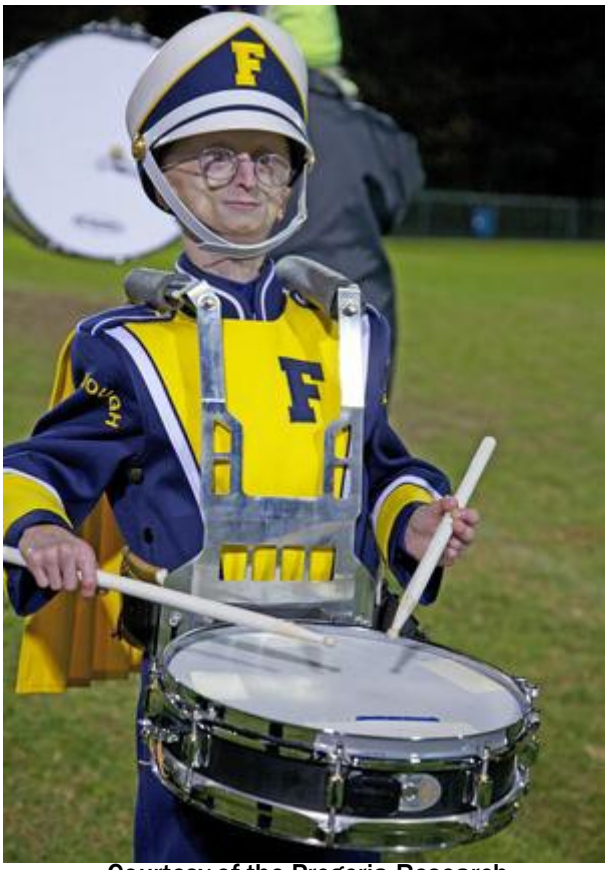
Media Highlights of the Discovery of the First-ever Treatment for Progeria

PRF funded the clinical drug trial that led to this historic announcement

Experimental Drug Is First To Help Kids With Premature Aging Disease

by JON HAMILTON
03:19 pm
September 24, 2012



Courtesy of the Progeria Research Foundation

Sam Berns, 15, who has the very rare premature aging disease progeria, plays the drums in his high school's marching band.

Researchers have found the first drug to treat progeria, an extremely rare genetic disease that causes children to age so rapidly that many die in their teens.

The drug, called lonafarnib, is not a cure. But in a study published today of 28 children, it reversed changes in blood vessels that usually lead to heart attacks and strokes.

The treatment also helped kids with the disease put on weight and it improved the structure of their bones. Children with progeria have small fragile bodies and can weigh just a third of a typical child their age.

"This is a fantastic first step," says Leslie Gordon, medical director for the Progeria Research Foundation and the mother of a child with progeria. A second study is underway to see whether combining lonafarnib with two other drugs will work even better, says Gordon, who is also a physician on the faculty of Boston Children's Hospital and Brown University.

The research that led to the drug also has led to a better understanding of how aging takes place in individual cells, Gordon says.

But perhaps the most remarkable thing about the new treatment is how fast it was developed. Just a decade ago, researchers didn't even know what caused progeria, let alone how to treat it.

The quick pace of research is in large part the result of Leslie Gordon and her husband, Scott Berns, who is also a physician.

Their son, Sam, was diagnosed with progeria in 1998, shortly before he turned two. At the time, they knew very little about progeria, which affects perhaps 100 people worldwide. And what the experts told them was discouraging, Gordon says.

"All children, we were told, die of heart attacks or strokes between the ages of maybe 7 and 20 years," she says. "Nobody knew the cause. No one was working on this and we were nowhere. There was no place for us to go to understand what was happening with our child."

So Gordon and her husband set out to find the cause of this rare disease and a cure. They started a foundation. Gordon began doing research on progeria. But things might have gone slowly without some help from a scientist named Francis Collins.

Collins is not just any scientist. These days he runs the National Institutes of Health. Back then he was in charge of the government's effort to map the human genome. And early in his career, Collins actually cared for a patient with progeria.

"It was a fascinating circumstance but a very frustrating one because there was nothing much known about the disease," he says. "So I didn't quite know what to offer this wonderful young woman."

The woman died in her 20s. But Collins never forgot her. "And then I met Leslie and her husband Scott and learned that they had a son with this condition," he says.

So Collins joined a consortium of genetic scientists set up by Gordon's foundation. He also asked a researcher in his lab to look for a genetic cause of the disease. He gave her a year.

"And in substantially less than a year we had the answer," Collins says, thanks to "a combination of a very good post-doc, a pretty good strategy, and a little good luck along the way."

The cause was a single, chance mutation on a single gene. Just one misplaced letter out of billions in the genetic code was leading to the production of a toxic protein that makes cells age prematurely.

Finding the cause of a genetic disease does not necessarily lead to a treatment. But in this case, Collins says, scientists had spent decades studying the gene where the error occurred.

"And it was really within only a short time after realizing what the problem was that we were also able to make a hypothesis about what might help," Collins says

All that happened about five years after Leslie Gordon's son Sam was diagnosed. And by this time, Sam was in grade school and living a pretty normal life, Gordon says.

