



Clinical Research News

THE NEWSLETTER OF THE CLINICAL RESEARCH PROGRAM

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Can we prevent the aging process in children with Progeria?

A CLINICAL TRIAL USING FTIs

For years aging research has been considered the domain of gerontologists studying the elderly.

If any aging research was done on the pediatric population, it tended to focus on children experiencing slow growth or delayed maturity. However, a new clinical trial at Children's Hospital may change all that.

In a truly collaborative effort, Study Chair Mark Kieran, MD, PhD from Dana-Farber Cancer Institute has joined with CHB Study Co-Chairs Monica Kleinman, MD (CHB Division of Critical Care Medicine), Leslie B. Gordon, MD, PhD (CHB Division of Critical Care Medicine and Brown University Department of Pediatrics), and David Miller, MD, PhD (Genetics), in a study of children with Hutchinson-Gilford Progeria Syndrome (Progeria or HGPS), a genetic disorder which predisposes children to premature aging.

Other CHB investigators contributing to the study are Robert Cleveland, MD, (Radiology), Nicole Ullrich, MD, PhD (Neurology), Catherine M. Gordon, MD, MSc (Endocrinology), Leslie B. Smoot, MD (Cardiology), Marilyn Liang, MD (Dermatology) and Andrew Sonis, MD (Dentistry). In addition, there are two Study Biostatisticians from Dana-Farber (Donna Neuberg, ScD, and Anita Giobbie-Hurder, MS), another Study Cardiologist from Brigham & Women's (Marie Gerhard-Herman, MD), and four senior scientists focusing on Biological Correlates (Elizabeth Nabel, MD, NHLBI; Francis S. Collins, MD, PhD, National Human Genome Research Institute; Stephen Young, MD, UCLA, Division of Cardiology; and Robert Bishop, PhD, Schering-Plough Research Institute).

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Hayley from England (left) and Michiel from Belgium.

**PROGERIA, OR HGPS,
IS A GENETIC DISORDER WHICH PREDISPOSES
CHILDREN TO PREMATURE AGING.**

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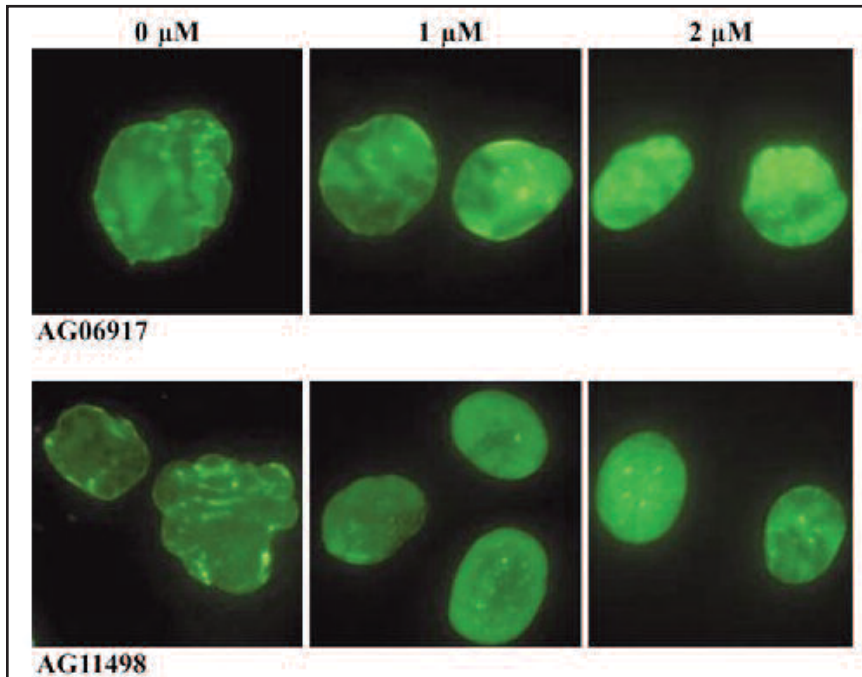


Figure 1.

FTI treatment causes reversion of the nuclear blebbing in two different progerin-expressing HGPS human fibroblasts. Cells were stained with anti-LA Ab after being treated for 3 days with 0, 1, or 2 μ M FTI lonafarnib/SCH66336. (Original magnification x60.) Brian C. Capell, Michael R. Erdos, James P. Madigan, James J. Fiordalisi, Renee Varga, Karen N. Conneely, Leslie B. Gordon, Channing J. Der, Adrienne D. Cox, and Francis S. Collins. Inhibiting farnesylation of progerin prevents the characteristic nuclear-blebbing of Hutchinson-Gilford progeria syndrome. *PNAS* 2005 102: 12879-12884; published online before print as 10.1073/pnas.0506001102.

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The Progeria Research Foundation funds the trial, and Progeria Research Foundation study coordinator Kyra Johnson arranges travel, lodging, and translators for patients and their families, who are coming to Boston from 16 different countries and speak 9 different languages.

