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SIDEBAR

GENETIC TREATMENT FOR MUSCULAR DYSTROPHY STILL FACES MAJOR ROADBLOCKS

Illustration: Photo

Source: BY JESSICA M. SCULLY, Special to the Mercury News

New research is providing scientists with insight into how to use gene therapy as a treatment for muscular dystrophy. But researchers say a giant roadblock to the therapy's success remains -- how to get the treatment to all cells that need it without severely damaging them in the process.

The first problem long plaguing gene therapy research is one of size.

Viruses are used in gene therapy to get new genetic material inside diseased cells and repair their damaged genetic material. But the safest known virus is too small to carry the genes for muscle proteins that might help muscular dystrophy patients. Researchers had to find a way to get the genes into the virus in order to repair the genetic problem behind the disease.

The second problem involves the immune system. Muscular dystrophy is caused by the genetic lack of certain muscle proteins. If researchers coaxed a muscular dystrophy patient's body to make the missing protein, the person's immune system might see the protein as an invader and attack.

The two earliest of three new studies seem to solve both these problems. In both cases, the scientists proved that boosting the amount of an existing protein could replace the protein that was genetically missing.

In the first study, published last March in the Journal of Cell Biology, a team of researchers from the University of Illinois at

Champaign-Urbana, led by Dr. Stephen Kaufman, used mice genetically engineered to lack the muscle proteins utrophin and dystrophin. This lack causes the mouse model of Duchenne muscular dystrophy.

Some of the mice were engineered to produce more of another protein, called integrin, than usual. These mice didn't get the severe muscular dystrophy found in the untreated group -- a sign that stimulating the production of one protein could help make up for the lack of the other.

Making miniature genes

In the next study, published in September in the journal Nature, researchers from the University of Basel in Switzerland added another layer to the research. Led by Dr. Markus Ruegg, they used a mouse model for congenital muscular dystrophy with mice genetically engineered to be deficient in laminin. They caused the mice to make more than the usual amount of a miniature version of the gene for agrin, another muscle protein that the mice's bodies already produced.

The mini-agrin made up for the lack of utrophin, largely preventing the development of the disease in the mice. The miniaturized gene was small enough to fit into AAV.

Scientists think this approach would avoid an immune system attack in humans because the enhanced protein already exists in a patient's body in smaller amounts. Besides their use for gene therapy, the studies raise hopes that a drug based on the same principle could be developed.

The third study, led by Dr. Johnny Huard of the University of Pittsburgh, avoids the issue of virus size by using stem cells. After isolating these cells from mice with Duchenne, Huard and his team infected the cells with a virus carrying a miniaturized, corrected version of the faulty gene. They then reinserted the stem cells into the mice.

The mice regrew some muscle tissue, but studies haven't yet proven that it's enough to alleviate symptoms of the disease. The results were announced in December at a meeting of the American Society for Cell Biology.

Studies like these are making a gene therapy treatment for muscular dystrophy closer to reality. But researchers caution that the biggest hurdle is yet to be cleared.

Delivery dilemma

While the therapy is showing some success in diseases that affect a small portion of the body, muscles make up about half a person's body weight, said Sharon Hesterlee, director of research development at the Muscular Dystrophy Association. If the treatment were injected, the number of injections needed to get the virus to all the muscles would cause extensive tissue damage.

''You're talking about billions of cells that would need to be corrected, so it becomes a very daunting process,'' she said. Stem cells may eliminate part of that problem because they could divide, she said. But getting them into deep muscles like the heart would be problematic.

''Delivery is always the problem, unless you're using a drug,'' she said.

Gene therapy is and will remain attractive because it has the potential to be a cure, according to Dr. Thomas Rando, director of the Muscular Dystrophy Association clinic at Stanford Medical School. But even with the findings from the new studies, Rando thinks a gene therapy treatment for muscular dystrophy is still a long way off. A drug that could alleviate some of the symptoms is closer to becoming reality, he said.

