AT purified from pooled plasma

Genetics of α1-Antitrypsin
- Autosomal recessive
- Classification based on isoelectric focusing of serum
- M type – normal
- Z, S – most common deficiency alleles
- >95% of individuals with emphysema or liver disease are ZZ homozygotes

Gene Therapy for α1-Antitrypsin Deficiency
Advantages of gene therapy:
- Single administration
- Steady state, rather than varying levels of α1AT
- No risk to pooled plasma viral contamination
- Lower cost

Strategy – Normal Human α1AT Gene Transfer to the Pleura with AAV Vectors
- Proposed intrapleural gene therapy strategy
- α1AT is normally produced in the liver
- The lung is only 2% body weight – most of the α1AT produced by the liver is wasted
- Gene therapy-mediated local production in the pleura should generate high local levels of α1AT

Pleura as a Site for Gene Transfer
- High density of parietal and visceral lymphatics with stomata open to pleural surface (5-10x10^3/cm^2)
- Both pleural surfaces behave as highly permeable membranes, allowing movement of proteins
- Pleural fluid turnover ~0.1 ml/kg/hr

Time Course of Serum Human α1AT Levels Following Intrapleural Administration of AAVrh.10hα1AT
- Evaluate
- Human α1AT level in serum (ELISA)

Human α1AT Levels in Bronchoalveolar Lavage Fluid Compared to Serum Following Intrapleural Administration of AAVrh.10hα1AT
- Evaluate
- Serum and lavage human α1AT (ELISA)

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