"Sam was acting like his age. And he had friends his own age," she says. "He was just much, much smaller than the rest of his friends and, yes, he had no hair. But that doesn't matter to your friends. And so he was going to school and growing up and doing, actually fantastic."

Even so, Gordon knew she was in a race against time.

At this point, researchers thought they knew what sort of drug might protect cells from the toxic protein that causes progeria. Developing a drug like that from scratch could have taken many years.

But by chance, pharmaceutical companies had some drugs that looked like good candidates already in production. These were experimental cancer drugs that just happened to affect the same process involved in progeria.

"Again, we got lucky because there was 10 years worth of pharmaceutical research into developing a drug that we asked to be moved over into the field of progeria," Gordon says.

But the progeria team needed help from someone who understood these unusual cancer drugs. Enter Mark Kieran, a pediatric brain cancer specialist at Boston Children's Hospital and the Dana Farber Cancer Institute.

"There were only a couple of people in the world that had been testing these drugs and one of them was me," Kieran says."

By the time Kieran got involved around 2006, researchers had already shown that a drug called lonafarnib could help mice with the progeria gene.

"They now had all of the science," Kieran says. "What they had never done before was actually figure out how to move it into the clinic to treat kids. And since that's what I do everyday, that's where we were able to kind of put our expertise together to make this thing happen."

It happened fast. The study began in 2007 and was designed to run for several years. It included 28 children from 16 countries, including Leslie Gordon's son, Sam.

The results appear in the Proceedings of the National Academy of Sciences and they are encouraging. Overall, lonafarnib helped children gain weight and improve their bone structure. But more important, Gordon says, it has reversed changes in blood vessels associated with the heart attacks and strokes that usually kill kids with progeria.

"That was an absolutely homerun pivotal finding for our study," she says.

This drug isn't a cure. But it's an important first step, Gordon says. And she notes that researchers have already moved on to a second study using lonafarnib and two other drugs.

The race against progeria has been run to benefit just a few dozen children around the globe. But there's been an unexpected payoff for the rest of humanity. Research on the toxic protein responsible for progeria is changing scientists' understanding of how normal cells age.

"It has told us something pretty profound, namely that all of us are making little bits of this same toxic protein," Collins says. "Kids with progeria are making a lot. We're making a little bit. And as our cells get older and older they start making more."

So as some researchers focus on progeria itself, others will be looking for ways to use this new information to ward off a range of diseases associated with aging.

As for Leslie Gordon's son Sam Berns, he's almost 16 now, working to become an Eagle Scout and likes to play percussion in his school band.

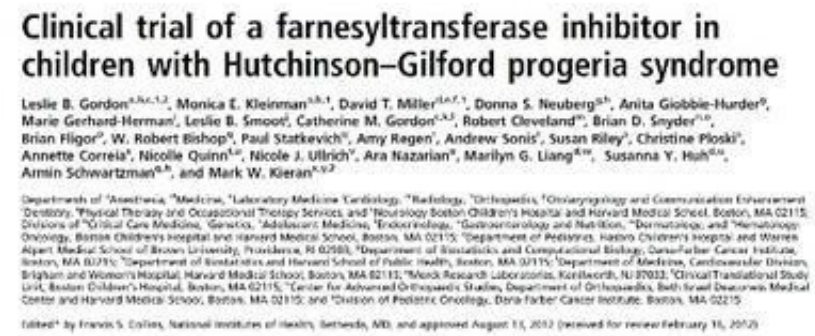
"For marching band I play the giant timpani drums," Sam says. "So that's a lot of fun. And I do a little bit of snare and bongos."

Progeria often means finding a different way to do what other kids are doing, Sam says. But the disease rarely stops him.

"We designed a new snare drum that's a lot lighter and more comfortable for me," he says. "So we always keep my health in mind. But 99.9 percent of the time I get to do exactly what I want."

Sam says the most important thing people should know about him is that he has a great family and a very happy life.

Hard Work and Dedication by a Non-Profit is Starting to Pay Off for Patients with Progeria



Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson–Gilford progeria syndrome

Leslie B. Gordon, Monica E. Kleinman, David T. Miller, Donna S. Neuberg, Anita Giobbie-Hurder, Marie Gerhard-Herman, Leslie B. Smoot, Catherine M. Gordon, Robert Cleveland, Brian D. Snyder, Brian Fligor, W. Robert Bishop, Paul Statkevich, Amy Regen, Andrew Sonis, Susan Riley, Christine Ploski, Annette Correia, Nicolle Quinn, Nicole J. Ullrich, Ara Nazarian, Marilyn G. Liang, Susanna Y. Huh, Armin Schwartzman, and Mark W. Kieran

Oct 3 2012
Last week in PNAS, Gordon et al [1] published a phase 2 clinical trial showing lonafarnib to improve several outcomes in children with progeria, a disease that currently has no treatment or cure. Here at Rare Disease Report, we enjoy sharing stories like this one because it has two very positive aspects. First, the story involves the results of a new clinical trial that provides hope for patients with a fatal rare disease. Second, it shows the dedication parents and non-profits have in the rare disease community to get things done when all seems lost.