''Treatments will become available before cures will become available,'' he said.

GENE THERAPY SHOWS PROMISE

NEW STUDIES ARE PROVIDING SOME HOPE, BUT GREAT CHALLENGES LIE AHEAD IN THE RACE TO FIND A CURE FOR MUSCULAR DYSTROPHY

RESEARCH MOVES FORWARD AFTER YEARS OF FRUSTRATION

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Source: BY JESSICA M. SCULLY, Special to the Mercury News

Sam Fogleman's best hope for life outside his wheelchair could lie in the fledgling science of genetic medicine.

The Sunnyvale 13-year-old was diagnosed with Duchenne muscular dystrophy,the most severe form of the debilitating disease caused by a genetic defect, when he was 2 1/2. The disease weakens and then kills muscle cells in the arm, legs and trunk. Eventually, it moves on to the heart and respiratory system.

Like most children his age with muscular dystrophy, Sam lost the ability to walk years ago. ''I can't do as much as regular kids,'' he said. ''I can't play sports. I can't go to amusement parks because I can't go on the rides. I can't go out as much because I'm in a wheelchair.''

No current treatments will stop Sam's disease from robbing him of his muscles and eventually leading to his death. Now, like the parents of other children with genetic disorders, Sam's father is watching developments in a controversial field -- gene-based medicine, a relatively untested treatment that may hold hope for a cure.

''I still have hope that they will come up with some kind of therapy that will slow down the progression or halt it,'' said Kent Fogleman, a seismologist with the U.S. Geological Survey. ''In his case, though, once the muscles are gone, I don't know what they'll do.''

For the past decade, researchers have been trying to use gene therapy to find a treatment for children like Sam. The therapy appeals to researchers looking for treatments for many diseases with genetic causes. While drugs may offer temporary relief from disease symptoms, gene therapy could mean a cure.

Promising human trials have been conducted using gene therapy, one for hemophilia B and another for a rare disorder in which children are born with deficient immune systems.

Faulty genetic material also causes the many types of muscular dystrophy. So gene therapy could, in theory at least, be the route to a solution for all varieties of the disease.

But problems in using the treatment for muscular dystrophy and larger concerns about gene therapy have made trials of the therapy in human muscular dystrophy patients almost non-existent.

Three recent animal studies are helping solve some of the problems in using gene therapy for the disease. Two also raise hopes that a drug could be developed to slow muscular dystrophy's progression.

Despite the advances, though, serious stumbling blocks remain, including the difficult question of how gene therapy can be administered. Scientists caution that it could be years before any kind of treatment is developed.

''We have increased our understanding of the disease, we have increased our understanding of how to get genes into cells, but we have a long way to go in terms of translating that into something that will be useful for patients,'' said Dr. Thomas Rando, director of the Muscular Dystrophy Association Clinic at Stanford Medical School and chief of neurology service at the Palo Alto Veterans Affairs hospital.

Disease rooted in genetics

Muscular dystrophy affects 250,000 Americans, about half of them children. The disease was given the name dystrophy -- which means ''without food'' --by doctors who thought their patients' muscle wasting was caused by the lack of some essential nutrient.

But faulty genes, not diet, are the real cause of the illness.

There are nine main kinds of muscular dystrophy, each caused by the genetic lack of a different kind of muscle protein. Not having the protein makes the muscles of muscular dystrophy patients weak and susceptible to damage.

As cells die, they are replaced by calcium and fatty tissue. The muscles become weaker and weaker until they are useless.

The disease's severity depends on how early it starts. Adult forms of the disease tend to be milder. But when symptoms appear in children, the disease usually leads to death. Over time, Duchenne and congenital muscular dystrophies, the two forms primarily affecting children, cause muscles to degenerate throughout a child's body. Many children with the disease are in wheelchairs before age 10 and dead of heart or respiratory failure before age 30.

Scientists discovered the faulty gene responsible for Duchenne in 1986. But ways to repair it and the other genetic defects behind muscular dystrophy have remained elusive.

