More than 5700 human conditions have now had their molecular causes defined, the majority of which are rare diseases that were molecularly characterized in the past 25 years. Yet, even today, approved therapies exist for only \( \approx 500 \) of these conditions. Clearly, an urgent need exists for therapeutic advances to help people suffering from rare diseases, a need fraught with many challenges.

The private sector’s interest in developing molecularly targeted therapies has been growing but still remains quite limited for the rarest diseases that have very little market potential. Given the costs, it is difficult to embark on such a therapeutic development effort from scratch; historically, the failure rate is very high, and it has taken an estimated 14 years and several billion dollars to develop and gain approval for a therapy aimed at a molecular target. The National Institutes of Health is working to overcome these obstacles through a variety of innovative efforts at its National Center for Advancing Translational Sciences, with repurposing of compounds developed for other applications being one particularly attractive option.

A poignant example of the pressing need for effective treatments is one of the rarest of rare diseases: Hutchinson-Gilford progeria syndrome (HGPS), and this issue of *Circulation* reports the results of a triple-combination therapy trial for HGPS. Characterized by accelerated aging, HGPS has a prevalence of \( \approx 1 \) in 20 million living individuals or \( \approx 350 \) children worldwide at any given time. Without treatment, children with HGPS, who have completely normal intellectual development, die of atherosclerotic cardiovascular disease at the average age of 14.6 years.

In 2003, my laboratory at the National Institutes of Health and another group in France determined that HGPS is caused by a point mutation (C-to-T) in the lamin A (LMNA) gene. The mutation activates a splice donor in the middle of an exon, leading to the production of an abnormal protein, now called progerin, that is missing 50 amino acids near the C terminus.

Nearly 2 decades of previous work by lamin A cell biologists furnished rapid insights into how this mutation might cause disease. Lamin A is posttranslationally modified, with the addition of a farnesyl group at the C terminus that assists in zipcoding the protein to the inner surface of the nuclear membrane. The protein then needs to be released from this tether, which is accomplished by an enzyme called ZMPSTE24. The abnormal splice event that gives rise to progerin eliminates the ZMPSTE24 cleavage site, so progerin remains permanently tethered, with negative consequences to cell morphology and longevity. Knowledge of these steps predicted that farnesyltransferase inhibitor (FTI) drugs, which reduce the amount of permanently farnesylated progerin, might hold therapeutic potential for this disorder. Indeed, tests in HGPS cells and mouse models of HGPS laid the groundwork for the first clinical trial of a potential therapy for HGPS: an FTI called lonafarnib, which
was originally developed for the treatment of cancer. In 2012, researchers reported that children with HGPS receiving lonafarnib showed modest improvement in weight gain and a large reduction in vascular stiffness.8

Although survival was extended by lonafarnib,9 lonafarnib was not a cure, so additional efforts to find a more effective therapy or combination of therapies were needed. An evidence-based rationale for a tripletherapy approach—adding a statin and a bisphosphonate to lonafarnib—was suggested by molecular pathway considerations and preclinical testing, including life-extending results of statin-bisphosphate combination treatment in a Zmpste24 mouse model of HGPS.10 A trial of a statin (pravastatin) and a bisphosphonate (zoledronic acid) was initiated in patients with HGPS in France in 2008, and a trial combining an FTI, pravastatin, and zoledronic acid was begun in 2009 in Boston.

Although the triple-combination therapy used in the Boston trial was well tolerated by children with HGPS, it demonstrated little benefit beyond that seen with lonafarnib alone. The small, additive benefit was increased bone mineral density, most likely attributable to the bisphosphonate. However, osteoporosis is not a primary contributor to premature mortality in HGPS, so it is not clear that this represents a clinically relevant advance. Furthermore, troubling evidence, presumably also secondary to bisphosphonates, was found of increased plaque formation in the carotid and femoral arteries, as well as apparent acceleration of the extraskeletal calcifications that are a feature of HGPS. It will be very interesting to learn the results of the French trial to see whether any of these same complications arose. The results reported here leave unresolved the question of whether an FTI plus a statin (without the bisphosphonate) might have provided benefit.

Because this and other clinical trials have shown that the benefits of FTI therapy are limited and certainly not curative, more treatment options are urgently needed to help children whose lives are being cut short by this rare disease. That leads us to the next big question facing HGPS researchers and advocates: What therapeutic strategy should be tried next?

