Data show five-year response for AAT deficiency gene therapy

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Data demonstrating sustained protein expression five years after a single intramuscular injection of a gene-based therapy for the treatment of alpha-1 antitrypsin (AAT) deficiency also shows improvements in multiple indicators of AAT biological activity. The study appears in the June issue of *Molecular Therapy*. Applied Genetic Technologies Corporation (AGTC), a clinical stage biopharmaceutical company, developed the gene-based therapy evaluated in the study, which was led by Terence R. Flotte, MD, the Celia and Isaac Haidak Professor of Medical Education, executive deputy chancellor, provost and dean of the School of Medicine, and colleagues at UMass Medical School.

AAT deficiency is an inherited genetic defect that results in severe loss of lung function. The study describes five-year follow-up results of a one-time intramuscular injection of a recombinant adeno-associated virus (AAV)-AAT vector in patients with AAT deficiency who had participated in a Phase 2a trial and had not received subsequent AAT protein therapy.

Key findings from the study include:

- Sustained expression of AAT protein over the five-year study period without re-administration of AAV-AAT vector and in the absence of immune suppression or corticosteroid therapy;
- Partial correction of disease-associated defects in neutrophils, a type of immune cell that contributes to lung damage in patients with AAT, including neutrophil elastase inhibition, markers of

degranulation and membrane-bound anti-neutrophil antibodies;
- Evidence of an active regulatory T-cell response that contributed to stable gene expression despite the presence of an immune response directed against the AAV vector; and
- Continuous, steady-state levels of AAT protein without the peak and trough effects observed following infusion of AAT protein replacement therapy.

"This is the first publication to demonstrate multi-year persistence of recombinant AAV expression in gene therapy trial participants without immune suppression or corticosteroid therapy," Dr. Flotte said. "We also observed specific regulatory T-cell responses directed against AAV1 capsid proteins, and believe that these responses may help the immune system become tolerant to AAV1. This would be beneficial in enabling the development of AAV-based therapies for AAT deficiency that provide durable responses following a single administration and may also allow for repeat dosing regimens with potential to improve long-term outcomes for patients with AAT deficiency."

The authors conclude that stable levels of serum AAT achieved in this study over five years may have beneficial clinical effects, despite being below the threshold of what is traditionally considered therapeutic. They hypothesize that continuous expression at a lower level may provide greater clinical benefit compared with levels that fluctuate drastically, as is observed with current AAT replacement therapy.

More information: Christian Mueller et al. 5 Year Expression and Neutrophil Defect Repair after Gene Therapy in Alpha-1 Antitrypsin Deficiency, *Molecular Therapy* (2017). DOI: 10.1016/j.ymthe.2017.03.029