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Life

Monday, March 31, 2008

A disease in the cross hairs

Genetic researchers have dedicated themselves to eradicating a childhood killer, spinal muscular atrophy

BY VICTOR GRETO • THE NEWS JOURNAL • FEBRUARY 24, 2008

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NEWARK -- Two years ago, University of Delaware scientist Eric Kmiec showed up at A.I. duPont Hospital for Children in Rockland to find a use for his patented gene therapy.

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He wanted to test the therapy, which basically edits a single letter code in a DNA sequence, on a disease.

The match: spinal muscular atrophy.

The disease, which affects fewer than 200,000 people nationwide, is nevertheless the greatest genetic cause of death among children under age two. Half die before their second birthday.

One in 40 people carry the defective gene; if two carriers reproduce, they have a one-in-four chance of having a child with the condition.

While at A.I. duPont, Kmiec met Darlise DiMatteo, a Wilmington native who had researched spinal muscular atrophy for more than a decade.

DiMatteo had learned all the ins and outs of the gene -- known as SMN1, and its near-copy, SMN2, both present in healthy people.

In those who have the disease, the indispensable SMN1 gene either has been deleted or made ineffective, and the one remaining, SMN2, holds the wrong information to signal protein production, essential for healthy muscles.

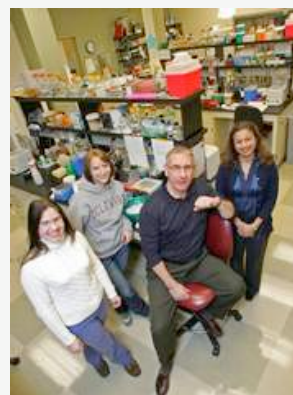
DiMatteo was impressed enough with Kmiec's therapy -- which would fix the code on SMN2 so it would do the work of the SMN1 gene -- to leave A.I. duPont to work on the disease with him.

"I thought it was a great opportunity to work toward a treatment for this disease," she says.

Now, the successful work by Kmiec and DiMatteo, done at the Delaware Biotechnology Institute, may ultimately help solve a disorder that affects about one in 6,000 newborns.

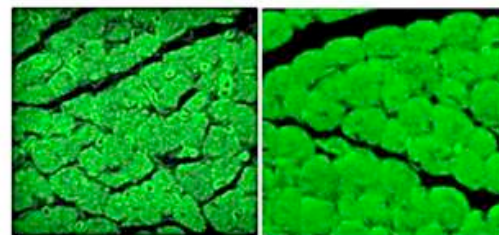
It's a first step -- a big one -- on the road to a treatment. "There's a lot more to do," Kmiec says. "But probably within two years we'll know if we'll have a real effect."

INTERACTIVE WEATHER



From left : Darlise DiMatteo, Stephanie Callahan, Eric Kmiec and Hetal Parekh-Olmedo. Kmiec has patented a gene therapy. (Buy photo)

The News Journal/JENNIFER CORBETT



Delaware Biotechnology Institute

Images of muscles from a SMA type II mouse. The muscle on the right was injected with oligonucleotide, a genetic "bandage." The muscle on the left was treated with saline. The oligonucleotide-treated muscle has fewer immature muscle fibers (hollow circles) than the left side and is healthier.



Skin cells from an SMA type I patient. The nucleus is shown in blue. The SMN

probably within two years we'll know if we'll have a real effect.

Using the "spell checker"

Kmiec and lab assistant Hetal Parekh-Olmedo's initial discovery of a gene therapy centered on the efficiency of DNA repair in cells. DNA is the double helix within a cell that contains an organism's genetic information.

DNA -- radically simple but randomly complex -- is made up of four base chemicals: adenosine, thymine, guanine and cytosine, together called AGTC.

If the information code within DNA has mutated -- if there is a "misspelling" in the array of AGTC -- it can cause a variety of diseases.

