Nationwide Children's Hospital Gene Therapy Researchers Announce First-Ever Restoration of Full-Length Dystrophin in Humans

COLUMBUS, Ohio – Researchers at Nationwide Children's Hospital have documented the first-ever creation of full-length dystrophin in a human as a response to gene therapy. Dystrophin is a protein normally found in skeletal muscle that is absent or abnormal in people with Duchenne muscular dystrophy (DMD). They announce their findings in an oral abstract presentation and an invited talk at the 2022 Annual Meeting of the American Society of Gene and Cell Therapy (ASGCT) this week in Washington, D.C.

"This is a landmark. We're very gratified to show — for the first time ever — the therapeutic expression of full-length dystrophin as a result of a human gene therapy," said Kevin Flanigan, MD, director of the Center for Gene Therapy in the Abigail Wexner Research Institute at Nationwide Children's and a leading expert in the development of gene therapies for patients with DMD.

The most common duplication-related form of DMD (affecting about 1% of all people with DMD) involves an extra copy of exon 2, which causes cells to stop making any dystrophin protein. Instead of using gene therapy to insert a gene that makes a miniature form of dystrophin (the approach taken with most gene therapy approaches for DMD) the therapy under study is an exon-skipping viral vector (scAAV9.U7-ACCA), which contains a non-coding gene that continually makes antisense RNA. The antisense RNA then targets exon 2 in the *DMD* gene, helping cells ignore at least one exon 2 copy and get on with making full-length, normal dystrophin.

"In contrast to approved exon-skipping therapies, this is not a weekly treatment, and it induces exon skipping at much higher levels," said Dr. Flanigan, who directs the neuromuscular clinical program at Nationwide Children's and is the Robert F. and Edgar T. Wolfe Foundation Endowed Chair in Neuromuscular Research. "And unlike microdystrophin gene therapies, this makes a complete, wild-type [natural] version of the protein."

Initial safety and efficacy outcomes for the cohort of three patients treated with the experimental therapy will be shared during the research team's presentations at ASGCT on May 16th and 17th. The study included the youngest patient (7 months of age) ever dosed with DMD gene therapy. By 4 months post-dose, a biopsy showed that 99% of his muscle fibers produced full-length dystrophin, at levels 70% of normal amounts. Two older patients (treated at 8.9 and 13.7 years of age) had some stabilization of disease and production of full-length protein, but their protein levels and clinical improvements were less pronounced than in the infant.

"The newest gene therapy results from Flanigan and colleagues are extremely exciting and provide several important new tools in the fight against DMD," said Jeff Chamberlain, PhD, the McCaw Chair in Muscular Dystrophy and Director of the Senator Paul D. Wellstone Muscular Dystrophy Research Center at University of Washington School of Medicine. Dr. Chamberlain is one of the country's leading experts in microdystrophin development and gene therapy for DMD patients. "The full, intact dystrophin protein is likely to be significantly more beneficial than the miniaturized versions. Furthermore, the efficiency of gene delivery is a significant limitation on current methods, so the ability to safely treat young patients could transform the field of muscular dystrophy therapeutics."

The exon-skipping viral vector therapy might enable long-term, normal muscle function if delivered early enough, the investigators speculate.

“In this study of only three subjects, we are clearly seeing that the younger the age at dosing, the better result in terms of dystrophin expression,” said Megan Waldrop, MD, a pediatric neurologist at Nationwide Children’s and principal investigator on the trial, who will present the trial’s early safety and efficacy findings at the ASGCT meeting. “I am looking forward to following our youngest subject to assess the persistence of response, and to conducting an additional study focused on dosing additional younger subjects to better assess this potential age-associated effect.”

The vector was developed in Dr. Flanigan’s lab with support from the CureDuchenne Foundation, and the production of the clinical vector used in the study was sponsored by the Beauhawks Foundation. Dr. Flanigan’s lab and other gene therapy colleagues at Nationwide Children’s have additional research underway investigating the use of similar U7snRNA vectors for other DMD-causing mutations.