Racing the Clock: Combating Accelerated Aging in Children

Dr. Seuss was no doctor but “The more that you learn, the more places you’ll go” could be the moral of an extraordinary story of basic research and a rare disease called Hutchinson-Gilford Progeria Syndrome (HGPS). Progeria, as it’s more commonly called, has been described as out of control, rapid aging in children. And yet a possible treatment for this “untreatable” disorder has suddenly emerged from basic cell biology, the Human Genome Project, and a new use for a “failed” cancer drug.

The progeria bench-to-bedside story has unfolded with breathtaking speed: only five years from discovering the progeria gene to a potential treatment for these children. Experts say this may be the fastest basic research to clinical application saga ever. By funding decades of “nontargeted” basic research at universities throughout the country, the National Institutes of Health (NIH) and taxpayer dollars have made this breakthrough possible. In addition, a nonprofit “disease” foundation, organized by parents of children with progeria, played a crucial role.

A Matter of Life and Death

A clinical trial began last spring in Boston with a class of drugs called farnesyl transferase inhibitors (FTIs); the trial will continue for two-and-a-half years. The outcome may be a matter of life and death for many of the 28 HGPS children enrolled in this trial since their average lifespan is currently 13 years. However, there are implications beyond this tiny population. Researchers say that a treatment for HGPS kids may open a whole new perspective on “normal” aging and its complications, particularly in cardiovascular disease.

HGPS, first described in 1886, is extremely rare. Worldwide, an estimated 35–50 children are known to be affected. From the beginning, doctors were struck by its parallels with normal aging. HGPS newborns begin life in apparent good health, but by 6–18 months stop growing and quickly develop signs of premature aging including hair loss, thin skin, loss of subcutaneous fat, stiff joints, osteoporosis, and rampant arteriosclerosis. A 10-year-old HGPS child typically looks like an 80-year-old. Children with progeria are often tremendously appealing—bright, physically active, and socially outgoing kids—trapped in rapidly aging bodies. They race a cruel clock, and are struck down by heart attacks or strokes.

Attracting Scientific Attention

Until recently, progeria was simply too rare to attract much scientific attention. Available medicine was limited to physical and occupational therapy, special nutrition, and adult-based strategies to control heart and circulatory disease.

Translating Progeria: A Bench-to-Bedside Story

Years of basic curiosity-driven research into the structure and function of the nuclear lamins by a handful of cell biologists has illuminated our understanding of the mechanism(s) responsible for the premature aging disease, Hutchinson-Gilford Progeria Syndrome (progeria). Unfolding with incredible speed, this remarkable story—and its exciting denouement: the recent implementation of drug trials on progeria patients—will be showcased on Sunday, December 13, at the ASCB Annual Meeting in San Francisco. The special translational session detailing the bench-to-bedside saga will feature an all-star lineup of expert panelists. Chaired by ASCB President, and pioneering nuclear lamin researcher, Bob Goldman, the panel will include:

- Leslie Gordon, Founder and Medical Director, Progeria Research Foundation, and parent of a child with progeria
- Francis Collins, Director of the Human Genome Research Institute, NIH
- Elizabeth Nabel, Director of the National Heart, Lung, and Blood Institute, NIH
In the summer of 1998, Sam Berns, the 21-month-old son of two Boston-area physicians, Leslie Gordon and Scott Berns, was diagnosed with HGPS. Realizing how little was known, the family mobilized to form the Progeria Research Foundation, with Gordon as director. As an M.D./Ph.D., Gordon was uniquely positioned to appeal to Francis Collins, Director of the National Human Genome Research Institute at the NIH, to map the HGPS gene.

