The New York Times

A Disease That Makes Children Age Rapidly Gets Closer to a Cure

Progress in the quest to help progeria patients suggests that gene editing techniques may help treat other ultrarare conditions.

Listen to this article · 9:05 min Learn more

Share full article 143

John Tacket, 15, of Bay City, Mich., at a news conference with Dr. Francis Collins in 2003, announcing the discovery of the progeria gene. John died the next year. Gerald Herbert/Associated Press

By Gina Kolata
July 24, 2024

A cure for an ultrarare disease, progeria, could be on the horizon. The disease speeds up aging in children and dramatically shortens their lives. But, until recently, there was no path toward a highly effective treatment.

Now, a small group of academics and government scientists, including Dr. Francis Collins, the former director of the National Institutes of Health, is working with no expectation of financial gain to halt progeria in its tracks with an innovative gene editing technique.

If gene editing is effective in slowing or halting progeria, researchers say, the method may also help to treat other rare genetic diseases that have no treatments or cures and, like progeria, have aroused little interest from drug companies.

After a quarter-century of research, the group is approaching manufacturers and planning to seek approval from regulators for a clinical trial on progeria gene editing.

The project "has merit, but also risk," said Dr. Kiran Musunuru, a gene editing researcher at the University of Pennsylvania, who also advises a gene editing company. He cautioned that although the editing worked well in mice, there is no guarantee that it will work in human patients.

Dr. Collins first became interested in progeria while he was training in medical genetics at Yale University in 1982, almost three decades before he was appointed to lead the N.I.H. One day, he saw a new patient, Meg Casey. She was less than four feet tall, hairless under her wig and wrinkled like an older woman. She was only in her 20s.

She had progeria.

Dr. Collins was saddened and moved. Almost nothing was known about the disease, which affects just one in 18 to 20 million people. According to the Progeria Research Foundation, there are only 18 known, living patients in the United States. While Ms. Casey and others have survived into their 20s, people with the disease often live to be only 14 or 15 years old, and many of them die from heart attacks or strokes.

"I thought, 'Gosh, somebody should work on this,'" Dr. Collins recalled. "Then I went on to other things."

Nineteen years later, Dr. Collins, who then headed a federal project to map the human genome, was at a party when he was approached by Dr. Scott Berns, a pediatric emergency room physician. He told Dr. Collins that his toddler, Sam, had a fatal disease.

"I don't know if you've heard about it," Dr. Berns said. "It's called progeria."

"I do know a little bit about it," Dr. Collins replied.

Dr. Scott Berns, right, with his son, Sam, 7, and wife, Dr. Leslie Gordon, in 2003. Credit...Evan Richman for The New York Times

He remembered Ms. Casey.

Dr. Collins invited Dr. Berns; his wife, Dr. Leslie Gordon, a pediatrics resident; and 4-year-old Sam to his house. Dr. Collins spoke to Sam's parents about the disease and played Frisbee with the boy. Sam lived to the age of 17.

Dr. Gordon told Dr. Collins she was under no illusions — the disease was a curiosity, but not a research priority because of its rarity. So she, Dr. Berns and her sister Audrey, a lawyer, established the Progeria Research Foundation to support promising studies.

"There was nothing else," she said.