Every one without spinal muscular atrophy has at least one copy of the healthy SMN1 gene. Within the cells of those with the disease, the SMN1 gene is gone. But the SMN2 gene has a different code.

In the SMN2 gene, the thymine occurs where there should be cytosine. Because of that switch, the gene doesn't make a protein that the motor nerves in the spinal cord need. Without it, the muscles responsible for actions as simple as breathing or swallowing, atrophy, or waste away.

Kmiec calls his method a "spell checker."

Other potential diseases with which Kmiec's therapy may prove fruitful include sickle cell anemia, Huntington's disease, and a handful of liver diseases.

Using the therapy, Kmiec and DiMatteo introduce a small fragment of this healthy gene's DNA -- a genetic 'bandage' called a oligonucleotide -- into the cell, triggering it to heal the DNA patch in SMN2.

So far, the bandage has fixed only about 5 percent of the cells in a specific [culture](#) of human skin cells of those with the disease.

"Five percent won't be enough to cure it," says Vicky Funanage, head of biomedical research at the Nemours Foundation. "Will it ameliorate some of the symptoms? It could."

At least it may for those with milder forms of spinal muscular atrophy, such as those who make it to adulthood, but who have trouble [walking](#).

There are three types of spinal muscular atrophy. Type 1 cases are the most severe; children up to 6 months of age are unable to keep their heads up or even sit up.

Type 2 includes children, often from 7 to 18 months old, who aren't able to stand or walk, but may be able to sit up.

Type 3 include adults with the defective gene who may be able to walk at times.

Tests of the gene therapy technique in mice with the defective gene showed some development of healthy muscle, Kmiec said.

"We've done muscle injections and have seen moderate improvements in muscle fibers," DiMatteo says. "We now have to do spinal injections in mice," which DiMatteo.

"We have to get this [treatment] into the motor neurons themselves. If we can stop the progression of motor neuron death, we can stop the progression of the disease, and the muscles would stop dying. Ideally, then we could strengthen them through physical therapy."

Kmiec says that much of the success they've had has been due to DiMatteo's extensive experience with researching the disease.

A dissection with art scissors

For DiMatteo, 40, it's been a fruitful two years in a scientific career that began, unsuspectingly enough, at the age of 8, with a dead bird she found outside her childhood [home](#) near Sixth and Lincoln streets in Wilmington. There was only one way to see what was inside: cut it open with her little art scissors.

"I always loved science," DiMatteo says. "Solving problems, riddles, and applying it toward life."

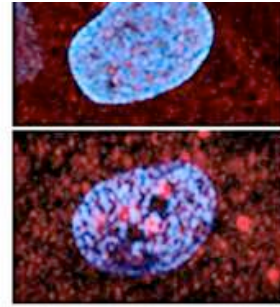
She thought she'd see organs in the bird. Not a chance.

The bird had been dead so long its insides had all but dissolved.

Ewwww? Not for her. She's not squeamish.

It was just a bummer for a budding scientist.

DiMatteo soon got a chemistry set and a microscope, and did so well at Wilmington High School, from where she graduated in 1985, she was accepted at both the University of Delaware and Johns Hopkins, in Baltimore.



protein forms a complex in the nucleus called a "gem." The "gems" are the bright pink spots. The cell in the lower picture was treated with the oligonucleotide, and the number of "gems" increased, indicating an increase in SMN protein.



Special to The News Journal/MATTHEW JONAS

Researcher Eric Kmiec (left) and Michael Herr are principals in a biotechnology start-up, Orphagenix. Herr is executive director. (Buy photo)

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She was the first in her [family](#) to go to college, and her divorced parents couldn't afford Johns Hopkins. She went to UD.

After graduating, she worked several years in a DuPont-Merck Pharmaceutical behavioral lab.

But her greatest experience accrued when she assisted Dr. Vicky Funanage at the A.I. duPont Hospital for Children for a dozen years.