Let's start with the clinical trial. Progeria, also known as Hutchinson-Gilford Progeria Syndrome (HGPS), is a rare, fatal genetic disease characterized by an appearance of accelerated aging in children. All children with Progeria die of the same heart disease that affects millions of normal aging adults (atherosclerosis), but instead of occurring at 60 or 70 years of age, these children may suffer heart attacks and strokes as early as age 5 years, with the average age of death at 13 years.

Every child completing the study showed improvement in an ability to gain additional weight, increased flexibility of blood vessels or improved bone structure. Results included improvement in one or more of the following areas:

***Weight*:** One in three children demonstrated a greater than 50 percent increase in annual rate of weight gain or switched from weight loss to weight gain, due to increased muscle and bone mass.

Bone Structure: On average, skeletal rigidity (which was highly abnormal at trial initiation) improved to normal levels after FTI treatment.

***Cardiovascular*:** Arterial stiffness, strongly associated with atherosclerosis in the general aging population, decreased as well. Pulse-wave velocity decreased overall by 35 percent, and vessel wall echodensity also improved with treatment.

While more studies are needed, these results are very promising in that it provides much needed hope for families struggling with the realities of this disease. The second part of this amazing story is that this study is a great example of how a small non-profit organization can help stimulate and translate basic biomedical and genetic research into human treatment.

The power of a non-profit organization

Dr. Leslie Gordon

The Progeria Research Foundation was founded in 1999 by Dr. Leslie Gordon and Dr. Scott Berns, after learning that their child had Progeria. And yes, it is the same Dr. Gordon who is first author of the study. In addition to being a parent, she is also a leading researcher at the Boston Children's Hospital. Since its inception, PRF has funded studies leading to the discovery of the gene responsible for Progeria, the development of animal models for Progeria, and finally, a clinical trial involving 28 children from 16 countries that came to the Boston Children's Hospital every 4 months over the course of the 2 year trial. And what was even more astonishing, those 28 children represented 75% of the known cases of Progeria at the time of the trial (2007).

As for the future, PRF remains optimistic that lonafarnib will prove to be beneficial to patients with Progeria but it is also not content to rest after completing that one study. More trials with lonafarnib are being conducted and PRF has registered lonafarnib with the FDA as an Orphan Drug. PRF is also conducting studies in more Progeria patients (n~45), from various countries (n=24) with other medications. Thanks to this small, family oriented non-profit organization, treatment for children with progeria will come much sooner than anyone previously thought possible.

Reference

1. Gordon LB, Kleinman ME, Miller DT, et al. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson-Gilford progeria syndrome. PNAS 2012 Sep; [Epub ahead of print].

THE WALL STREET JOURNAL.

Drug Shows Promise for Rapid Aging in Kids

Updated September 24, 2012, 3:32 p.m. ET

By AMY DOCKSER MARCUS

A drug first developed for cancer has shown promise as a treatment for progeria, a rare and fatal rapid-aging disease in children, and it may have implications in treating cardiovascular problems associated with normal aging.

In a paper published Monday in Proceedings of the National Academy of Sciences, scientists reported results after a 2½-year trial of 28 children who took Merck MRK +0.69% & Co.'s lonafarnib. The drug appeared to slow, and in some cases reverse, damage caused by the disease, including arterial stiffness, which also is linked to heart problems in the normal aging population.

Aaron Vincent Elkaim for The Wall Street Journal

Devin Scullion, 16 years old, has been undergoing an experimental therapy for his condition called progeria, a rare fatal rapid-aging disease that kills children at an average age of 13.

Although the number of participants in the study is small, the disease is so rare that the children represented 75% of the known cases of progeria in the world at the time they enrolled in the trial at Boston Children's Hospital in 2007.

Children with progeria, also known as Hutchinson-Gilford Progeria Syndrome, die of heart attacks or strokes at an average age of 13 because of the accumulation of a protein called progerin.

Researchers have long wondered whether progeria might offer clues into the normal aging process. Over the past few years, papers have been published demonstrating that progerin, a mutant form of the Lamin A protein, which is critical in organizing the genome inside the body's cells, accumulates in everyone as they age. The thinking is that a drug that mitigates cardiovascular problems in children with progeria might also affect cardiovascular problems more broadly.

"More data suggests that this mechanism at least in some cases may be related to things that happen in normal aging, and the study is of interest in that regard," said Brian Kennedy, president and chief executive of the Buck Institute for Research on Aging in Novato, Calif. Dr. Kennedy has tested other drugs

for progeria and normal aging and wasn't involved in the lonafarnib study. "I also think for progeria this is an encouraging start."

None of the researchers involved in the trial think lonafarnib alone will arrest the disease, and the results raised questions that need to be addressed. For example, although all the children benefited from the drug, they didn't all benefit the same way, and researchers aren't sure why.

Aaron Vincent Elkaim for The Wall Street Journal
Devin Scullion sat in his bedroom in his home in Hamilton, Ontario.

Nine children showed greater than a 50% increase in annual rate of weight gain, a statistically significant result, but six children lost weight, perhaps because of disease progression or side effects of the medicine. Children also showed improvement in hearing, skeletal rigidity or cardiovascular changes such as decreased arterial stiffness and improved vessel-wall density. But researchers can't predict or explain yet why someone benefits in one area but not another.

