EVOLUTION OF THE ALPHA-1 ANTITRYPSIN MUSCLE GENE THERAPY: TRANSLATION FROM CLINICAL TRIAL TO BENCHTOP AND BACK AGAIN

Alisha M. Gruntman DVM, PhD¹,²,⁵, Gwladys Gernoux PhD¹, Gensheng Wang PhD³, Janet Benson PhD³, Jeff Chulay MD⁴, Dave Knop⁴, Christian Mueller PhD¹,⁵, Terence R Flotte MD¹,⁵
¹Horae Gene Therapy Center, University of Massachusetts Medical School; ²Department of Clinical Sciences, Tufts Cummings School of Veterinary Medicine; ³Lovelace Respiratory Research Institute; ⁴Applied Genetics Technologies Corporation; ⁵Department of Pediatrics, University of Massachusetts Medical School

Alpha-one antitrypsin (AAT) deficiency is a genetic disease affecting the lungs due to inadequate anti-protease activity in the pulmonary interstitium. On-going human trials use intra-muscular delivery of adeno-associated virus (rAAV1), allowing expressing myofibers to secrete normal (M)AAT protein. In the Phase Ib trial, patients in the highest dose cohort (6x10¹²vg/kg) were given 100 intra-muscular (IM) injections of undiluted vector, with serum AAT levels still substantially below target levels. Previous work has shown that delivering rAAV vector to the musculature via limb perfusion leads to widespread gene expression in myofibers. We hypothesize that widespread delivery would result in an overall increase in serum AAT levels with the same dose of AAV gene therapy vector and allow for increased volume and thereby dose of vector. In macaques, similar serum myc-tagged rhAAT was produced using regional venous infusion when compared to direct IM delivery at the same total vg dose with either rAAV1 or rAAV8, while not being limited to a small volume as with IM injection. These data prove the concept that a 30-fold expanded volume of rAAV-AAT could be delivered to myofibers using limb perfusion without loss of potency on a per vg basis, thereby enabling potential achievement of therapeutic AAT levels in patients. This will allow us to proceed to a phase IIb clinical trial in AAT patients employing venous limb perfusion.

Contact:
Alisha Gruntman
University of Massachusetts Medical School
Alisha.Gruntman@umassmed.edu