

# NEWS

SPECIAL EDITION



June 2007: All eyes are on Megan as she becomes the first child with Progeria to take lonafarnib.

## WE DID IT!!

### First-ever Treatment for Progeria Discovered!

History has been made! Every child in the first-ever Progeria clinical drug trial showed improvement, making the FTI drug **lonafarnib** the first known treatment for children with Progeria.

The clinical trial showed that lonafarnib significantly improved participants' rate of weight gain, bone structure, hearing and/or vascular stiffness. The vascular finding is the most exciting - improving the cardiovascular status of children with Progeria is critical, as heart attacks and strokes are the ultimate cause of death.

"To discover that some aspects of damage to the blood vessels in Progeria can not only be slowed by lonafarnib, but can even be partially reversed within two and a half years of treatment is a tremendous breakthrough," said PRF Medical Director and the study's lead author Dr. Leslie Gordon.

Results of the clinical trial, funded by The Progeria Research Foundation and conducted at Boston Children's Hospital, are published in the *Proceedings of the National Academy of Sciences* this month. Download your free copy at [www.pnas.org/cgi/doi/10.1073/pnas.1202529109](http://www.pnas.org/cgi/doi/10.1073/pnas.1202529109).

### READ MORE ABOUT THIS REMARKABLE DISCOVERY INSIDE.

*"The results of this study provide our family with excitement and hope for Megan's future. We're grateful to PRF and all of the doctors for their commitment to helping my daughter and all children with Progeria."*

*– Sandy Nighbor, mother of 12-year-old Megan, who participated in the clinical trial*





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 To discover treatments  
 and the cure for Progeria  
 and its aging-related  
 disorders.

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**Progeria is a fatal, “premature aging” disease that afflicts children, who die of heart disease at an average age of 13 years - the same heart disease that affects millions of normal aging adults.**

**Because of Progeria’s connection to general heart disease and aging, what we learn from Progeria research has the potential to benefit all of us.**

**Message from the Executive Director and Chairman of the Board**

Hello everyone,

**The day has finally come!** What a remarkable journey so far. We started with a blank slate, and with help from thousands of dedicated people – many of whom are mentioned in this special issue – we have discovered a treatment for Progeria.

For PRF, the past 13 years have been a whirlwind of progress, and we have no doubt that these findings will help to push the research further and faster than we could ever have imagined, but had hoped for; just a few short years ago. FTIs are a treatment, not a cure, but these results are a huge step toward that ultimate goal.

We have come to learn the true meaning of hope, determination and passion – the vital ingredients that drive us and our volunteers, scientists, and families of the children. This news is a perfect example of what it takes to come so far, so fast, to help save these wonderful children.

This kind of success requires partnership and expertise from many organizations and the talented people within them. Doctors from Boston Children’s Hospital, Dana-Farber Cancer Institute and Brigham and Women’s Hospital have dedicated themselves to the clinical trials and to the children. Priceless drug supply and expertise has been completely donated by Merck. And drug discovery continues with other major companies. This is a testimony to the promise and progress we’ve been able to attain, and the reason we are able to make this historic announcement.

To our donors and volunteers, we cannot thank you enough for your steadfast commitment, your unwavering generosity, and your endless energy. To the children with Progeria and their families, thank you for your inspirational spirit and boundless courage. ALL of this is what got us to a treatment. And it is what will lead us to the cure.

Audrey Gordon, Esq.  
 President and Executive Director

Scott D. Berns, MD, MPH, FAAP  
 Chairman of the Board

# WE DID IT!! (continued from front cover)

## ABOUT THIS HISTORIC TRIAL

Twenty-eight children from 16 countries, ages 3-15 years, traveled to Boston Children's Hospital every four months for two and a half years to receive trial medication and comprehensive medical testing by research team members. At the time, that represented 75 percent of all identified Progeria children worldwide. Each participant took lonafarnib orally twice a day.

The study was led by Trial Chair Dr. Mark Kieran, and Co-chairs Drs. Monica Kleinman and Leslie Gordon, all of Boston Children's Hospital and Harvard Medical School. The 25-member research team closely followed many key disease characteristics. They found positive changes in weight, the cardiovascular system, bone and hearing.

