Clinical trial for muscular dystrophy demonstrates safety of customized gene therapy

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Researchers at the University of North Carolina at Chapel Hill have shown that it is safe to cut and paste together different viruses in an effort to create the ultimate vehicle for gene therapy. In a phase I clinical trial, the investigators found no side effects from using a "chimeric" virus to deliver replacement genes for an essential muscle protein in patients with muscular dystrophy.

"This trial demonstrates that gene therapy is no longer limited by the viruses we find in nature, and should usher in the next generation of viral delivery systems for human gene transfer," said senior study author R. Jude Samulski, PhD, professor of pharmacology and director of the Gene Therapy Center at UNC. The study appears online in the Nov. 8, 2011 issue of the journal *Molecular Therapy*.

Through gene therapy, scientists treat diseases by correcting a patient's faulty genes. Most of the time, this approach involves commandeering a natural system for infecting and introducing new genes into cells; thus, the virus. But even though there are lots of relatively innocuous viruses available for this purpose, none of them are perfectly suited for gene therapy.

Rather than rely on nature, Samulski and his colleagues decided to engineer their dream gene therapy virus in the laboratory. First they chose the adeno-associated virus or AAV, a small nonpathogenic virus

that most humans are exposed to at some point in life. They then took their favorite attributes from different forms of AAV – such as AAV type 1's ability to sneak into muscle, and AAV type 2's safe track record – and combined them into one "chimeric" virus. In the first trial of this form of gene therapy, the investigators gave six boys with Duchenne muscular dystrophy (DMD) this new virus. An x-linked inherited disorder, DMD affects one in 4,000 newborn boys.

The virus was engineered to contain the dystrophin gene, which is missing in patients with muscular dystrophy and is the ultimate cause of the disease's progressive muscle weakness. The replacement genes were injected into the bicep in one arm and a placebo was injected into the other arm of each of the patients. The researchers were able to detect the new genes in all of the patients treated with the gene therapy, but no immunological response.

As they move on to the next phase of clinical trials, Samulski says they are carefully considering how best to administer the gene therapy vectors to patients. Delivering enough replacement genes to a therapeutic effect could require larger doses of virus, which in turn could elicit an unwanted immune response. So the researchers are exploring a number of different options, including using a new high pressure technique developed by William J. Powers, MD, professor and chair of neurology at UNC, reported last July in the same journal, to get the virus into muscle at lower doses.

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