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## **Serum Levels of Alpha-1 Antitrypsin following Vascular Limb or Intra-Muscular Delivery of AAV1 or AAV8 Gene Therapy Vectors in Rhesus Macaques.**

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Alpha-one antitrypsin (AAT) deficiency is a genetic disease that results in both lung disease and potentially liver failure in affected patients. In un-affected people AAT is produced in the liver and secreted to act as an anti-protease (primarily counteracting the effects of neutrophil elastase) in the lung. On-going human clinical trials have focused on intra-muscular delivery of adeno-associated virus (AAV1) to patients. The goal of delivery to the muscle is to have the myocytes serve as bio-factories to produce normal AAT protein and secrete it into the blood where it can exert its normal function in the lung. In the last Phase II trial patients in the highest dose cohort were given 100 intra-muscular (IM) injections with serum AAT levels still below therapeutic thresholds.

Previous work has shown that delivering AAV vector to the musculature of the limb via the vasculature, while blood flow is obstructed using a tourniquet, leads to wide-spread gene expression in myocytes. We hypothesize that local delivery via IM injection results in saturated AAT expression within the myocytes surrounding the injection sight and that a more widespread delivery would result in an overall increase in serum AAT levels with the same dose of AAV gene therapy vector due to production by a larger overall number of myocytes. We have been able to show that we can attain similar or slightly higher (573.0 ng/ml versus 562.5 ng/ml) serum AAT levels using a vascular delivery method in rhesus macaques when compared to IM delivery. These results have been obtained using AAV1. Animals receiving either AAV1 or AAV8 show a decrease in muscle immune cell infiltrates following intra-vascular delivery versus IM delivery, which may improve long-term expression. Serum AAT data from animals dosed using AAV8, a serotype shown to better target muscle following vascular delivery, are currently being processed.

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