"The drug prevents the abnormal protein collecting in places where it seems to do the most damage, but it doesn't stop the abnormal protein from being made," said Mark Kieran, principal investigator in the trial and director of pediatric medical neuro-oncology at the Dana-Farber/Children's Hospital Cancer Center in Boston.

Dr. Kieran said another trial, involving a cocktail of lonafarnib and two additional drugs, is under way at Boston Children's Hospital to try to achieve even greater benefits and that a fourth drug is being tested in mice and may be tried in the children in another trial.

Leslie Gordon, medical director of the Progeria Research Foundation, which raised $2 million to fund the lonafarnib trial, said the foundation plans to ask the Food and Drug Administration to approve the drug for use in progeria because of the results released Monday. Dr. Gordon is an author of the paper published Monday and the mother of a child with progeria.

A spokeswoman for Merck said the company is supporting the filing and has agreed to supply the drug "for the foreseeable future," but the company isn't pursuing development of the drug more broadly. Merck developed the drug for cancer, but it failed to show efficacy in a trial with patients with advanced head-and-neck cancer.

Francis Collins, director of the National Institutes of Health and one of the discoverers of the gene that causes progeria, said the drug's usefulness for vascular stiffness in normal aging is an important question to study. But the drug "hits a lot of targets, and one concern is to make sure you are not inducing an untoward effect in people who are not as severe as kids with progeria," Dr. Collins said. He said his lab is

testing a form of the drug rapamycin in mice with progeria that could eventually be tried as part of a drug-treatment cocktail.

The Buck Institute's Dr. Kennedy led a team earlier this year that found that another form of rapamycin was effective in increasing the life spans and improving symptoms in mice with two different diseases caused by other mutations in the progeria-connected Lamin A gene. Rapamycin also is being studied for its impact on the normal aging process.

Jamie Madley of Hamilton, Ontario, said her 16-year-old son, Devin Scullion, a high-school junior, was part of the lonafarnib trial and is part of the continuing triple-drug-cocktail trial. Devin has had arthritis since the age of 2 and suffered two major strokes when he was 6. He uses a walker to get around. Ms. Madley said Devin has shown improvement in the trials. He weighed 23 pounds at the start of the lonafarnib trial and is now up to 31 pounds. She said his eating habits, energy level and sleep also have improved.

When Devin was born, said Ms. Madley, she was told there were no treatments for progeria. "Now at least there is hope," she said. "We got our foot in the door."

CNN Health

Advances in kids' early aging disease

By Sandra Young. September 25, 2012: 11:52 AM

(CNN) – Four months after his birth in Hamilton, Ontario, Devin Scullion was diagnosed with one of the rarest diseases known to humans.He was born two months premature, and his mother, Jamie Madley, said she knew right away something was wrong.
"He was big for a preemie," Madley said. "His joints were tight, his movements were robotic, his skin was thin – you could see his veins everywhere. I just didn't know what it was."
Devin's doctors were also baffled, she said, surmising he might have a dermatological problem or a lack of calcium.

But Devin had a genetic condition called Hutchinson-Gilford progeria syndrome, also known as progeria, which causes premature, accelerated aging. Children with the disease have a genetic mutation that causes them to produce the protein progerin, which blocks normal cell function.
Progeria affects approximately one in every 4 million to 8 million infants. There are only about 200 children living with the disease worldwide. There is only one other child in Canada with the disease, according to Madley.

As they age rapidly, these children suffer from a loss of body fat and hair and an inability to gain weight. They are prone to developing osteoporosis, a disease where bones become weak and are more likely to break.

According to the National Osteoporosis Foundation, most girls develop about 90% of their bone mass by age 18 and boys by age 20.
Building strong bones during childhood helps prevent osteoporosis in adulthood. This is why children with progeria have such issues with bone density and rigidity.
Heart disease due to atherosclerosis, also known as hardening of the arteries, is a critical problem for children with progeria. These children can have heart attacks or strokes as early as age 5. Most die of heart disease by age 13.

However, encouraging results from the first clinical drug trial for children with progeria has researchers hopeful that the first treatment for the disease could be on the horizon.
When Devin was diagnosed, the cause of progeria was unknown and the prognosis was bleak.
"There wasn't much information. It was pretty much, 'There's nothing we can do for your son, take him home and enjoy him while he's there,'" Madley said.

"There was pretty much no hope. There really wasn't any kind of medication. I did what I could – I put him on a diabetic diet, had him on vitamins."
Doctors told her the life span for a child with progeria was about 13 years, but Devin would likely live about 7 years.
That was 16 years ago. There have been ups and downs. When Devin was 6, he suffered two strokes just three weeks apart. He fought through paralysis and hip dysplasia, and had to learn how to walk again.
But much has happened in the past 16 years. In 2003, Dr. Francis Collins and his team of researchers at the National Human Genome Research Institute at the National Institutes of Health discovered the gene that causes this fatal disease.
Now, results from the first clinical drug trial are offering hope for researchers, children with progeria and their parents.