Gene therapy holds promise for muscular dystrophy because it offers a way to get inside a muscle cell and correct the genetic problem causing the disease.

One way to fix a diseased cell is to use a virus, called a vector, to carry therapeutic genetic material through cell walls. As the virus ''infects''the cell, it fixes the problem gene.

But a major stumbling block in using gene therapy for muscular dystrophy has been the size of the genes for the missing muscle proteins.

Adeno-associated virus, or AAV, is considered one of the safest viruses for gene therapy.

But AAV is very small, and the genes for most muscle proteins are too large to fit into it. Even if the gene for the missing protein could fit in the carrier virus, adding it could provoke an immune system response because the person's body doesn't make the protein.

Recent breakthroughs

Three recent studies represent breakthroughs for getting inside the cells of muscular dystrophy sufferers and correcting the genetic problems.

In two studies published last year, researchers found that genetically engineered mice with different kinds of muscular dystrophy could make up for the lack of one critical protein by making more of another necessary one that their bodies already produced. Using an existing protein to replace themissing protein eliminated the threat of an immune system response.

The second study used a miniature version of the replacement gene for the critical protein, eliminating the problem of gene size. These studies also raise hopes that a drug using the same principles could be developed.

A third study, announced in December at the annual meeting of the American Society for Cell Biology, combines stem cells and gene therapy.

Researchers removed stem cells from mice with Duchenne. They corrected the problem on the gene responsible for the disease and reinserted the cells into the mice's bloodstream and muscles.

The treatment resulted in some regrowth of muscle fibers, though tests on the mice had yet to prove that the treatment has strengthened the muscles enough to alleviate symptoms of the disease.

The studies are welcome advances in research on the disease, said Sharon Hesterlee, director of research development at the Muscular Dystrophy Association.

Gene therapy, along with stem cell therapy or some combination of the two, ''is a big hope, despite all the problems associated with it, because nothing else has worked,'' she said.

The promise is even greater because an advance in one variety of the disease could help others. Duchenne, congenital and limb-girdle muscular dystrophies involve genetic problems with the same protein complex, Hesterlee said.

The complex, a group of proteins that binds together near the muscle cell membrane, is thought to prevent the kind of damage that eventually kills the muscle cells of people with muscular dystrophy, she said.

Muscle cells change shape dramatically as a muscle tenses and relaxes. The protein complex is thought to lend strength and stability to the cells, to keep the membranes from tearing, Hesterlee said. The muscle cells of people with muscular dystrophy get torn more easily than normal cells.

Eventually, the constant tearing kills the cell.

''You can see these cells have holes in them; they're sort of moth-eaten,''Hesterlee said. Anything that helps stabilize the protein complex and prevent the tearing is expected to help any kind of muscular dystrophy related to the complex, she said.

History of setbacks

The recent studies aren't the first time gene therapy has seemed a promising option for muscular dystrophy. But problems with research into gene-based medicine have stalled the development of treatments.

In August 1999, the Muscular Dystrophy Association ran a long feature about the bright future of gene-based treatments in its magazine. The first gene therapy trial for humans with muscular dystrophy started at the University of Pennsylvania that September, and researchers seemed closer than ever to circumventing the problems plaguing the treatment.

The trial used AAV as a vector against limb-girdle muscular dystrophy. But all that promise ended on Sept. 17, 1999, with the death of Jesse Gelsinger,an 18-year-old volunteer in a different gene therapy trial for an unrelated disease.

After Gelsinger's death, the Food and Drug Administration shut down his trial and several others at the University of Pennsylvania, including the muscular dystrophy trial. It was never resumed, Hesterlee said.

Exactly what caused Gelsinger's death isn't clear, and no one else was seriously harmed in the study he was part of, or any other gene therapy study. But one concern that arose was the kind of virus used in the study.