- **Rate of weight gain:** Children with Progeria experience severe failure to thrive. One in three children in the clinical trial boosted their annual rate of weight gain by more than 50 percent or changed from a negative to a positive rate due to lonafarnib treatment.
- **Arterial stiffness:** Extreme blood vessel stiffening contributes to the premature heart disease that causes death in Progeria. Increased arterial stiffness is also a predictor of heart attack and stroke in the general population. The two measures of blood vessel stiffening tested in the trial both improved significantly.
  1. **Pulse Wave Velocity**, a dynamic measure of arterial stiffness through calculating rate of blood flow, decreased by 35 percent overall.
  2. **Arterial wall echodensity**, a measure of the arterial wall structure, improved to normal levels overall
- **Bone rigidity:** Children with Progeria have highly abnormal bone structure, and this may contribute to their bone fragility. For the subset of 11 children who could be tested, their severely abnormal skeletal rigidity achieved normal levels overall with treatment.
- **Sensorineural Hearing:** Improvement in this type of nerve-dependent hearing is dependent on the inner ear and its communication with the brain.

The success of this clinical trial was the result of years of coordinated efforts. PRF's International Progeria Registry, Diagnostic Testing Program, Medical and Research Database and Weighing-in Program were crucial to this process. The trial required identifying children and their home doctors from around the globe, obtaining essential pre-trial clinical

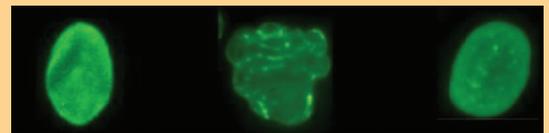


*Devin in for a visit at Boston Children's Hospital*

information, transporting families to and from Boston, supplying translators both inside and outside of the hospital setting, and putting together a multidisciplinary clinical team to assess treatment effects. The Devon Nicole House and Yawkey Family Inn generously provided housing through Boston Children's Hospital and The Yawkey Foundations, respectively. Children and families showed tremendous courage and fortitude throughout this process. We are thrilled that all of these efforts resulted in positive clinical trial results.

To learn more, visit [www.progeriaresearch.org/clinical\\_trial](http://www.progeriaresearch.org/clinical_trial)

## WHAT ARE FTIs?



Normal Cell

Progeria Cell

Progeria Cell + FTI in 36 hrs

Children with Progeria have a genetic mutation that leads to the production of an abnormal protein called progerin. Part of progerin's toxic effects is caused by a tail-like molecule called a farnesyl group. FTIs—short for farnesyltransferase inhibitors—block the farnesyl group from attaching to progerin. The hope was that FTIs would “inactivate” progerin and improve the symptoms of Progeria.

In 2003, when the gene that causes Progeria was discovered, researchers turned to FTIs as a possible treatment. FTIs were already being studied in children with cancer.

“We realized that my team's experience using FTIs to treat children with brain cancer could bring together PRF's pre-clinical research and the expertise we needed to study the drug in children with Progeria,” said Dr. Kieran.

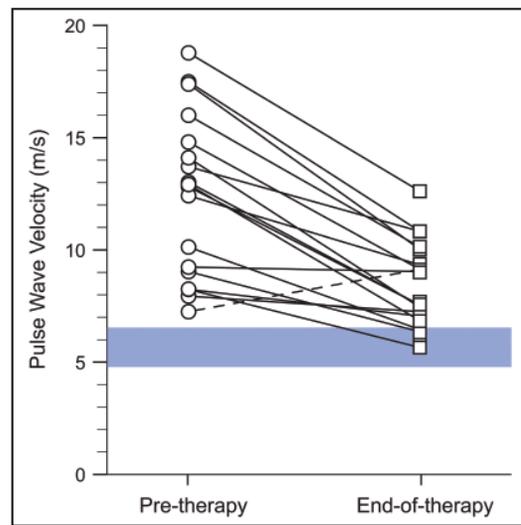
His instincts proved correct! The FTI lonafarnib has become the first effective treatment for children with Progeria.



*“The partnership between PRF, Boston Children’s Hospital and these courageous families was essential for success. I believe we have set in motion a blueprint for successful treatment trials for children with Progeria and for other rare diseases.”*

*– Dr. Leslie Gordon,  
PRF Medical Director and first author  
of the treatment discovery paper.*

The study is titled *“Clinical Trial of a Farnesyltransferase Inhibitor in Children with Hutchinson-Gilford Progeria Syndrome.”* Study team authors are pictured below.