The drug, called Lonafarnib, was originally developed by Merck & Co. to treat numerous adult cancers and pediatric brain cancer. For the past 2½ years, 26 children with progeria from 16 countries took Lonafarnib orally twice a day. Devin Scullion is one of those children.
Researchers say every child in the study either gained weight or showed improvements in bone structure or arterial stiffness. Side effects from the drug were manageable: upset stomach, weight loss and diarrhea. No one dropped out of the study as a result.
The results, published Monday in the Proceedings of the National Academy of Sciences, are called exciting by researchers.

"It's huge," said Dr. Leslie Gordon, lead author of the study and medical director of the Progeria Research Foundation. "Progeria has always been a 100% fatal pediatric disease for which there was not treatment. "Now, we not only have our first treatment, but we know for the first time that some aspects of the disease can be improved, and this inspires us to work harder and faster toward additional treatments for progeria that could hopefully work in conjunction with Lonafarnib to make a difference in the health of children with progeria."

Gordon is also a scientist on staff at Boston Children's Hospital where the trial was conducted. Her 15-year-old son, Sam Berns, has Progeria. Gordon said the results give her hope that a cure is possible.
"I think that we have just sort of just broken open the first of many possibilities here for the children," Gordon said. "It is possible that some systems affected in Progeria may be resistant to treatment. But if a cure means getting rid of progerin and really affecting the cardiovascular system in a big way so that these children live longer lives, then trials gives us a lot of hope. I think we can do this for the children and I think it's what the children deserve."

Dr. Mark Kieran, director of pediatric medical neuro-oncology at Boston Children's Hospital and Dana Farber Cancer Insititute, is the principal investigator of the study.

In general, the weight gain seen among patients was small, but still measurable, he said. The real surprise was the reduction in stiffness and thickness of major arteries, which decreased 35%, according to the study.
"The fundamental question is whether this treatment is actually going to extend the life span of these kids," Kieran said. "This is a hard question to answer, because you will have to treat them for years and years before you would know that.

"The fact that you can see a number of things getting better, particularly some of the cardiovascular parameters, is pretty exciting and gives both us and the families hope that we're on the right track."
So far, that track has led to another trial. Researchers are two years into a second study involving 45 children from around the globe, including 20 of the original participants, Kieran said.
Scientists have added two more drugs that attack the abnormal protein in a different way. Researchers have also identified another 35 children with progeria, making a total of 80, and there are plans for a third trial that will include these children and a fourth drug.
"It's incredibly fast when you think that the mutation causing this disease was discovered less than 10 years ago," Kieran said.

But even that optimism is tempered. More research is needed, Gordon said.
"We will not know whether heart attacks, strokes or longevity are influenced by this very short study," she said. "We may need another 10 years to determine if heart attacks, strokes and length of life are influenced by Lonafarnib.

"The key thing is that, for the first time, we've shown that some aspect of the cardiovascular disease can be improved in Progeria, and we never knew that before. Whether this will translate into fewer heart attacks, strokes or greater longevity we won't know for a very long time."
Dr. Francis Collins, whose discovery of the gene led to the current advances, agreed.

"It's an encouraging development," he said. "Ten years ago, we had no idea what caused this disease ... in a rather dramatically accelerated period of time, we have evidence of a treatment that seems to provide benefit.

"But let me be clear, this is not a cure," he said. "These children are not suddenly going to have a life like any other kids. We still have a lot to do before we will know if we are really prolonging life and reducing serious medical problems."

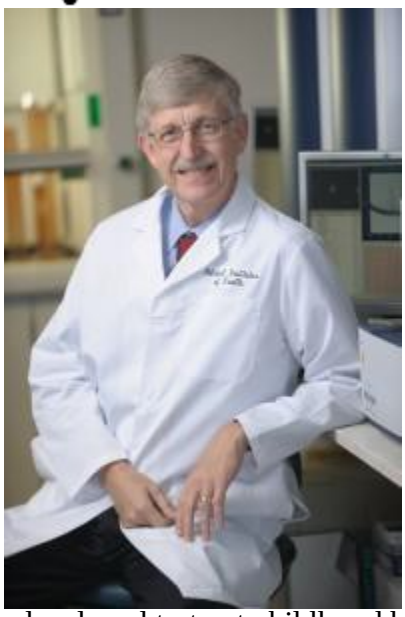
Still, Collins said, what has happened so far is pretty remarkable.
"Oftentimes this kind of progress takes two decades or more. It's almost unprecedented that researchers went from discovery of the cause to starting a clinical trial just four years later. One of the lessons is the value of looking for new uses of drugs that have already been developed for some other disease and are already known to be safe in humans.

To inspire similar success stories, he said, the National Institutes of Health and the drug industry have recently partnered to "crowd source" the potential to repurpose drugs, "effectively teaching old drugs new tricks."

According to Collins, the need is great. There are 4,700 diseases where molecular causes have been discovered, mostly within the past 10 years, he said. But only about 250 of them are treatable.

