

Gene Therapy Trial Succeeds In Boosting Protective Protein In Patients With Hereditary Lung Disease

ScienceDaily (Aug. 11, 2009) — Researchers at the University of Massachusetts Medical School and the University of Florida in Gainesville have safely given new, functional genes to patients with a hereditary defect that can lead to fatal lung and liver diseases, according to clinical trial findings slated to appear this week in the online early edition of the Proceedings of the National Academy of Science.

"This trial represents a very important step toward a potential gene therapy for the 100,000 or more Americans who suffer with alpha-1 antitrypsin deficiency," said Terence R. Flotte, MD, dean of the School of Medicine and provost & executive deputy chancellor of UMass Medical School. Dr. Flotte, senior author on the study, was formerly the chair of pediatrics at the University of Florida, where the study was conducted.

Patients with alpha-1 antitrypsin deficiency cannot produce a protective form of the protein alpha-1 antitrypsin, which is normally produced in the liver and protects the lungs from inflammation. Those lacking alpha-1 antitrypsin are vulnerable to infections or irritants in the air, such as cigarette smoke, and often develop life-threatening lung disease. Some people with the deficiency lead disease-free lives, never knowing they have defective genes. In others, the deficiency can lead to emphysema and cirrhosis, both progressive diseases that can be fatal.

In the clinical trial, three patients who received injections of a harmless virus containing copies of a correct gene for alpha-1 protein in their upper arms were able to produce trace amounts of alpha-1 antitrypsin for up to one year. Although the levels produced were not considered therapeutic, the study provided critical "proof of principle" that a corrected, functioning gene could trigger production of the protein. The National Heart, Lung and Blood Institute recently awarded a five-year, \$2 million grant to Dr. Flotte for further clinical trials studying the use of an adeno-associated virus to deliver the alpha-1 antitrypsin gene.

"When you deliver this therapy into the deltoid muscles of the arm, the muscle becomes a factory for making the protein that these individuals are missing," said Mark L. Brantly, MD, a professor of medicine and molecular genetics and microbiology at UF's College of Medicine and first author of the study.

The trial established the safety of the adeno-associated virus used to "infect" patients' cells with replacement genes, which then do the vital work of producing the alpha-1 protein. Nine patients were divided in three groups to receive the gene therapy at the General Clinical Research Center at Shands at UF Medical Center. Patients received nine injections in their non-dominant upper arms, with the dosage increasing in each group. At 365 days after the injections, the transferred genes were measurably producing alpha-1 protein in the three patients who received the highest dose, showing that the normal gene was successfully transferred and had begun doing its intended job in the patients' muscles.

"I hope the alpha-1 community is as encouraged as I am that although this trial does not give us any guarantee, there is a fighting chance to develop a therapy using this method," said Dr. Flotte. "In patients receiving the highest dose in this study, we saw transgene expression. And although it approached just 1 percent of what we ultimately want, we can be reasonably optimistic that we can achieve much closer to normal values in people by using the same approach with an increased dose."

Although patients showed some elevated immune response to the gene therapy vector — which is designed to quickly break down after delivering its cargo — researchers did not detect any evidence that the patients' bodies rejected the transferred genes or the newly created protein.

"That's a really good sign," said Brantly, a member of the Powell Gene Therapy Center and the UF Genetics Institute, who sees about 150 alpha-1 patients in his medical practice. "After we gave the injections, the individuals stayed on the ward for five days while we monitored them. There were no ill effects, only a minimal amount of redness, and by the end of the five days most of the subjects were actually bored."

Currently, the only limitedly effective treatment for patients with serious breathing symptoms involves weekly intravenous injections of alpha-1 protein derived from human plasma. The injections must continue throughout a patient's life, according to the American Lung Association. They do not cure the disease, but they do appear to slow its progression.

"This study gives us encouraging evidence that gene therapy for alpha-1 is a realistic possibility," said John Walsh, president and chief executive officer of the nonprofit Alpha-1 Foundation, which has been supporting research of this kind for more than a decade. "The augmentation therapy available now has slowed down the progression of our lung disease and extended many of our lives. The hope of gene therapy is that we may have a one-time, brief series of injections that could allow our own bodies to produce the alpha-1 protein we need to live a normal lifetime. The alpha-1 community is incredibly grateful for the progress that these dedicated investigators have made," Walsh said.

The study was funded by grants from the National Heart, Lung and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, UF, the National Center for Research Resources, the Alpha-1 Foundation and from the study sponsor, Applied Genetic Technologies Corp., or AGTC, a company formed by UF researchers to develop gene therapies. UF holds an equity interest in AGTC. Brantly is the Alpha-1 Foundation Research Professor at UF and is a consultant for the organization.