That study used adenoviruses, the kind of virus that causes colds and influenza. After Gelsinger's death, many researchers switched to AAV.

Until recently, no known side effects were associated with the virus.

But in fall 2001, two human gene therapy trials using AAV were halted because a researcher found a link between gene therapy using the virus and liver cancer in mice. The trials were later restarted after FDA officials decided there wasn't enough evidence to link the virus to the tumors.

Hesterlee said Gelsinger's death made gene therapy for muscular dystrophy more difficult in another way. The University of Pennsylvania was one of the few places where AAV was made. But after Gelsinger's death, the FDA closed down the university's virus production lab, she said. Few companies make amounts of the virus large enough for the association's needs, and many aren't interested in providing the virus

because muscular dystrophy affects relatively few people, Hesterlee said.

Trying the trial again

The association is now partnering with the University of Florida to re-create an updated version of the stalled University of Pennsylvania trial using AAV. Human trials are about a year away, she said.

Hesterlee said the University of Florida has produced a lot of data that convinces her the virus is safe, and that it is using a new version of AAV that should be more effective and even less likely to trigger an immune system response.

The stalls and delays in research have been frustrating, Hesterlee said.

When the problem gene that causes Duchenne muscular dystrophy was first cloned in 1986, ''we thought we were a year or two away from a cure, but we didn't know how much we didn't know,'' she said.

Hesterlee said it's hard to explain to families of muscular dystrophy patients why no cure has yet been found. She said she tells them, ''Look at any problem mankind has tried to conquer: We almost always eventually do it. With time and perseverance, we get there.''

Like Hesterlee, Kent Fogleman has faith that a treatment may one day be found. But he knows that it may not come in time for his son Sam.

''Gene therapy is such a long-term, difficult process, that it's not so much frustrating as just realizing that it may take many, many years before they have a viable treatment or even a cure,'' he said.

''I would call it more a realization that it's not going to come in time for him,'' Fogleman said. ''It would be better to have a kid who was just born with the disease than where we're at with it.''

Infobox:

DUCHENNE MUSCULAR DYSTROPHY

Muscular dystrophy is a genetic disorder that starts with muscle breakdowns on the molecular level. Muscle fibers are unable to get protein for strengthand they degenerate.

A child with the disease suffers muscle weakness at age 3, and weakening in the muscles in the arms, legs and trunk.

This causes difficulty in rising, climbing stairs, and maintaining balance.

Nearly all children lose the ability to walk between age 7 and 12. By the early teens, sufferers experience weakening of heart and

Respiratory muscles. Teens require assistance or mechanical support when performing activities involving the arms, legs or trunk.

By age 30, many experience heart or respiratory failure.

Other common types:

There are nine main kinds of muscular dystrophy, most with several subgroups. Duchenne is the most common variety and also the most severe. Others are extremely rare.

Congenital is the catch-all classification for dystrophies other than Duchenne that appear in children. Some cases are as severe as Duchenne and lead to death from the same causes; others are milder.

Myotonic muscular dystrophy causes muscle stiffness. People have trouble releasing muscles after contracting. It also can cause heart problems, diabetes, cataracts, intestinal and cognitive problems. Some problems are life-threatening but usually treatable. Age of onset ranges from late teens to early 30s, though it can occur in children, in whom it is most severe.

Facioscapulohumeral muscular dystrophy usually starts in the 20s. The disease causes weakness in the facial, back, shoulder and hip muscles. Scapular bones in a person's back stick out, giving them a birdlike appearance. It progresses more slowly than other kinds of muscular dystrophy, though people are usually in wheelchairs in their 30s or 40s.

Limb-girdle muscular dystrophy causes weakness in the hip and shoulder muscles. Most forms are mild, though some can be more severe. People usually begin showing symptoms in their late teens or 20s, though

symptoms can appear in a person's 40s or 50s. The most severe forms occur in children.

One sub-variety causes heart problems, but limb-girdle usually isn't life-threatening.

Source: Muscular Dystrophy Association