"This encouraging example from progeria, one of the rarest of all human diseases, should give a shot in the arm to make this therapeutic story happen again and again," he said.
Madley feels the clinical trial gave Devin a "shot in the arm." He's participating in the second study and while she doesn't have his individual trial results yet, she knows the drug has helped him.
"He's doing great, much better than before the trial," she said. "His energy level is higher, it's easier to get him up, his eating habits changed, he eats a lot more. They don't need to tell me that his cardiovascular has improved, I know it. He's more active, moving better – he still uses his walker, but not as often."
He also has gained weight. The 4-foot-tall high school junior weighed 23 pounds when he started the trial. Now, he's up to 31 pounds.
"It's huge. It's a miracle," Madley said. "I feel I'm going to have him longer, I really, really do. I feel I may see him become a man. That would be more than words could describe. I never thought I would live to see this. ... He's already talking about going to college, getting out in the world and getting a job."
Devin has new hope, she said. "He's got dreams. He wants to be a pilot. He wants to fly planes. His saying is, 'Dream big or go home.'"

PLOS | BLOGS



Wednesday, October 17, 2012 | Genetics in context

From Rapid-Aging to Common Heart Disease

By Ricki Lewis, PhD
Posted: October 11, 2012

Francis Collins, MD, PhD, Director of the NIH, began pursuing a treatment for progeria early in his career.

Last week the dna science blog looked at how Dr. Francis Collins became involved in the quest to discover the genetic defect that causes the rapid-aging disorder Hutchinson-Gilford progeria syndrome. Preliminary results of a possible drug therapy — one originally developed to treat childhood brain cancer — were about to be published. Dr. Collins isn't on that paper, perhaps sidetracked with things like running the NIH.

We All Have Progerin

Between the progeria gene discovery in 2003 and the recent repurposed drug news lies perhaps the most important paper of all: a 2010 report comparing the arteries of two children with progeria who'd died of heart attacks – a girl just under age 10, and a boy aged 14 – to blood vessels from 29 people.

Not only did the researchers find progerin – the stunted protein at the root of progeria — in the arteries of normal individuals, but they calculated that build-up in nuclear membranes increases at the rate of 3.34% a year. A one-month old had progerin in one out of 1,000 blood vessel cells; a 97-year-old had 20 cells per thousand bogged down with progerin. The protein was even in people without cardiovascular disease risk factors (CVD).

Dr. Collins explained the significance of the finding. "We've learned that the same pathway that is activated strongly and prematurely in kids with progeria is also happening in you and me. That toxic protein they make from the beginning is also in our cells as we approach senescence. So cell senescence is not just a running down of the system – it's an active process. A signal turns on this protein."

And that aging signal, Dr. Collins added, is connected to the shortening of the chromosome tips that serves as a cellular clock. So the glimpse into aging the kids with progeria provide may have illuminated a new risk factor that can damage blood vessels even in a star athlete who eats only broccoli.

A Repurposed Drug

The beauty of identifying a gene that causes a disease when mutant is that it provides a target. Genetics offers precision.

Leslie Gordon, MD, PhD, who founded the Progeria Research Foundation (PRF) and is first author on the drug paper, remembers the gene discovery. "We didn't have any idea that finding the gene mutation would do what it's done for us, but we knew it was very, very important." Soon after, the PRF broadened its mission: *"To discover treatments and the cure for progeria and its aging-related disorders."*

Once researchers knew the enemy — progerin – the hunt for a treatment began. A class of drugs called farnesyl transferase inhibitors looked like they'd compensate for the basic defect in progeria, which is inability to remove a small organic molecule called farnesyl from one end of a protein called lamin A. The progeria community lucked out, for lamin A was well-studied and already known to be behind several muscle and heart conditions. "The minute we found the gene mutation, we brought in great lamin biologists and learned all about what could be going wrong," Dr. Gordon recalled.

Their luck continued when some of the biologists mentioned that Schering-Plough, now Merck, had been working for a decade on farnesyl transferase inhibitors and had already spent millions. Farnesyl enables the most common oncoprotein, ras, to alter cell signaling in a way that causes cancer. But ras finds its way around the drugs, and they failed in combating childhood brain cancer.

"Merck saw a chance to do something for children with progeria and they jumped at it. They supplied the drug at no cost. We approached Dr. Mark Kieran, who was conducting clinical trials with the drug on kids with brain cancer. He'd never seen progeria, so we invited him to a meeting, and he jumped right in," said Dr. Gordon.

Dr. Kieran, a pediatric neurooncologist at Boston Children's Hospital and the Dana-Farber Cancer Institute, picked up the story.

"When Francis Collins discovered the progeria mutation and found that the defect wasn't an alteration in the encoded protein, but loss of a splice site that allows the molecule to remove its farnesyl site," that suggested a drug mechanism. "Since there's no way to fix the mutation, maybe we could prevent the abnormal molecule from adding on the farnesyl group, prevent the molecule from moving up in the nuclear membrane and getting stuck there and causing progeria. Would the farnesyl transferase inhibitors I was testing in kids with brain tumors prevent the toxic effects of progerin?"

Clinical Trial Brings Elderly Kids From All Over

The PRF found 96 kids from 40 countries, and 25 of them have completed at least two years of the ongoing first clinical trial, testing the drug lonafarnib. “They were incredibly courageous. They trust us. They have to sign 40-page consent forms every 4 months. Some of these people have never been on a plane, and it takes them two days to get here. It was an unbelievable experience and privilege,” Dr. Gordon said.

“Many of the families had never seen snow. They have different cultures, languages, climate. It makes you aware of how different yet how similar we all are,” added Dr. Kieran.

