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Combined therapy could repair and prevent damage in Duchenne muscular dystrophy

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New research on two promising gene therapies suggests that combining them into one treatment not only repairs muscle damage caused by Duchenne muscular dystrophy, but also prevents future injury from the muscle-wasting disease. The work, led by a team at The Research Institute at Nationwide Children's Hospital, is the first to look at the approach in aged mice, a key step toward clinical trials in patients. The findings were published in July in *Human Molecular Genetics*.

"We're excited about the fact that these are older mice and we're still able to see a sustained functional benefit from this combined therapy—this hasn't been shown before," says Louise Rodino-Klapac, PhD, a principle investigator in the Center for Gene Therapy at Nationwide Children's and lead author of the research.

Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy in children, affecting about one out of every 3,500 to 6,000 male births. Symptoms usually begin between the ages of 3 and 5 years and progress rapidly. Most patients are unable to walk by age 12 and ultimately need a respirator to breathe.

Patients with DMD lack the gene that makes dystrophin, a protein vital for healthy muscle tissue. Dystrophin acts as an anchor to support muscle fiber strength and prevent injury. Without it over time, the muscle degenerates, scar tissue builds up and fat slowly replaces the dead muscle. The gene that produces dystrophin is huge—the largest known gene in the body—so a much smaller version, called micro-dystrophin,

has been developed for gene replacement therapeutic studies.

Another gene replacement therapy currently under study in patients with different forms of muscular dystrophy is follistatin 344, which produces a protein that enhances muscle strength and prevents atrophy.

While preliminary studies in animals of each of these therapies suggest they offer some benefit when used individually, the team at Nationwide Children's wanted to see what would happen if the therapies were combined.

Dr. Rodino-Klapac and her colleagues packaged the micro-dystrophin and follistatin therapeutic genes into adeno-associated virus, which doesn't cause disease and isn't absorbed in the genome. The virus and its genetic cargo were delivered via injection to dystrophic mice that were either 6 or 12 months old. The virus "infects" cells, the therapeutic genes are released, and the body ideally begins to produce micro-dystrophin—which prevents future muscle injuries—and follistatin—which repairs existing muscle damage.

The researchers analyzed skeletal muscle strength in the mice at 12 and 20 months of age. Mice that received the combined therapy showed a significant increase in muscle strength compared to mice treated with either the micro-dystrophin or follistatin 344 alone. Equally important, the treated mice also suffered less muscle damage over time.

A clinical trial of micro-dystrophin in patients with DMD will begin at Nationwide Children's this fall. Another trial of follistatin is already under way with support from Milo Biotechnology, a clinical stage startup company whose lead product is an adeno-associated virus (AAV)-delivered follistatin protein. That trial should conclude next year.

If both trials are successful, the next step would be to create a clinical

study to look at the use of the combined therapies in patients.

"This study suggests we could do two very important things—repair existing damage and prevent additional damage—and that's key, because when most patients would come in for treatment, they would have already incurred a great deal of muscle damage," says Brian Kaspar, PhD, a principal investigator in the Center for Gene Therapy at Nationwide Children's and co-author of the new study.

This combined therapy may offer greater benefit to patients if we can effectively move this towards clinical trials," says Dr. Kaspar, who also is an associate professor of pediatrics and neuroscience at The Ohio State University College of Medicine. "We've got novel therapeutics moving forward and a number of promising therapeutics in the pipeline. There's excitement in the field right now."

"We're very enthused about this study because of the potential synergistic impact that follistatin could have with dystrophin delivery for treatment of muscular dystrophy," says Al Hawkins, CEO, Milo Biotechnology. "Our follistatin pilot trial at Nationwide Children's is independent and ongoing, but one could someday imagine a combination therapy that could have great benefit to patients."

The number of physician-scientists at Nationwide Children's is one of the reasons these studies seem to move from the lab to clinical trials so quickly, says Jerry Mendell, MD, director, Center for Gene Therapy and professor of pediatrics and neurology at The Ohio State University College of Medicine. Physician-investigators are developing therapies for diseases at the same time they are caring for the patients who have these diseases.

"We are learning more about the disease every day because we see it in the children we treat. You find out the things you need to tweak and go

back to the lab and perfect it. This is all part of our basic science process," says Dr. Rodino-Klapac, who also is an assistant professor of pediatrics at The Ohio State University College of Medicine. "We have a unique setting where we can take things from bench to bedside more quickly."

Provided by Nationwide Children's Hospital