A recent international scientific workshop hosted by the Progeria Research Foundation11 attempted to tackle that issue. The workshop participants, myself included, presented data that resulted in a list of at least 17 potential therapeutic options. Among the many possibilities were treatments that could block the abnormal splice site (eg, RNA therapy, see below), reduce progerin production (eg, FTIs), increase progerin clearance (eg, mammalian target of rapamycin inhibitors, see below), and protect or restore the nuclear lamina (eg, resveratrol, remodelin).

However, along with this growing list of therapeutic opportunities come many sobering realities. Most of these approaches lack sufficient preclinical data to be ready for human applications. Furthermore, the extremely limited pool of patients with HGPS available for clinical trials means that only 1 or 2 new approaches can be studied at any given time, and trial end points so far have had to depend on historical control subjects rather than having sufficient patients to conduct randomized, double-blind, controlled trials. Attendees at the workshop thus were forced to grapple with the complex issue of how to decide the criteria for testing potential HGPS therapies.

Points that we agreed should be considered, and that are mostly echoed in a recent essay,12 included the following: Is the mechanism known? Does it work in an HGPS cell model? Has it been shown to be safe and effective in one of the well-characterized HGPS mouse models? Are there likely to be off-target effects? Has it ever been used in humans before; is its toxicity understood and its pharmacokinetic/pharmacodynamic profile known? Has it ever been used in children? Has it been given over a prolonged period of time? Is it orally available? Does it have the potential to interact positively or negatively with lonafarnib? After carefully weighing these factors, I would like to highlight 2 options (although a case could certainly be made for many of the others): A short-term option is the use of mammalian target of rapamycin inhibitors; in the longer term, morpholinos to block the abnormal splice event could provide an even more direct approach to correction of the fundamental molecular defect.

Work in cell culture first raised the possibility of mammalian target of rapamycin inhibitor therapy by showing that this class of small-molecule drugs could reverse nuclear abnormalities and promote proliferation in HGPS fibroblasts.13 Preliminary tests in a mouse model of HGPS have also suggested increased survival in animals receiving oral doses of everolimus, a mammalian target of rapamycin inhibitor approved by the US Food and Drug Administration as an immunosuppressant drug to prevent rejection in organ transplantation (A. DuBose, PhD; U.L. Tavarez; F.S. Collins, MD, PhD; unpublished data; 2016).

Building on this evidence and knowledge gained from its FTI and triple-therapy clinical trials, the Boston team very recently launched a phase I/II dose-escalation trial of everolimus in combination with lonafarnib in children with HGPS and progeroid laminopathies.14 The first phase of the study will determine the safest maximum dose of everolimus for children with progeria. If toxicity is manageable, the trial will move on to determine if the effects of the 2-drug combination are better than lonafarnib alone (https://clinicaltrials.gov/ct2/show/NCT02579044).

An appealing longer-term option might be the use of RNA therapeutics aimed at blocking the abnormal splice site that leads to progerin. Several groups have shown promising evidence that this strategy can work.15-18


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However, this therapeutic strategy also presents significant challenges. Among the questions that still need to be answered is whether these agents can be effectively delivered to the key tissue affected by HGPS: vascular smooth muscle cells of the medial layer of large arteries. One version of this approach, which we are pursuing with colleagues at Sarepta Therapeutics, is the use of peptide-phosphorodiamidate morpholino oligomers. Encouraging preliminary results have been developed in cultured cells and animal models, but for human applications, this novel strategy also presents significant regulatory challenges.

Obviously, the development of a truly curative therapy for HGPS remains elusive. However, the track record is already noteworthy: Proceeding from gene discovery to the first molecules driven clinical trial in <5 years was unusually rapid and might be considered a paradigm for translational medicine for rare diseases.\(^\text{19}\) Although the results of the second published trial, the triple-drug trial reported here, are disappointing, additional therapeutic options are emerging, and there is more momentum than ever in the basic and clinical research communities. Progress in progeria research has depended on the collaborative contributions from researchers and clinicians from many diverse nations, sectors, and disciplines and has been greatly benefited by the prominent involvement of a nonprofit foundation devoted to promoting research. Although the vantage points may be many, all are united by a common goal: to find a cure.

**REFERENCES**


Seeking a Cure for One of the Rarest Diseases: Progeria
Francis S. Collins

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