So how do you test a drug to treat a disease that affects one in a million kids, striking them down with a heart attack or stroke? Using a placebo is unthinkable, and there are too few kids to worry about statistically significant sample sizes anyway. The researchers devised a clever approach: track weight. “Each child served as his or her own control. These kids just stop growing at age 3. The curve is close to flat. So we predicted that if the drug really worked, we’d see an upturn in the rate of weight gain,” Dr. Collins explained.

And that’s what they saw: 9 of the 25 children had a greater than 50% increase in the rate of weight gain. In 6 kids rate of weight gain fell, possibly due to drug side effects of nausea and diarrhea. For ten kids, weight stabilized.

But what really excited the research team were the cardiovascular changes.

The researchers used a technique called pulsed wave velocity to assess stiffness of the arteries, because this is gentler than cardiac catheterization for these very fragile children. “Stiff arteries are a characteristic of the advanced atherosclerosis in these kids and older people with the same problem. Not only did we see the stiffening stop getting worse, but it got better!” said Dr. Collins.

Disease reversal appeared in echocardiography too. “The thickness of the carotid is considerably greater than it should be for a child this age, but the thickness reduced over the 2 years. That was unexpected and may be the most encouraging part of the trial,” Dr. Collins said. Some of the kids also developed stronger bones and better hearing.

In fact, each patient improved in some way. And while some people pointed out that the results were incremental, possibly even “no ise, ” I think that even small signs of improvement in an otherwise untreatable disease, based on countering the underlying disease mechanism, is a leap forward.

The researchers are careful to temper their excitement. “The only thing we can say now is we make parts of the cardiovascular system get better on the drug and assume cardiovascular risk will go down because

of it. But what we think and what we believe are not the same as knowing. Time will tell," said Dr. Kieran.

More kids have signed up for expanded clinical trials, which will test three additional drugs that have had promising results in mice, over at least the next dozen years.

Dr. Kieran put it all into perspective. "When we think that less than 10 years ago we didn't know what this disease was … we didn't know the gene, the protein, the molecule. And in 10 years we're already going to a treatment that may change the course of the disease. The hope is that all four drugs will begin to make the rapid and significant changes needed to help kids in the long term."

And when gene variants are discovered that track with progerin-mediated cardiovascular disease, a once-discarded drug candidate may find a huge new market, a possibility clearly not lost on the folks at Merck.

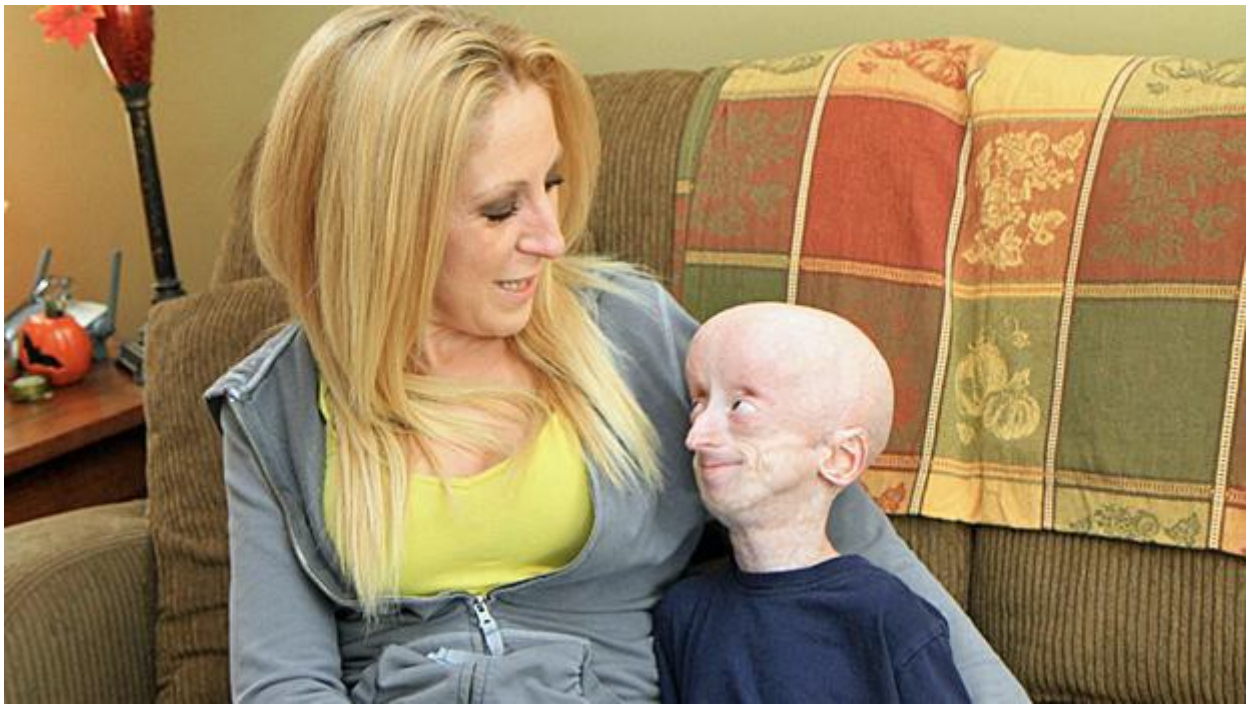
"Should we all start taking lonafarnib? No. But for researchers who want to understand healthy aging, and have a better chance to help those in whom aging is happening sooner than it should, we now have a conclusive study in which a rare disease turned out to provide good insight into a molecular mechanism," said Dr. Collins.