Think of Progeria as a disease in which some aspects of aging move at warp speed. Symptoms of this disease run the gamut from the purely external of aged-looking skin, to painful joint stiffness, to the more significant morbidity factors, stroke and heart disease. Affecting 1 in 4 million newborns, Progeria results in premature death at an average age of thirteen (range 7-20 years). While the incidence of Progeria is low, the stakes are high because of the features it shares with the natural aging process. By studying Progeria we will be able to understand better the progression of cardiovascular disease in people of all ages.

The Phase II clinical trial began this past spring and involves the use of a farnesyltransferase inhibitor or FTI, a drug that was used previously as a cancer treatment. The FTI, lonafarnib, is taken orally twice a day by patients.

Over the first four months, the study enrolled 1-2 children per week between April and October. Twenty-eight children have been enrolled to date, and the study is no longer recruiting new subjects. If participants tolerate the lonafarnib, they continue the therapy for 24 months. They return to CHB every 4 months over a period of two years, for testing and to receive their new supply of FTI. The patients remain in Boston for three to seven days during each of these visits. In between visits, while they are home, their local doctors are responsible for their medical care and provide a detailed monthly health report to the Boston investigators.

Staff of CHB's Clinical Research Program (CRP) are currently assisting study investigators with project and data management support and research database development. Specifically, Team Leader, Susan McDermott and Data Managers, Aruna Jayashankar and Rajna Filip-Dhima worked closely with Study Coordinator William Fletcher and investigators to develop the study case report forms. CRP Data Managers and software Engineers from the Clinical Research Information Technology (CRIT) team also are working on the design and development of the

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clinical research database using our newest clinical research database technology, InForm™ by Phase Forward (See page 7 for further details on InForm™).

Team Leader Susan McDermott said, “It’s exciting to contribute to such an important study. We’re thrilled to be a part of a trial that may develop actual treatment options for children born with Progeria.”

CHB’s GCRC is the main site for the clinical trial and patient care activities. In the implementation of the protocol, the GCRC research nurses perform measurements, vital signs, sample collection of blood and urine, pharmacokinetic testing, and study drug teaching. The DXA and pQCT testing, as well as nutritional assessments, also take place on this unit. GCRC laboratory personnel are very involved in complex sample processing, recording, and storage. Parents and the children participating in the trial use the GCRC as “home base” during their visits, which are from three to seven days in duration.

WHAT IS THE PROGERIA GENE MUTATION?

Progeria is caused by a mutation in the gene called *LMNA*. The *LMNA* gene produces the Lamin A protein, the glue for holding the nucleus of a cell together. Researchers now believe that the defective Lamin A protein (called progerin) makes the nuclear membrane unstable. The nuclei of cells whose membrane contains progerin have a characteristic “blebbed” appearance, believed to be responsible for the cellular instability, which in turn, plays a major role in the disease process in Progeria.

HOW DO FTIs WORK?

Beginning on April 16, 2003, when The Progeria Research Foundation’s research team announced the discovery of the *LMNA* mutation that is responsible for Progeria, some researchers have focused their labs and clinical research on finding targeted treatments. Specifically, they have turned their attention to the production of the Lamin A protein. In order for progerin to be created, a farnesyl group molecule must attach itself to the pre-lamin A protein. The CHB study team is now researching whether blocking this attachment with FTIs will prohibit the production

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— MARK KIERAN, MD, PHD

of progerin. By inhibiting the formation of progerin and favoring production of normal Lamin A, FTIs may decelerate or even reverse the progression of the disease (see: Figure 1). The CHB researchers are hoping that this is indeed the case. “The on-going clinical trial has become a model for diseases that affect known cellular pathways,” stated Dr. Kieran. “Even when diseases are exceedingly rare, the ability to bring together a wide breadth of expertise, and patients from around the world, allows us to focus our efforts on improving patient outcomes while furthering our understanding of critically important pathways.”

OUTCOMES OF THE CLINICAL TRIAL

Because children with Progeria reach a final height of approximately 3 feet and weight of approximately 30 pounds, the researchers will be particularly interested in the change in the patients’ rate of weight gain over baseline. The primary endpoint will be an increase of at least 50% in the annual rate of weight gain over the weight rate pre-trial pattern.

Furthermore, the protocol calls for measurements of the levels of pre-Lamin A, mature Lamin A, progerin, and HPI α protein that are isolated from PBL (Peripheral Blood Leukocytes). The researchers will also examine changes in leptin levels, glucose utilization, skeletal abnormalities consisting of bone mineral density and X-ray findings, joint contracture and function, hearing loss, dental anomalies, dermatologic findings, energy expenditure, body composition analysis by DXA scan, and cardiovascular function. “This is truly a multi-disciplinary study,” said Dr. Kieran. “It involves experts in cardiology, neurology, oncology, endocrinology, radiology, audiology, dermatology, genetics and dentistry. We’re not just looking at aging from one field—we’re taking on aging and all of its corollary consequences.”