*The study showed that Pulse Wave Velocity was very high prior to treatment (shown here as circles). This meant that the children’s blood vessels were very stiff. By the end of treatment, 17 of 18 children who could perform the test showed decreases in their Pulse Wave Velocities toward normal (shown here as squares). The blue stripe shows the normal range for children.*

## MEET THE TEAM that made it possible



Trial Chair Mark Kieran, MD, PhD with Meghan



Trial Co-chair Monica Kleinman, MD with Sam



Trial Co-chair Leslie Gordon, MD, PhD with Hayley



W. Robert Bishop, PhD  
Merck, Pharmacodynamics



Robert Cleveland, MD  
Radiology



Brian Fligor, ScD  
Audiology



Catherine Gordon, MD  
Endocrinology



Susanna Huh, MD  
Nutrition and Gastroenterology



Marilyn Liang, MD  
Dermatology



David Miller, MD, PhD  
Genetics



Ara Nazarian, PhD  
Orthopedics



Donna Neuberg, ScD  
Statistics



Nicolle Quinn, MS, RD, LDN  
Nutrition



Armin Schwartzman, PhD  
Statistics



Leslie Smoot, MD  
Cardiology



Brian Snyder, MD, PhD  
Orthopedics



Andrew Sonis, DMD  
Dentistry



Paul Statkevich, PhD  
Merck, Pharmacokinetics



Nicole Ullrich, MD, PhD  
Neurology



Nicole Wake, Cardiology,  
Marie Gerhard-Herman, MD Cardiology  
with Sam



Trial Coordinator Kelly Littlefield  
with Hana

### Not pictured:

Annette Correia, OT - Occupational Therapy  
Anita Giobbie-Hurder, MS - Statistics

Christine Ploski, PT, MS, PCS - Physical Therapy  
Amy Regen, DMD - Dentistry  
Susan Riley, PT, MS, DPT, PCS - Physical Therapy

## HOW WE GOT HERE

The success of the FTI trial was made possible by more than 10 years of hard work – and a little good luck!

It started in part with a **serendipitous encounter**:

Back in 2001, Dr. Scott Berns, chair of the PRF Board of Directors, met a physician-scientist named Dr. Francis Collins at an event in Washington, D.C. Intrigued by the story of Scott's son Sam and the newly formed Progeria Research Foundation, Dr. Collins agreed to help. His lab at the National Human Genome Research Institute has been conducting Progeria research ever since.



Priya



Meghan mixes *lonafarnib* with a liquid sweetener

Dr. Collins went on to become Director of the National Institutes of Health, and includes the topic of Progeria and its connection to aging in many of his national lectures.

In 2003, Dr. Collins and a team of researchers from the PRF Genetics Consortium discovered the cause of Progeria: a mutation in the LMNA (lamin A) gene. This pivotal finding threw open doors of science, enabling researchers to advance toward a better understanding of the disease process, and identify possible treatments.

Progeria researchers teamed up with cell biologists who specialized in lamins to deepen our knowledge of how abnormal lamin proteins like the Progeria-causing progerin damage cells. Researchers quickly began investigating FTIs, which showed great promise in counteracting the damage caused by progerin. Many years of work were saved by the fact that other researchers had already studied FTIs in children with cancer.



Sumaira

*“From 1999, when the organization was founded, to today, PRF helped discover the genetic mutation that causes the disease, funded preclinical research, completed this trial, initiated a second trial, and it is currently working with our team here at Boston Children’s Hospital to plan yet another trial with drugs that, like FTIs, have shown exciting results in Progeria cells. That’s an awesome track record of accomplishment.”*

– Trial Co-chair Dr. Monica Kleinman

## PRF’s Programs Greatly Contributed To The Science That Led To This Trial

- The PRF **International Progeria Registry** identified children from 16 countries who participated in the clinical trial.
- Only children with a definitive diagnosis of Progeria could enroll, and The PRF **Diagnostics Testing** Program provided the diagnosis for many trial participants.
- Analysis of medical records gathered through the PRF **Medical & Research Database** Program resulted in identifying weight gain as the primary measurement of treatment success.
- The PRF **Weighing-in Program** gathered the required pre-trial weight data.
- Cells from the PRF **Cell & Tissue Bank** were used in the gene discovery and FTI studies.
- PRF-funded basic science **research grants** showed that FTIs had a positive effect on Progeria cells.