The continuing story of conquering progeria is a glorious illustration of the value of basic research in discovering how something happens – and that's the heart and soul of science.

CBC | Hamilton

Progeria research gives hope to Hamilton teen

By Samantha Craggs: September 28, 2012, 7:36 AM ET



2 Jamie Madley and her son Devon Scullion are heartened by new advancements in progeria research.

It's being hailed as a scientific advancement in an otherwise mysterious illness, and a Hamilton teen is a part of it.

Devin Scullion, a 16-year-old Mountain resident, is part of a more than two-year drug trial proven to alleviate some of the symptoms of progeria, a disease that causes rapid aging in children.
When Devin was born, doctors told his mom Jamie Madley to essentially “take him home and enjoy him while he's here.” So the advancements are a ray of hope for the family.

“It's encouraging to see him as healthy as he is,” Madley said. “I believe without this trial, he wouldn't be here.”

Madley first noticed a difference in Devin in August 1996, when he was born two months premature and still weighed more than four pounds. He also looked different from other babies in the nursery.

In some respects, he advanced quickly. He gained weight like an ordinary baby. When he was four months old, he could hold onto her fingers and walk.

Rare disease

Then came the diagnosis. Madley still remembers how old he was - “four months, three weeks, two days.”

“Progeria is so rare that only about 200 children in the world have it. There are only two in Canada,” Madley said.

It causes decreased muscle and bone density and makes children prone to heart attack and stroke, which is how most of them die.

Because of its rarity, little was known about the disease in 1999, when the Progeria Research Foundation was formed, said Dr. Leslie Gordon, the foundation's founder and medical director.

“There was nothing out there - no research, no resources, no place to go,” Gordon said. “There was absolutely no prospect of treatment and no understanding of what the disease was.”

Reduces hardening of arteries

Because of this, Madley and Devin were happy to take part in the drug trial at Boston Children's Hospital.

“We were excited,” Madley said. “Whether or not it worked, somebody was doing something.”

Progeria causes a loss of body and bone mass. Children with progeria usually die from heart attack or stroke.
While the drug has not caused the weight gain researchers hoped, it has reversed the hardening of arteries by 35 per cent.

Ordinarily, a child with progeria may have vascular stiffening like that of an 80 or 90-year old.

“This brings it down to what a 40-year-old's would be,” Gordon said.

Originally a cancer drug

The drug, Lonafarnib, was originally developed to treat pediatric brain cancer. But it proved ineffective, said Dr. Mark Kieran, director of pediatric medical neuro-oncology at Boston Children's Hospital and Dana Farber Cancer Institute.

The current trial, which involves about 26 kids with progeria, involves taking two pills a day for the last two and a half years.

There are some side effects, such as nausea and diarrhea. But the benefits have been worth it, Devin said. His weight has increased from 24 to 31 pounds, and “I feel a lot healthier.”

Two more trials are about to start, one that combines three drugs and another that combines four. Money for the research is fundraised through campaigns. That includes everything from road races to online donations, Gordon said.

“There are a lot of supporters out there willing to get behind these kids.”

Biological clock

There is reason for the world at large to pay attention to progeria research, Kieran said. Researchers have discovered that everyone creates a small amount of perogeron, which “stays in our cells and tells us how old we are.

“What is the biologic clock that tells your cells when it's time to stop living?” he said. “Many people believe progeron may be a part of that.”

Progeria aside, Devin is “a normal 16-year-old,” Madley said. He attends Cardinal Newman high school. He collects model airplanes and likes to play video games.

This advancement “is nothing short of a miracle,” Madley said. “It's amazing how far we've come in 12 years.”

The results of the study were published this week in the journal Proceedings of the National Academy of Sciences.

Dcut/1 Syndtome
*r*ovndat\on

Saving li\es thwugh education. advances in treatment. and fmding a cun:for Barth t--yndrome.

September 26, 2012

Audrey Gordon, Esq.
Progeria Research Foundation
P.O. Box 3453
Peabody, MA 01961-3453

Dear Audrey,

Congratulations! We at the Barth Syndrome Foundation are elated to hear about the promising results shown during the recent Progeria clinical trial. What an exciting and remarkable accomplishment in such a short amount of time. Please know that we are sharing in your joy: cheering for the fumilies, the foundation, the doctors, the scientists, and for everyone who loves a child with Progeria This is a prime example of effective translational research; originating from the concern/anguish of parents and involving the dedication and hard work of many professionals and individnals. Thank you for paving the way for other rare disease/disorder communities like the Barth Syndrome Foundation.

Sincerely,

Lindsay Groff

Lindsay B. Groff, MBA
Executive Director

Lindsay· B. Groff, Executive Director
Barth Syndrome Foundation, Inc.
P.O. Bm. 618 / Larchmont. NY 10538 / Phone:*(850)* 223-1128/ E-mail: lind.">a).grofPO;barth.syndrome.org