

Progress on Gene Modification Rx for Muscular Dystrophy

By Gil Ross — January 4, 2016



In an amazing, salutary coincidence, three independent

research groups recently reported progress utilizing gene modification approaches to reducing the muscular dysfunction characteristic of sex-linked Duchenne-type Muscular Dystrophy, the most common and severe form of the disease.

The current studies were done on mice, but in this instance mouse and human gene mutations are quite similar, both biochemically and pathophysiologically re: the muscular dysfunction resulting from the genetic aberration.

Duchenne muscular dystrophy (DMD) is the most common fatal genetic disorder diagnosed in childhood, affecting approximately 1 in every 3,500 live male births (about 20,000 new cases each year worldwide). Because the Duchenne gene is found on the X-chromosome, it primarily affects boys; however, it occurs across all races and cultures.

The muscle abnormalities are caused by a mutation in the gene that encodes for dystrophin. Dystrophin is a protein located primarily in muscles used for movement (skeletal muscles) and in heart (cardiac) muscle. Dystrophin is essential for proper muscle function. When dystrophin is absent or functionally deficient, the muscle cells are easily damaged, and as DMD patients age, their muscles are progressively wasting away.

DMD usually manifests initially as delayed ability to walk; infants with DMD rarely walk before age 2. The full spectrum of muscle weakness appears most often between ages 2 and 3. One characteristic feature is "pseudohypertrophy" of the calf muscles, in which they appear enlarged but remain quite weak. Progressive loss of strength occurs over time, in some cases faster than others, but most affected boys lose the ability to walk by age 10 or so, and death frequently occurs before age 30 from respiratory muscle impairment or heart failure.

The new studies used a groundbreaking gene-altering/modification technique known as CRISPR/Cas-9 (*clustered regularly interspaced short palindromic repeats*), which is analogous genetically to the "find and replace" function on document manipulation. The scientists attached dystrophin-specific CRISPR/Cas-9 technology to a virus ("AAV," adeno-associated virus) and used the virus as a carrier to transport the corrective gene modifier to ailing muscle cells in mice.

The studies were undertaken at the following institutions: [Duke University](#) [1], Durham NC, led by Dr. Charles A. Gersbach; The [University of Texas Southwestern](#) [2] Medical Center in Dallas, TX, led by Dr. Eric N. Olson; and [Harvard University](#) [3] and the Harvard Stem Cell Institute, Cambridge MA, led by Dr. Amy J. Wagers. They were published in *Science* magazine. Each of the groups studied a mouse model (*mdx*) known to develop aberrant-dystrophin-related DMD-like disease. Each utilized the CRISPR/Cas9-mediated genome editing technique and the AAV viral transport. Both local injection and systemic (intravenous, bloodstream) injection improved both functional and cytological (cellular) features of muscle deterioration.

As the Duke group's conclusion states, "This work establishes CRISPR/Cas9-based genome editing as a potential therapy to treat DMD." I believe patients with DMD and their families can look forward to this technology being useful to help slow the progress of DMD within the next decade, and perhaps even "cure" the disease within a similar timeframe.

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[1] <http://www.sciencemag.org/content/early/2015/12/29/science.aad5143.abstract?sid=9dd9bcd2-1f87-4623-9313-defc1a41a203>

[2] <http://www.sciencemag.org/content/early/2015/12/29/science.aad5725.abstract?sid=d8e79b34-6cd7-4a6d-acd3-db3c00c4d26e>

[3] <http://www.sciencemag.org/content/early/2015/12/29/science.aad5177.abstract?sid=a34944ef-555c-43fc-b7b3-88d4b80467d1>