In an exciting discovery with wide-ranging implications, scientists showed along the way that progerin relates to **normal development and aging** – the protein is produced in the general population and its levels increase as we age. Researchers will continue studying *progerin* and the effect of FTIs not only to help children with Progeria, but also to learn more about cardiovascular disease and the normal aging process that affects us all.

*“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...”*

– Francis Collins, MD, PhD, Director,  
National Institutes of Health

## THE STORY CONTINUES...

We've come a long way in a short time. And even though we are thrilled with the discovery of the first drug treatment for Progeria, our work is far from over. FTIs are a treatment, not a cure. PRF will continue to push forward at an unprecedented pace until we reach that ultimate goal of a cure!

### Trial #2 in Progress

Building upon the knowledge gained from the FTI trial, PRF is testing additional drugs in a larger clinical trial. The Progeria **Triple Drug Trial** began in 2010 and involves 43 children from 24 countries. It is testing two drugs in addition to the successful FTI lonafamib. Each of the three drugs targets different points along the pathway that leads to production of the disease-causing progerin. Taken in combination, they may provide an even more effective treatment for Progeria than FTIs alone.

Visit [www.progeriaresearch.org/clinical\\_trial](http://www.progeriaresearch.org/clinical_trial) for more details.

### Future Trial in Planning Stages

We continue to seek ways to improve and ultimately cure this disease. In addition to increased research grant funding, we are planning future trials with another drug that has proven promising in research studies, and exploring other drugs that may allow children with Progeria to live longer and healthier lives.

*“We are using the knowledge gained from this trial to push research forward and help children with Progeria even more... We want children with Progeria to live until they're 80 and beyond. We want them to live full, healthy lives.”*

*– Dr. Leslie Gordon  
Trial Co-chair and Sam's mom*



*Dr. Scott Berns and Dr. Leslie Gordon with Sam*



*Jesus & Vasile*



*Lindsay & Sarah*



*Niccolo & Julieta*



*Devin & Julia*



*Hana & Josiah*



*Linsay & Kaylee*



*Milagros & Maria*



*Hayley & Michiel*



*Mateo, Milagros & Fernando*



*Niccolo & Sammy*

The children came in to the Boston trial in pairs. This was an important part of their ability to withstand the rigors of a clinical trial schedule. This same concept applies to everything we do. Working together is exponentially better than working alone.

# THANK YOU ALL!

We achieved breakthrough results in this first trial because of the tremendous supporters who provided their time, talents and treasure, helping get us one step closer to achieving our ultimate goal of a cure for Progeria. YOU gave money, plane tickets and toys. YOU provided the drug, housing, and rides to and from the airport. YOU lent us your expertise in translation, legal and design services. And YOU worked tirelessly with the children and their families before and during the trial to ensure they could participate and come to Boston. **We couldn't have done it without YOU!**

And a very special thank you to John Tacket and all the other children who are no longer with us. Your courage and selflessness helped make this day possible.

*You are gone from our sight, but never our memories.  
Gone from our touch, but never our hearts.*



*"This is an exciting day for me and my friends. And while this discovery may not help me, I know it will help other children with Progeria in the future."*

- John Tacket, PRF's first Youth Ambassador, addressing reporters on April 16, 2003 at a press conference held at the National Press Club in Washington, DC to announce the discovery of the Progeria gene.

John passed away 11 months later at the age of 16.

## PLEASE CONTINUE TO SUPPORT OUR WORK

Our first trial cost \$2 million. YOU made it possible to enroll every child who wanted to join. The triple trial involves more children from around the globe, and the next trial will be even bigger and costlier as we identify more children than ever.

We hope you will DONATE NOW to support groundbreaking research at  
[www.progeriaresearch.org/ways\\_to\\_donate](http://www.progeriaresearch.org/ways_to_donate)

**Together, we WILL find the cure!**



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# PRF MAKES HISTORY!

This special issue is dedicated to all of the children who participated in this history-making clinical trial, and to their families. YOU made it possible to discover the first treatment for Progeria!