Through the database of the Human Genome Project, the progeria gene, LMNA, was mapped in 2003. LMNA encodes important structural proteins in the cell nucleus, which houses chromosomes. These proteins, named lamins, form tough but adaptable rope-like filaments that line the inner membrane of the nuclear envelope and extend throughout the nucleus. The most common HGPS-causing mutation is sporadic, meaning that the DNA change occurs spontaneously in the child, and is not inherited from either parent. The mutated LMNA gene creates a defective lamin A protein, known as “progerin,” which lacks a large section (typically, 50 amino acids) near its C-terminal end. This deletion wreaks havoc because the defective protein can still associate with normal lamins and disturbs their organization in the nucleus.

Lamins were first described in the 1950s, and their protein structure was unraveled in the 1970s. The biochemistry of lamin A/C processing was characterized in the 1980s. Until the late 1990s, however, funding for nuclear lamina research was sparse. Senior researchers remember their grant proposals being dismissed as irrelevant and “boring.” Gradually, connections were made between lamin defects and other diseases, starting with Emery-Dreifuss muscular dystrophy. Still, the link to progeria in 2003 electrified the field, since lamin researchers had a good hunch about what might be going wrong.

Lamin A is first made as a precursor protein (“pre-lamin A”), with extra amino acids at the C-terminus that attract an enzyme that attaches a molecular “tag.” This tag, called a farnesyl, is a greasy anchor that helps dock the protein at the nuclear membrane. A second enzyme recognizes the tagged precursor, and (for reasons that remain obscure) cuts off the tagged end, generating mature lamin A. Progerin lacks this cleavage site, and therefore retains the greasy farnesyl tag (plus the extra amino acids that are normally removed) and accumulates at the nuclear inner membrane. Over time, normal lamins become trapped and the nuclei—usually round—become lumpy and misshapen. Lamin filaments are needed to organize chromosomes and regulate gene activity. As nuclear structure unravels, genetic confusion grows.

Researchers at several universities and institutions already knew that lamins and certain other proteins rely on enzymes to add their greasy farnesyl tag. After the mapping of the LMNA gene, researchers wondered whether drugs known as FTIs could block the enzymes. Remarkably, these drugs had already been tested in children with certain types of cancer caused by overactivity of the “Ras-MAP Kinase” signaling pathway. The Ras protein, like lamin A, is tagged with farnesyl. Pharmaceutical companies had rushed to develop and test FTIs in these young cancer patients, but with disappointing results. FTIs were “safe,” that is, they had minimal side effects on the already sick children, but they have so far been ineffective against cancer. Now farnesyl tags were implicated in progeria. Might FTIs block the buildup of defective lamins?

First, basic researchers needed to take a closer look at FTIs in cells. They forced human cells to express progerin, and saw that nuclei acquired the characteristic lumpy shape. In cells treated with FTIs, nuclei regained normal shape. In 2005, the research question moved to mice that were genetically modified to model human progeria. Again FTIs were administered, and nuclear shape was gradually restored. Importantly, these mice also visibly lost many of their progeria symptoms.

Offering FTIs…and Hope

Now the science returned full circle to HGPS children. In May 2007, the first two HGPS children were enrolled in a clinical trial at Children’s Hospital Boston. They were given a complete baseline evaluation and their first doses of an FTI drug. By October, the trial was fully enrolled with 28 HGPS patients, ages 0-20.
From all over the world. It took just under five years from gene discovery to the first dose of FTI drugs administered to children with HGPS.

While this clinical trial is not expected to demonstrate an FTI cure for progeria, any extension of lifespan would be a major cause for celebration for the HGPS children. As with all clinical trials, physicians and lamin researchers are watching closely for unexpected consequences. Farnesylation regulates many pathways in cells, and the potential long-term effects of inhibiting these enzymes are unknown.

Meanwhile, basic research has made a new connection between progeria and “normal” aging. In December 2007, researchers reported finding low levels of progerin in skin samples from 150 individuals unaffected by HGPS, and ranging in age from newborn to 97 years old. Trace levels of progerin are expressed at all ages, but the defective protein accumulates in the skin over time. Older people have more, especially in cells that lie deeper in the skin. Other tissues have not yet been tested, but are likely to show similar results. The 2007 finding makes progerin a “biological marker” of cellular aging, and a new player in senescence studies.

