

Gene Delivery: Mouse study shows new therapy may reverse muscular dystrophy

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For people with the most common type of muscular dystrophy, one faulty gene wreaks devastating consequences. Researchers have now found a way to deliver a working copy of the gene to the entire muscular system in mice that suffer from the muscle-wasting ailment. With one injection into the bloodstream, the animals' conditions improved markedly.

"No one's been able to get a delivery system to work very well before," says Jeffrey S. Chamberlain of the University of Washington in Seattle. "We were able to show a very significant effect in halting and reversing this disease."

To the genome of a virus that doesn't trigger an immune response or replicate in mice or people, the researchers added the dystrophin gene, the faulty version of which causes Duchenne muscular dystrophy. The investigators also included a promoter gene that ensured that only muscle cells would manufacture the protein encoded by the dystrophin gene.

That protein acts like a girder in a building, providing structural support to muscle cells. Without it, muscle tissue develops holes and tears.

The researchers injected the engineered virus, along with a chemical to facilitate its diffusion through blood vessels, into mice with muscular dystrophy. Weeks later, the scientists examined these animals' muscles, including those in the arms, legs, and ribs, and compared them with muscles of similar mice that hadn't received an injection.

"The [treated] muscles looked tremendously better under the microscope," says Chamberlain. He and his colleagues report their results in the August *Nature Medicine*.

One injection into the bloodstream spread the virus—and the dystrophin gene it carries—to skeletal muscles and the heart. "This research shows that it's possible to deliver a therapeutic gene throughout the body," comments Thomas A. Rando of Stanford University, who studies muscle diseases. "That's been a real hurdle."

Because the dystrophin protein in the test functioned only in muscle cells, the procedure overcomes an additional obstacle to gene therapy—limiting a therapeutic gene's activity to the desired cells and tissues.

Other experimental attempts at gene therapy for muscular diseases rely on local injections directly into muscle, and any beneficial effects are limited to that area. This research sets a new standard for gene delivery to the entire muscular system, says Rando.

The same gene-delivery method could prove useful for treating a variety of muscular disorders, including heart disease and muscle wasting associated with aging, Rando says.

Adding to the technique's promise is evidence that the virus infiltrated many organ systems. To target genetic therapies to disorders of organs such as the liver and kidney, investigators might load viruses with different combinations of healthy genes and promoters, Chamberlain speculates.

While the treatment appears to be safe and effective in mice, it's too soon to say whether it will be suitable for use in people. Chamberlain is embarking on safety studies in larger mammals and hopes to begin human-safety studies in a few years.

Well before the results become available, this new method will provide laboratory and clinical researchers with a powerful new means of gene delivery, says Kevin P. Campbell of the University of Iowa in Iowa City.

References:

Gregorevic, P. . . . and J.S. Chamberlain. 2004. Systemic delivery of genes to striated muscles using adeno-associated viral vectors. *Nature Medicine* 10(August):828-834. Abstract available at <http://dx.doi.org/10.1038/nm1085>.

Further Readings:

Seppa, N. 2000. New gene-therapy techniques show potential. *Science News* 157(May 13):309. Available to subscribers at <http://www.sciencenews.org/articles/20000513/fob3.asp>.

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