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Alisha M. Gruntman
University of Massachusetts Medical School

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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 IIa trial, patients in the highest dose cohort (6x10^{12}vg/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