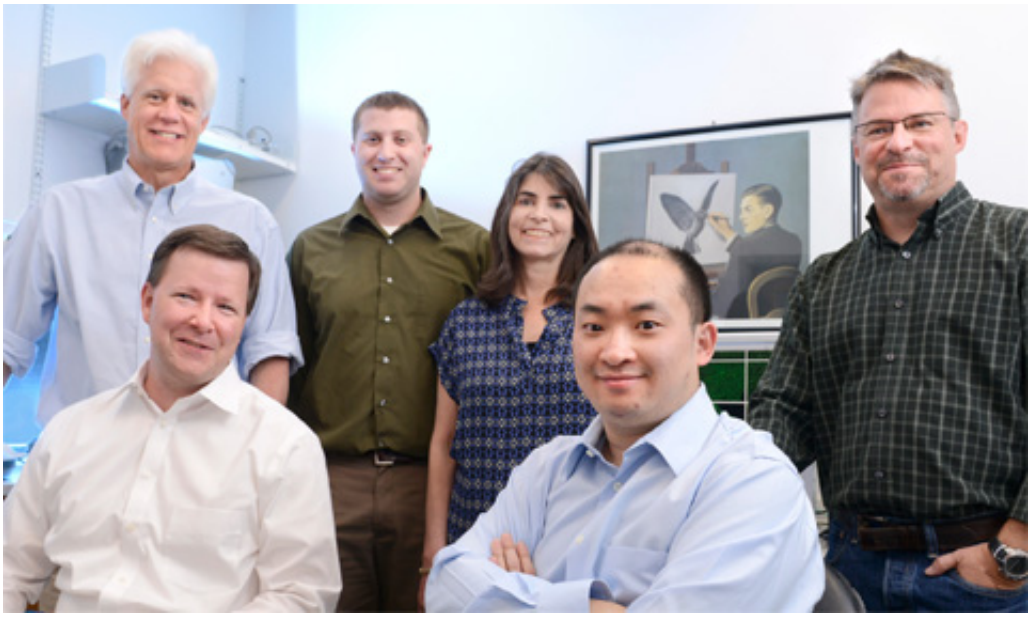
New gene editing method shows promising results for correcting muscular dystrophy

August 14 2014



This image depicts in front (l-r) John McAnally and Chengzu Long; and in back (l-r) Dr. Eric Olson, Alex Mireault, Dr. Rhonda Bassel-Duby, and John Shelton Credit: UT Southwestern

UT Southwestern Medical Center researchers successfully used a new gene editing method to correct the mutation that leads to Duchenne muscular dystrophy (DMD) in a mouse model of the condition.

Researchers used a technique called CRISPR/Cas9-mediated genome editing, which can precisely remove a mutation in DNA, allowing the

body's DNA repair mechanisms to replace it with a normal copy of the gene. The benefit of this over other gene therapy techniques is that it can permanently correct the "defect" in a gene rather than just transiently adding a "functional" one, said Dr. Eric Olson, Director of the Hamon Center for Regenerative Science and Medicine at UT Southwestern and Chairman of Molecular Biology.

Using CRISPR/Cas9, the Hamon Center team was able to correct the genetic defect in the mouse model of DMD and prevent the development of features of the disease in boys, which causes progressive muscle weakness and degeneration, often along with breathing and heart complications.

"Our findings show that CRISPR/Cas9 can correct the genetic mutation that leads to DMD, at least in mice," said Dr. Eric Olson, holder of the Pogue Distinguished Chair in Research on Cardiac Birth Defects, the Robert A. Welch Distinguished Chair in Science, and the Annie and Willie Nelson Professorship in Stem Cell Research. "Even in mice with only a subset of corrected cells, we saw widespread and progressive improvement of the condition over time, likely reflecting an advantage of the corrected cells and their contribution to regenerating muscle."

He also pointed out "this is very important for possible clinical application of this approach in the future. Skeletal muscle is the largest tissue in the human body and current gene therapy methods are only able to affect a portion of the muscle. If the corrected tissue can replace the diseased muscle, patients may get greater clinical benefit."

Although the genetic cause of DMD has been known for nearly 30 years, there are no treatments that can cure the condition. Duchenne muscular dystrophy breaks down muscle fibers and replaces them with fibrous and/or fatty tissue causing the muscle to gradually weaken.

DMD affects an estimated 1 in 3,600–6,000 male births in the United States, according to the Centers for Disease Control (CDC). Left untreated, those with DMD eventually require use of a wheelchair between age 8 and 11, and have a life expectancy of 25 years. Initial symptoms include difficulty running and jumping, and delays in speech development. DMD can be detected through high levels of a protein called creatine kinase as it leaks into the blood stream, and is confirmed by genetic testing.

Genome editing through the CRISPR/Cas9 system is not currently feasible in humans. However, it may be possible, through advancements in technology, to use this technique to develop therapies for DMD in the future, Dr. Olson said.

"At the moment, we still need to overcome technical challenges, in particular to find better ways to deliver CRISPR/Cas9 to the target tissue and to scale up," Dr. Olson said. "But in the future we might be able to use this technique therapeutically, for example to directly target and correct the mutation in muscle stem cells and muscle fibers."

Added Chengzu Long, a graduate student in the Olson lab: "We are working on a more clinically feasible method to correct mutations in adult tissues, and have already made some progress."

The research, published online in the journal *Science*, is the inaugural paper from UT Southwestern's newly established Hamon Center for Regenerative Science and Medicine, made possible earlier this year by a $10 million endowment gift from the Hamon Charitable Foundation. The Center's goal is to understand the basic mechanisms for tissue and organ formation, and then to use that knowledge to regenerate, repair, and replace tissues damaged by aging and injury.

Degenerative diseases of the heart, brain, and other tissues represent the

largest cause of death and disability in the world, affecting virtually everyone over the age of 40 and accounting for the lion's share of health care costs. Regenerative medicine represents a new frontier in science, which seeks to understand the mechanistic basis of tissue aging, repair, and regeneration and to leverage this knowledge to improve human health.

More information: "Prevention of muscular dystrophy in mice by CRISPR/Cas9-mediated editing of germline DNA," by C. Long et al. *Science*, www.sciencemag.org/lookup/doi/ … 1126/science.1254445

Provided by UT Southwestern Medical Center