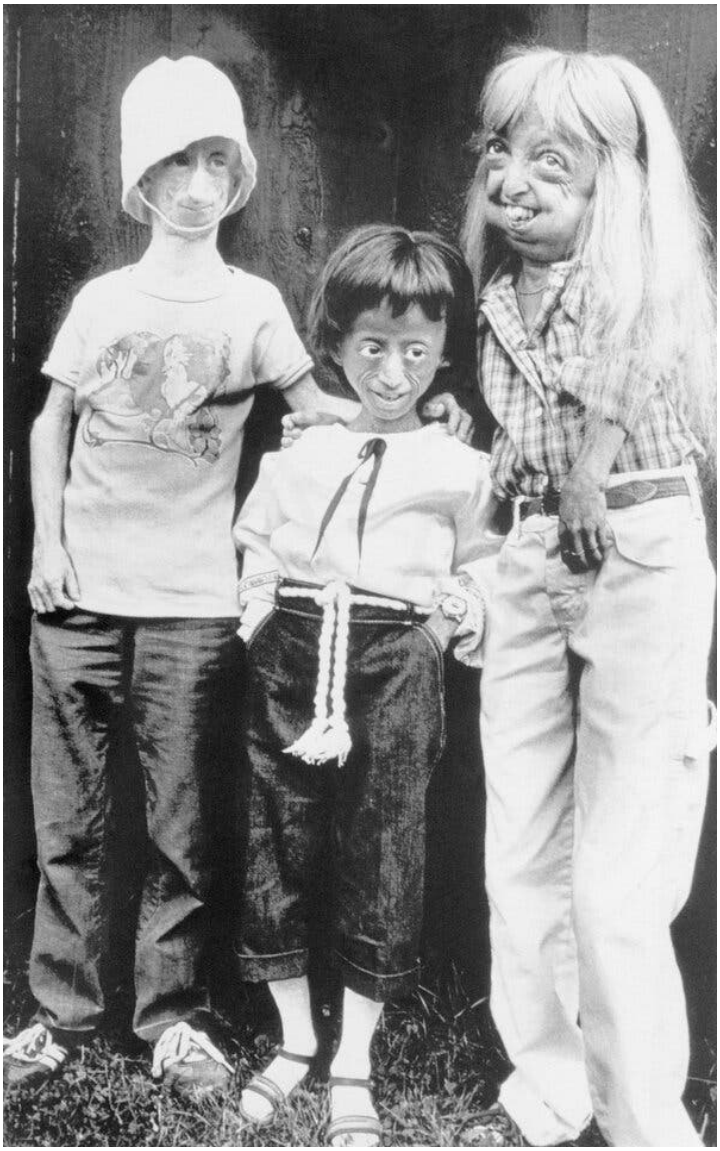
Dr. Collins was inspired. Although he was an administrator at the N.I.H., he also had a small lab and was free to study whatever he wanted. He decided to take on progeria.

But it took years, and the emergence of a new era of molecular medicine with advances in gene editing, for the prospect of a cure for progeria to seem possible.

The new types of gene editing are “potentially the answer to a dream we all want to come true,” Dr. Collins said. “There are roughly 7,000 genetic diseases for which we know the mutation.”

Of these genetic diseases, 85 percent are ultrarare, affecting fewer than one in a million people.

And among them, Dr. Collins said, “only a few hundred have treatments.”



From left, Becky Moltros, 15; Alicia Gowans, 12; and Meg Casey, 26, at a progeria conference in 1982.Credit...Bettmann/Getty

The Easy Part

Dr. Collins began by giving a new postdoctoral fellow in his lab an assignment: Find the cause of progeria.

“Let’s give it a year,” he told her.

That turned out to be the easy part. It took Maria Eriksson, the fellow, just a few months. A single letter among the string of three billion individual letters — each either a G, A, C and T — that make up human DNA was changed. In a particular spot in a gene known as lamin A, one of those letters is substituted for another. The result is the production of a toxic protein, progerin, which disrupts the scaffolding that keeps the nucleus of a cell in its proper shape.

Dr. Eriksson, Dr. Collins and colleagues published a paperexplaining the finding in 2003.

The mutation in lamin A occurs in a sperm or egg cell before fertilization. It is simply a random bit of terrible luck.

With the aberrant progerin, cells start to deteriorate after a few divisions, looking more and more unusual. Eventually, the deterioration sets off a signal in the cells to self-destruct.

The next step in the research was to put the lamin A mutation into mice. As in humans with the disease, the animals aged quickly, developed heart disease, had wrinkled skin and lost their hair. And they died young.

