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Gene Therapy With a Difference

By ANDREW POLLACK

Terri Ellsworth is convinced that her 12-year-old son Billy, who has Duchenne muscular dystrophy, is being helped by an experimental drug that counteracts the genetic mutation causing his disease.

His ability to walk has not deteriorated in the two years he has been on the drug, whereas many boys with the disease would be in wheelchairs by his age. Billy opened a Gatorade bottle by himself recently, beaming from ear to ear. He even took off down an uneven dirt path without falling.

“He never would have done that, ever,” said Ms. Ellsworth, 55, a kitchen and bath designer from Coraopolis, Pa., outside Pittsburgh. “Without this drug, he would not be walking today.”

Such anecdotal reports, and data from small clinical trials, have raised hopes that a new genetic technique called exon skipping may slow the progression of Duchenne muscular dystrophy, finally yielding a treatment for which parents have prayed for decades. Scientists say the technique or related ones might also point the way to treatments for other inherited diseases, including Huntington’s.

The idea behind exon skipping is an ingenious one: a disease can be cured, or at least ameliorated, not by replacing a defective gene, as is done in gene therapy, but by correcting it.

“We’re sort of manipulating what the gene is ultimately making,” said Adrian R. Krainer, a professor of molecular genetics at the Cold Spring Harbor Laboratory.

Hopes for the new technique suffered a big blow on Friday when the results of the first large randomized clinical trial of a drug designed to induce exon skipping were announced. The drug, called drisapersen, was no better than placebo in preserving muscle function of boys with Duchenne muscular dystrophy.

The announcement was devastating to some parents of boys with muscular dystrophy and has raised questions about whether exon skipping will ever work. Could parents like Ms.

Ellsworth be seeing only what they wish to see?

But some scientists and parents of children with muscular dystrophy said it was too early to write off the technique.

“We are fully confident in the exon-skipping technology as a viable platform to develop a treatment for Duchenne, and Duchenne families should not give up hope,” Debra Miller, chief executive of CureDuchenne, an advocacy group that sponsored research on the technique, said in a statement.

Drisapersen is being developed by GlaxoSmithKline and Prosensa, a small Dutch company whose stock lost 70 percent of its value after the announcement.

Billy Ellsworth is taking a different exon-skipping drug, eteplirsen, developed by Sarepta Therapeutics. The two drugs are different chemically, and it is possible that eteplirsen may prove more effective.

Protein Malfunction

Duchenne, which affects as many as 15,000 Americans, mainly boys, is the most severe common form of muscular dystrophy, the focus of those Jerry Lewis telethons. There is no good treatment, though steroids help. Boys with Duchenne are typically in wheelchairs by their early teenage years and die from cardiac or respiratory failure in their 20s.

People with Duchenne have a genetic mutation that prevents their bodies from producing dystrophin, a protein that is a sort of coiled spring and acts as a shock absorber for muscles.

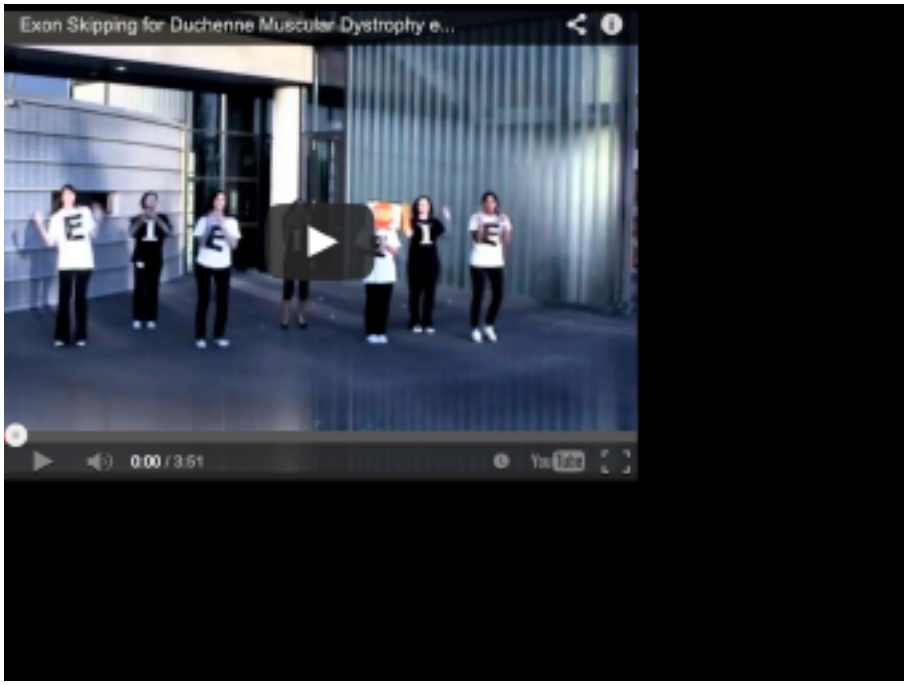
Genes contain the recipes for the body’s proteins. They exist in the chromosomes in discrete segments called exons that are spliced together in RNA to form templates for proteins. Mutations resulting in missing exons can lead to the wrong proteins being produced, or none at all.

The chemical units in RNA, typically represented by the letters A, C, G and U, are read three letters at a time, with each three-letter combination specifying a particular amino acid, the building blocks of proteins. Sometimes, a three-letter combination starts in one exon and continues into the next.