It was at A.I. duPont where she studied neuromuscular diseases, including muscular dystrophy and spinal muscular atrophy.

When Kmiec came and talked about his therapy, DiMatteo says, "I thought I could make a difference with the disease," she says.

Finding the money

Spinal muscular atrophy is an "orphan" disease, a relatively rare disease that has not been "adopted" by the pharmaceutical industry because it provides little opportunity to make [money](#).

Without pharmaceutical industry money, researchers must look elsewhere for funding.

With several other investors coordinated by First State Innovation, a nonprofit group at the Biotechnology Institute (www.dbi.udel.edu) led by the technology park's CEO and president Mike Bowman, Kmiec began Orphagenix (www.orphagenix.com), a biotechnology start-up company.

Although Kmiec's and DiMatteo's research has been supported by grants from the National Institutes of Health and by \$477,500 from Delaware's cut of the National Tobacco Settlement funds, further testing, including clinical trials on people, will need millions of dollars more.

Orphagenix, led by executive director Michael Herr and chief medical officer Mitchell Glass, has been working to inform investors of the qualified success of Kmiec's technique.

"The Kmiec lab's results are very exciting," Herr says. But there's a lot to do before any clinical trials are done on people.

The company has hired an expert to see if Kmiec's therapy is the "the best possible 'drug' to edit the SMA gene," he says.

The therapy has to be tested for safety, and the company plans to hire clinical experts in the disease to determine how to structure the best clinical tests.

"And we have to be sure we have enough money to finish what we start," Herr says.

To obtain the money, Herr said his company is in talks with an undisclosed biotech firm. Further testing probably will be done at area hospitals and medical centers, including A.I duPont and Johns Hopkins, Glass says.

"If all goes well," he says, "we'll have a treatment in 2 1/2 years."

It's a gamble. If it works, the company could do an initial public offering, or be bought up by a large pharmaceutical company.

Or, the tests may show that the treatment may not be effective enough to matter.

Kmiec, DiMatteo, Glass and Herr stress that the therapy is "not a cure."

At least not yet.

"A 5 to 10 percent success rate is important," Glass says, referring to the percentage of cells Kmiec and DiMatteo have been able to transform at a time. "Even that low, it may improve the health of those with the most mild form of the disease."

Undergraduate Stephanie Callahan, who has been helping Kmiec and DiMatteo, plans to work as a graduate student on the project.

"I want to see how much I can push it up from 5 percent," she says, "by adding reagents [chemicals] and looking at the effect of DNA damage, if correction comes at a price."

Regardless of what happens next, Funanage says it's part of doing science.

"Research is about patience and diligence," she says. "We're adding to a body of knowledge and this advances the field in many ways."

F.Y.I.

For more information about spinal muscular atrophy, go to www.curesma.org.

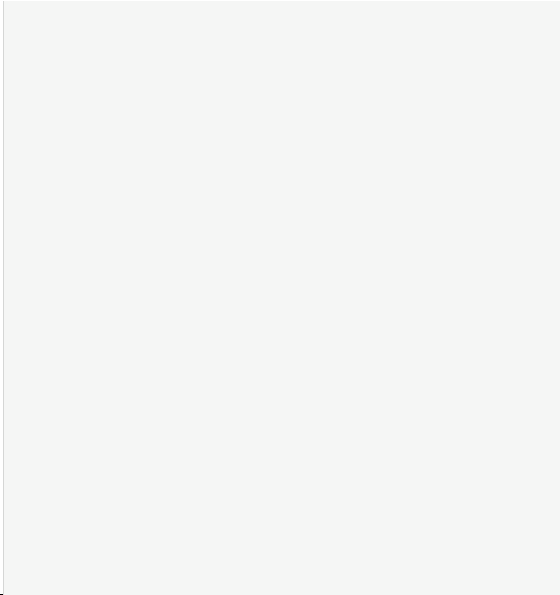
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