

Concern following gene therapy adverse events

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The Editor-in-Chief of *Human Gene Therapy*, the first journal devoted to the field of gene therapy, and one of the world's leading experts on gene therapy have co-authored a new editorial, Moving Forward After Two Deaths in a Gene Therapy Trial of Myotubular Myopathy, in response to the news of two deaths in a now-halted gene therapy clinical trial.

The editorial, published in *Human Gene Therapy*, is co-authored by James M. Wilson, MD, Ph.D., director of the Gene Therapy Program at the University of Pennsylvania and former Editor *Human Gene Therapy* Clinical Development, and Editor-in-Chief Terry Flotte, MD, who is also the Dean of the University of Massachusetts School of Medicine.

The editorial is in response to the recent report of

the deaths of two children receiving high doses of a gene therapy vector (AAV8) in a Phase I trial for X-linked myotubular myopathy (MTM). The news "is a tragic reminder of how difficult it is to predict outcomes in first-in-[human studies](#)," the authors wrote.

The sponsor of this clinical study is Audentes Therapeutics, which was acquired by Japan's Astellas Pharma in 2019. Wilson and Flotte say preclinical studies had been very promising. But in the ongoing trial, three patients were given a three-fold higher dose than other participants; they all experienced severe hepatotoxicity, which proved fatal in two of these subjects.

Wilson and Flotte note that some signs of toxicity have been reported in other AAV trials over the past year or two, including trials for [spinal muscular atrophy](#) and Duchenne muscular dystrophy, which are being run by companies such as Solid Bio, Sarepta, and Pfizer. Fortunately, all the affected subjects in these trials have recovered.

In early 2018, Wilson published a landmark paper in *Human Gene Therapy* describing severe toxicity in [nonhuman primates](#) infused with high doses of AAV.

Although data are limited at present, Wilson and Flotte suggest the deaths of the MTM trial "more closely resembles those of the [non-human primate] studies rather than those of the [Duchenne] trials." One possibility the authors discuss is the role of antibodies to AAV that either pre-exist or accumulate following vector infusion.

With much more work needed to understand immune-mediated gene therapy vector toxicities, Wilson and Flotte conclude that "the early clinical development of [gene therapy](#) vectors may require an iterative process, especially if unexpected toxicities are observed." Additional studies in preclinical models should help evaluate the

variables associated with [immune response](#).

The MTM trial is on hold while authorities investigate further; the fate of the candidate [therapy](#) is unclear.

"Whether this product can be revived is unclear, the fact remains that patients with MTM and many other rare genetic diseases have no treatments," the authors state. "It is imperative that the scientific community work together with full transparency and cooperation to learn from these tragedies to assure that we can deliver safe and effective treatments to individuals living with rare genetic diseases such as MTM."

More information: James M. Wilson et al, Moving Forward After Two Deaths in a Gene Therapy Trial of Myotubular Myopathy, *Human Gene Therapy* (2020). [DOI: 10.1089/hum.2020.182](https://doi.org/10.1089/hum.2020.182)

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