But it wasn’t until the emergence of CRISPR, a DNA-cutting technology, in 2012 that the small research group thought a bold new treatment could be devised. CRISPR can slice DNA and disable a gene. That, though, was far from ideal — what was really needed was something that could repair a gene.
The solution arose in 2017 from the lab of David Liu, a Harvard professor who is director of the Merkin Institute for Transformative Technologies in Healthcare. His group invented a gene editing system that acts like a pencil at the site of a mutation, using an enzyme to erase one of the DNA letters — adenine, or A — and write in a guanine, or G. That is exactly what is needed to correct the progeria mutation.
Image

Dr. David Liu and Sammy Basso, 27, currently one of the oldest living progeria patients, at a conference in Sweden last year.Credit...David Liu

That gene editing enzyme is never seen in nature. Nicole Gaudelli, who was a postdoctoral researcher in Dr. Liu's lab at the time, produced one anyway with a survival-of-the-fittest experiment: Dr. Gaudelli forced bacteria to either make the enzyme or die. (Dr. Liu is a co-founder of several gene editing companies aimed at treating more common diseases.)

Dr. Liu called the system invented by his group "base editing" because it directly edits the letters, or the bases, that make up DNA.

In one test, Luke Koblan, a graduate student working in Dr. Liu's laboratory, tried to fix the progeria mutation in patients' cells growing in petri dishes. His experiment succeeded.

Dr. Liu was thrilled. He'd watched documentaries on progeria, and the patients had touched his heart.

In 2018, Dr. Liu was invited to give a seminar at the N.I.H. He knew Dr. Collins would be in the audience, so he added a few slides on base editing cells from progeria patients.

Dr. Collins was riveted. He called Dr. Gordon to tell her what he'd heard.

"It was like a lightning bolt," Dr. Gordon said.

Here, at last, was real hope.

"I'm like, 'Oh my gosh, let's go,'" Dr. Collins recalled.

Dr. Collins at a House budget hearing in 2020.Credit...Anna Moneymaker/The New York Times

The Hard Part

N.I.H. researchers first sought to improve the health of mice with progeria. They started with a tentative single infusion of the base editor.

The results, documented in a 2021 paper, far exceeded their cautious hopes. Almost all of the damage to large heart arteries, a hallmark of the disease, was reversed. The mice looked healthy. They kept their hair. And they lived to the

start of old age in mice — around 510 days — instead of dying at 215 days with progeria.

To streamline manufacturing and minimize potential side effects of the delivery method, Dr. Liu's group had to shrink the size of the gene editor, which was too large to be delivered to cells in a single molecular carrier. That was a tall order because even the original DNA-cutting CRISPR scissors system from nature does not fit into a single such delivery mechanism.

Once they achieved the shrinking, the researchers had to test the new gene editing enzyme in mice and see if the editing was still working. It was.

Now, they are running a longer experiment to see if the mice live to old age.

While they wait, the researchers are figuring out the next steps to use their innovations to cure children with progeria. The team meets on Zoom every Monday at 4 p.m.

Their goal is to obtain permission from the Food and Drug Administration to start a clinical trial.

A key step will be finding a manufacturing partner to make the base editor for use in humans.

"We want to start this trial in two years or less," Dr. Collins said.

And if it works? If progeria base editing helps show the way for the thousands of other genetic diseases with no treatment?

"Then wow," Dr. Collins said.

Gina Kolata *reports on diseases and treatments, how treatments are discovered and tested, and how they affect people. More about Gina Kolata*

https://www.nytimes.com/2024/07/24/health/progeria-dna-base-editing.html

Imagine living inside such a body, imagining what other people are thinking.

And, once again, if there isn't big money in it, Big Pharma isn't interested. Human health is secondary at best to profits that are churned into dividends for shareholders who, the more they are rewarded, allow corporate actors to claim more rewards for themselves. Public relations and community responsibility can't even move corporations to devote resources to "good works" like this. TJB