Consider this stretch of oversimplified hypothetical exons: CA-UUUU-CAA-GAAG-CC. The protein recipe would be read CAU-UUU-CAA-GAA-GCC. But if the second exon, UUUU, were missing because of a mutation, the sequence would be read CAC-AAG-AAG. The wrong

amino acids would be specified and the correct protein would not be made.

A clever, perhaps counterintuitive solution to this problem: create a drug that causes an additional exon to be deleted, or skipped, in a way that restores the proper reading. In this example, if the drug caused the initial exon, CA, to be deleted, the remaining sequence would be read CAA-GAA-GCC. The first two amino acids specified by the original sequence are missing, but the amino acids after that are the correct ones.



Video by DuchenneNederland

Exon skipping for Duchenne muscular dystrophy explained in dance.

In muscular dystrophy, this exon-skipping technique results in a dystrophin protein missing a piece in the middle. But scientists are hoping that the protein is at least partly functional.

“It’s a shock absorber,” Hans Schikan, the chief executive of Prosensa, said. “If you miss a ring in a shock absorber, it still works.”

Indeed, people with a related disease called Becker muscular dystrophy make defective dystrophin, but their condition is typically milder than those with Duchenne. Exon skipping, in a sense, is designed to turn Duchenne into Becker muscular dystrophy.

But scientists aren’t sure how much dystrophin is produced in patients taking the experimental drugs, how functional it is, or how much is needed.

Some studies have suggested that more than half of the muscle fibers of patients in the early studies produced some dystrophin after treatment with exon-skipping drugs.

Dystrophin is thought to mainly protect muscles from damage, and some experts say that restoring its production cannot be expected to reverse the injury, only to delay the time before boys end up in wheelchairs.

That suggests treatment should begin "as early as possible to minimize the damage," said Steve Wilton, a professor at Murdoch University in Australia, who helped develop eteplirsen.

The main measure used to assess the progression of Duchenne is how far a patient can walk in six minutes. Before beginning treatment, the 186 boys in the big drisapersen trial could walk an average of about 340 meters, about 372 yards, in six minutes.

After 48 weeks of injections, the distance covered by those receiving placebo was about 53 meters less, on average, while those getting the drug walked 42 meters less. The difference was far from statistically significant. In smaller, earlier trials the difference had been closer to 30 meters.

Serepta's exon-skipping drug, eteplirsen, is being studied in only 12 boys. Two lost the ability to walk soon after starting on the drug. The others though, have had an average decline of only about 20 meters, or 6 percent, over 84 weeks.

Four boys who received a placebo drug weren't able to walk as far after the first six months of the trial, but they have stabilized since being switched to the drug.

Tailoring Treatments

There are few disease-related proteins that can still function when a chunk is missing, which could limit the wider application of exon skipping. But there are related techniques that try to influence how exons are spliced together to form the final template for the protein.

Dr. Krainer at Cold Spring Harbor is trying what might be called exon inclusion, rather than exon skipping, to treat spinal muscular atrophy, a disease that can be fatal to infants.

People with the disease lack a necessary protein because of a mutation in a gene called SMN1. There is a second gene, SMN2, that could make the same protein. However, SMN2 differs from SMN1 just enough to cause one of its exons to be skipped, resulting in a dysfunctional protein.

Dr. Krainer helped develop a drug, now in early clinical trials, that can keep the exon from being skipped, hopefully restoring production of the functional protein.

Another drawback of the exon-skipping strategy is that different exons must be deleted to counter different mutations that can give rise to Duchenne. Skipping exon 51, the target of both drisapersen and eteplirsen, could help the most children — but still only 13 percent of all patients with the disease.

Theoretically, exon skipping could be used to develop treatments for 83 percent of Duchenne patients, said Annemieke Aartsma-Rus, an associate professor of human genetics at Leiden University Medical Center, where drisapersen was invented.

But that would require drugs that are able to induce skipping of 100 different exons or combinations of exons. Developing that many drugs, some for a relative handful of people, would be impractical.

For now, the question is whether any exon drug will ever be approved.

GlaxoSmithKline and Prosensa say they will continue to analyze the data from the disappointing late-stage trial and others to see if certain patients might still benefit from drisapersen.

Sarepta plans to apply for approval of eteplirsen based on the results of its 12-patient trial. If it succeeds, the drug could get to market by the end of 2014.

Parents of children with Duchenne have met with the Food and Drug Administration to plead for early approval, saying any delay would sentence more boys to wheelchairs. Ms. Ellsworth said Friday that the failure of drisapersen made it even more important for the agency to approve eteplirsen early.

But the F.D.A. may be reluctant to do that. After all, drisapersen also showed signs of effectiveness in early studies

Ms. Ellsworth said that for a long time she was reluctant to talk about Billy, mindful that most boys with Duchenne do not have mutations amenable to correction by eteplirsen.

But around April, Billy came down the stairs and jumped off the last step, landing cleanly, something he had not done before. “It was like he stuck it at the Olympics,” Ms. Ellsworth said.

She wrote about it an online discussion group for Duchenne families. The reaction was swift — and not the condemnation she feared. “You give the rest of us hope,” wrote one commenter.

That turned Ms. Ellsworth into a crusader. “I have to let the other parents know not to give up,” she said.

Given Friday’s results, however, that hope will be harder to keep alive.