Gene therapy success in Wiskott-Aldrich syndrome

November 15 2010

A pediatric immunologist at The Children's Hospital of Philadelphia collaborated with European gene therapy researchers who achieved marked clinical improvements in two young children with Wiskott-Aldrich syndrome, a very rare but often severe immunodeficiency disorder.

Jordan S. Orange, M.D., Ph.D., an expert in Wiskott-Aldrich syndrome (WAS), performed sophisticated cell imaging and analysis for the study, led by German researcher Christoph Klein, M.D., Ph.D., of Hannover Medical School. Orange was a senior co-author, and Children's Hospital was the only U.S. institution represented in the study, published in the Nov. 11 New England Journal of Medicine.

The proof-of-principle study marks the latest example of a recent upswing in clinical success for gene therapy. In 2009, researchers from The Children's Hospital of Philadelphia and the University of Pennsylvania reported dramatic vision improvements in patients with Leber congenital amaurosis (LCA), a form of inherited blindness. In the same year, Parisian researchers announced success in treating adrenoleukodystrophy, the disease depicted in the movie "Lorenzo's Oil." And scientists at the University of California are reporting preliminary clinical benefits in gene therapy for adenosine deaminase deficiency, an immune deficiency disorder related to "bubble boy disease."

Like WAS, all are very rare inherited disorders and have the potential to

be severe and (except for LCA) life-threatening.

Wiskott-Aldrich syndrome is a complex X-linked immunodeficiency disorder characterized by recurrent infections, eczema and thrombocytopenia—a low platelet count. Mutations in the WAS gene disable its ability to produce WAS protein, which plays a crucial role in different types of immune cells. Without WAS protein, immune cells are disabled, incapable of providing immune defenses. Hence, patients are susceptible to premature death from infection, cancers or bleeding.

Although WAS has a range of severity, the only current cure is stem cell transplantation, which carries its own risks.

In the current study, based in Germany, the research team treated both children, three-year-old boys diagnosed with WAS soon after birth, by first collecting some of their hematopoietic (blood cell-forming) stem cells. They then transferred normal WAS genes into those cells and returned the cells to the boys' bloodstreams.

After treatment, the patients experienced fewer and less severe infections. Bleeding episodes decreased after platelet counts improved. Severe autoimmune anemia disappeared in one boy and severe eczema completely resolved in the other. Three years after the gene therapy, treatment-limiting adverse effects had not occurred, and the clinical benefits persisted. Significantly, the researchers reported that the treatment corrected thrombocytopenia, a hazardous and difficult-to-treat complication of WAS.

On reporting encouraging results in the first two children, the researchers noted the need to expand the study to additional patients, while conducting longer-term follow-up and analysis.

The study team found increased levels of the normal WAS protein

expressed by the gene they had introduced. Orange's laboratory at Children's Hospital performed analytic imaging studies that provided evidence that the corrected immune cells were functioning normally. "Our highly quantitative imaging studies assessed natural killer cells, a critically disabled immune cell in Wiskott-Aldrich patients, and demonstrated a remarkable return to normality after gene therapy," Orange said.

Orange Translates Basic Science to Possible Immunotherapy for WAS

Orange drew on his deep background in investigating how natural killer cells function in the immune system. While a graduate student, in 1996, he discovered that natural killer cells produce cytokines, important signaling proteins, to participate in immune defense against viruses. Over the past decade he has defined the field of human natural killer cell deficiencies in various genetic disorders.

At Children's Hospital, where he treats patients, Orange is investigating a treatment for WAS distinct from gene therapy. In a current clinical trial in WAS, his immunotherapy approach bypasses the gene defect in the disease, instead using the cytokine IL-2 to boost immune function. He expects to publish initial results shortly.

"If our immunotherapy approach is safe and effective, it may represent a treatment for the full spectrum of WAS patients," he said, noting that the gene therapy trial is currently limited to the most severe cases. "Even patients with less severe WAS are at risk for lymphoma and other blood cell cancers, so broadening treatment options would be an important advance in treatment."

More information: Boztug et al, "Stem-Cell Gene Therapy for the

Wiskott-Aldrich Syndrome," *New England Journal of Medicine*, Nov. 11, 2010.

Provided by Children's Hospital of Philadelphia