Value of Basic Research

The progeria story is a classic illustration of how unexpected discoveries in basic research can lead to unsuspected connections in human health. Our knowledge of nuclear lamins stems from decades of “untargeted,” investigator-initiated, NIH-funded basic research on seemingly boring structures and obscure enzymatic reactions. Without this knowledge, identifying the progeria gene would have been a medical dead end, and FTIs would not have been understood. Finding the progeria gene would have been a hopeless task without the grand-scale Human Genome Project.

Without a “failed” cancer trial, FTIs would not have been available immediately to test in HGPS children. With their interest in cellular processes, biochemistry, and genetic mutations, basic researchers were able to illuminate an area with critical, clinical implications. With more links between basic research and clinical results from the HGPS trial, new discoveries about age-related heart disease could be ahead. After all, the more you learn, the more places you’ll go.

—John Fleischman
Nuclear meltdown: Mutant lamins cause premature aging

Children diagnosed with Hutchinson-Gilford Progeria Syndrome (HGPS) race through life against an unfairly fast clock. Cases are extremely rare—one in 8 million births—but time plays cruel tricks on HGPS newborns. They begin life in apparent good health but by six–eighteen months develop the first signs of premature aging, including hair loss, stiff joints, osteoporosis and atherosclerosis. Typically, the HGPS race through life runs out by age 13, finished by heart attacks or strokes.

But progeria researchers made a breakthrough in 2003, tracing HGPS to a spontaneous mutation in a gene encoding an important structural component of the cell nucleus, the organelle in which our DNA is stored, read out, and copied. As the so-called “Mothership of the Human Genome,” the cell nucleus must keep all this vital genetic information safe but accessible inside a strong protective envelope. The inner membrane of the nuclear envelope is lined by tough but adaptable proteins called lamins. The mutated gene for HGPS affected the nuclear lamin A (LA) protein.

The discovery that progeria was a “laminopathy,” a disorder caused by a nuclear lamin failure, gave HGPS families new hope because it gave clinical researchers new targets for drug or other interventions. But the discovery gave cell biologists a new problem. If HGPS was cellular aging run wild, was it a warp-speed version of “normal” human aging? If so, what was it about the mutated LA protein behind HGPS that causes cells to age so rapidly?

Robert Goldman and his collaborators at the Northwestern University’s Feinberg School of Medicine and elsewhere have zeroed in on the defective lamin A proteins linked to HGPS. While lamins polymerize into fibrous structures that hold the “walls” of the nucleus, they also serve as an internal scaffold for the complex machinery involved in DNA replication and gene expression. It was in this later role that the researchers have been looking for clues to premature and possibly to normal aging.

Reporting on two sets of experiments, Goldman et al say that the mutant LA protein seems to interfere with key controls of gene expression and of the cell cycle. The first study discovered that the most common HGPS-linked mutant LA protein alters the organization of regions of chromosomes that are critically important in regulating gene expression. These so-called heterochromatic regions include the inactive X (Xi) chromosome found in normal female cells. One of the hallmarks of Xi heterochromatin is its association with proteins known as methylated histones. In the cells from a female HGPS patient, the researchers found that levels of this molecular hallmark and of an enzyme required for histone methylation of Xi are sharply lower.

The second set of results reveals mutant LA proteins turning up in the wrong place—too tightly linked to the membranes of the nuclear envelope—to be of much help during key stages of the cell cycle. The researchers believe that this localization failure of mutated LA proteins would severely compromise the ability of HGPS cells to engage in normal DNA replication, a probable factor in their rapid march to premature senescence. Whether similar missteps and miscues by nuclear lamins are part of “normal” human aging is the question that draws researchers onward, says Goldman.

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The human face of HGPS: Lindsay, age 18 months. Photo courtesy of the Progeria Research Foundation.