A step forward toward muscular dystrophy treatment: 'Antisense' compound rids muscle cells of toxic RNA

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Scientists have reversed symptoms of myotonic muscular dystrophy in mice by eliminating a buildup of toxic RNA in muscle cells. The work, carried out by scientists at the University of Rochester Medical Center, Isis Pharmaceuticals Inc. and Genzyme, is published in the August 2 issue of *Nature*.

After experimental antisense compounds were administered to mice twice a week for four weeks, symptoms of the disease were reduced for up to one year – a significant portion of a mouse's lifespan.

The investigators say that while the work is an encouraging step forward against myotonic dystrophy, one of the most common forms of muscular dystrophy, it's too soon to know whether the approach will work in patients. But they are cautiously optimistic, noting that the compound is extremely effective at reversing the disease – whose genetic underpinnings make it particularly vulnerable to an antisense approach – in a mouse model.

"These results give us strong encouragement about the possibility of developing a treatment that could fundamentally alter the disease. It's an important step on a long path," said senior author Charles Thornton, M.D., a neurologist at the University of Rochester Medical Center who has been pursuing new treatments for the disease for more than two decades.

"But, it's too early to know if this treatment will work as well in people as it did in the laboratory. Unfortunately, in biomedical research there are previous examples of compounds that worked in mice but not in people," added Thornton, the Saunders Family Distinguished Professor in Neuromuscular Research.

About 35,000 Americans have myotonic dystrophy, an inherited disorder that is marked by progressive muscle weakness and stiffness; eventually many patients have difficulty walking, swallowing, and breathing. The disease can also affect the eyes, the heart, and the brain. While there are medications to treat some of the disease symptoms, there is no drug to stop its progression.

The recent progress comes about a decade after several scientists, including Thornton, discovered that the genetic defect that causes the disease works quite differently than most other inherited diseases. In many diseases, a genetic flaw means that an important protein is not made correctly, or not made at all.

But in myotonic dystrophy, the defect results in the creation of an abnormal messenger RNA, which accumulates in the nucleus, getting in the way and stopping other proteins from doing their jobs. One of those proteins is MBNL1, which helps create chloride channels that are important for electrical control of muscles. When that process is thwarted, muscles send errant electrical signals, causing symptoms.

The approach outlined in the Nature paper exploits the roots of the defect, harnessing an enzyme whose usual job is to cut RNA into pieces. Working closely with the Rochester and Genzyme teams, scientists at Isis created synthetic compounds – short snippets of chemically modified DNA – that bind to the toxic RNA, modifying it in such a way that it was targeted for destruction by one of the body's own enzymes, RNase H.

With the team's most effective compounds, symptoms in the mice were reversed. The level of toxic RNA was reduced by more than 80 percent; stiffness in muscles eased dramatically; the microscopic structure of muscle was improved; and electrical signaling in muscles returned to normal.

The possibility of targeting "toxic RNA" – a buildup of abnormal RNA causing cellular processes to go awry – makes myotonic dystrophy an excellent target for antisense drugs, said Thornton.

The compounds are called "antisense" because their genetic code is the mirror image of the target RNA strand, known in scientific parlance as the "sense" molecule. The antisense compound will only stick to the precise RNA that is part of the myotonic dystrophy gene, leaving thousands of other vitally important RNAs alone.

While antisense technology has been in development for a couple of decades, it has not been effective at eliminating RNA in muscle cells until now. Results like those in the Nature paper are creating enthusiasm particularly among scientists who study neurodegenerative diseases, Thornton says. He points to promising work by a team from the University of California at San Diego on Huntington's disease, as well as research out of Cold Spring Harbor Laboratory on spinal muscular atrophy.

"For 20 years we studied myotonic dystrophy, hoping that someday we would learn enough to spot its Achilles heel," said Thornton. "This work comes close to doing that.

"I know it is unscientific for me to think so, but I can't help but see a little glimmer of 'medical justice' in this approach. For the same reason that the toxic RNA makes people sick, by hanging around too long in the nucleus and gumming up the works, it also becomes more susceptible to

antisense drugs, because these drugs seem to work extraordinarily well against RNA in the nucleus," he added.

"Based upon these exciting preclinical data, we have initiated a drug discovery project for myotonic dystrophy with Dr. Thornton's team to identify an antisense drug to begin clinical testing," said C. Frank Bennett Ph.D., Senior Vice President, Research at Isis Pharmaceutical, Inc. "Myotonic dystrophy represents an ideal opportunity for an antisense drug as the disease-causing gene produces a toxic RNA that is not easily targeted with other therapeutic approaches. In just a few years, we have been able to expand our severe and rare disease franchise and maintain a broad research program, in which we are evaluating many different diseases that could be treated with an antisense drug."

Thornton was inspired to create a robust research effort to address the disease largely because of his experience treating patients. He is co-director of the Medical Center's Wellstone Muscular Dystrophy Cooperative Research Center, one of the world's top centers for the treatment of muscular dystrophy. He is also a scientist in the Center for Neural Development and Disease, where he runs a laboratory looking at the roots of the disease and exploring new treatments. On any given day, he is both seeing patients coping with conditions like myotonic dystrophy, as well as running laboratory experiments aimed at stopping the disease altogether.

As the research progressed, Thornton struck up a collaboration with Isis Pharmaceuticals Inc., the creator of the only antisense medication on the market, and Genzyme, a company with experience treating muscle diseases. Earlier this summer Isis announced an agreement with Biogen Idec Inc. to explore antisense treatments for myotonic dystrophy – an effort closely linked to Thornton's work.

Now scientists at Isis and the University of Rochester are working to

improve their lead compound further, developing antisense compounds with stronger activity against the toxic RNA, but with minimal effects on the rest of the body. An unknown factor at this point, Thornton says, is whether the compounds will also improve the muscle-wasting aspect of the disease. That symptom, which causes great difficulty for patients, has been hard for scientists to create in mice, and so it's difficult to predict how it might respond to antisense knockdown technology.

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