Cell

Leading Edge
Essay

Progeria: A Paradigm for Translational Medicine

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Rare diseases are powerful windows into biological processes and can serve as models for the development of therapeutic strategies. The progress made on the premature aging disorder Progeria is a shining example of the impact that studies of rare diseases can have.

The premature aging disorder Hutchinson-Gilford progeria syndrome (HGPS, or progeria) is one of the rarest human diseases. Yet its study over the last decade has attracted attention from basic scientists, clinicians, the pharmaceutical industry, and policy makers. Why is the scientific community intensely watching the activity surrounding a disease that affects a mere 350 children worldwide (Gordon, 2013)? There are two important reasons. First, progress in HGPS can be viewed as a paradigm of modern translational medicine: basic science informing clinical medicine in a bench-to-bedside approach to medical discovery. Second, discoveries in rare diseases often offer new possibilities for understanding of cellular and organismal mechanisms, such as normal aging and cardiovascular disease in the case of HGPS. This Essay summarizes advances made in the understanding of HGPS and discusses the implications of research into rare diseases on basic cell biology, understanding of physiological processes, drug discovery, and clinical trial design.

A Short History of HGPS

HGPS was first described by Drs. Jonathan Hutchinson and Hastings Gilford in 1886 and 1897, respectively (Gilford, 1904; Hutchinson, 1886). For more than 100 years, its cause was a medical mystery. The disease was designated as a premature aging syndrome by Gilford based on the overall resemblance of patients to aged individuals and the presence of aging-associated symptoms, including lack of subcutaneous fat, hair loss, joint contractures, progressive cardiovascular disease resembling atherosclerosis, and death due to heart attacks and strokes in childhood (Merideth et al., 2008) (Figure 1).

The mapping of the disease gene revealed that HGPS is a sporadic, autosomal dominant disease caused by a mutation in *LMNA* (De Sandre-Giovannoli et al., 2003; Eriksson et al., 2003). This gene codes for the inner nuclear membrane proteins lamins A and C, two prominent structural components of the eukaryotic cell nucleus. HGPS is a member of a group of diseases called laminopathies, resulting from mutations throughout the *LMNA* gene that result in a wide spectrum of overlapping disorders. These include muscular dystrophies, a peripheral neuropathy, lipodystrophy syndromes, and accelerated aging disorders (Worman and Bonne, 2007).

The disease-causing mutation in HGPS activates what is normally a only sporadically used alternative splice site in *LMNA* exon 11, resulting in partial deletion of the exon (Figure 1). Although the discovery of disease genes does not always inform about disease mechanism, the identification of an *LMNA* mutation as the cause of HGPS inspired intense basic and clinical research into this disease and its relationship to aging. The reason for the rapid progress in our understanding of HGPS was that the gene identification dovetailed with extensive prior work by basic cell biologists on the complex posttranslational processing events of lamin A, which would turn out to be key for understanding the HGPS disease mechanism (Sinensky et al., 1994).

Normally, lamin A is produced via a prelamin intermediate whose C-terminal cysteine residue is first modified by farnesylation and carboxymethylation followed by enzymatic cleavage of the terminal 15 amino acids, including the farnesylated cysteine, by the ZMPSTE24 endoprotease. However, in the HGPS mutant prelamin A isoform, this cleavage site is missing as a result of the aberrant splicing event. Thus, the HGPS mutation leads to the accumulation of a permanently farnesylated, uncleaved lamin A isoform named progerin (Figure 1). This aberrantly modified, lamin A intermediate triggers, by yet-to-be discovered mechanisms, the many cellular and organismal disease symptoms.

A Rare Disease Provides Insight into Fundamental Cell Biology

Elucidating the cascade of damaging events is a critical step in the understanding of any disease, and it is often crucial for identifying candidate drug targets. HGPS patient cells have numerous defects, and studying them has become a

powerful tool for both basic scientists and clinicians to ask questions about the roles of major cellular processes in health and disease (Figure 1).

Nuclear Morphology and Function

The most overt cellular defects in HGPS are dramatic changes in nuclear morphology (Eriksson et al., 2003), a phenotype that is not surprising given the prominent architectural role of lamin A in the nucleus. Whereas the lamin proteins in healthy cells move dynamically between the nuclear lamina polymer at the nuclear periphery and the nucleoplasm, they become immobilized in HGPS patient cells, leading to thickening of the lamina (Goldman et al., 2004; Dahl et al., 2010). Probably as a consequence of these structural changes, the mechanical properties of HGPS nuclei are altered and patient cells exhibit increased stiffness compared with cells from healthy individuals (Dahl et al., 2010). These alterations are likely relevant in disease pathology, as they might affect the response of cells in tissues that are particularly exposed to mechanical stress such as the vasculature, bone, and joints—three tissues that exhibit some of the most prominent symptoms in HGPS patients. These defects are of great interest to the study of lamin biology because despite the known major functions of the nuclear lamins, the structural properties of the nuclear scaffold have remained elusive (Burke and Stewart, 2013). For example, it is unclear precisely how lamins polymerize and how they interact with a myriad of inner nuclear membrane complexes and chromatin or how they transmit mechanical signals to mechanosensitive genes. Lamin mutants such as the one causing HGPS are promising tools to begin to elucidate fundamental aspects of nuclear organization.

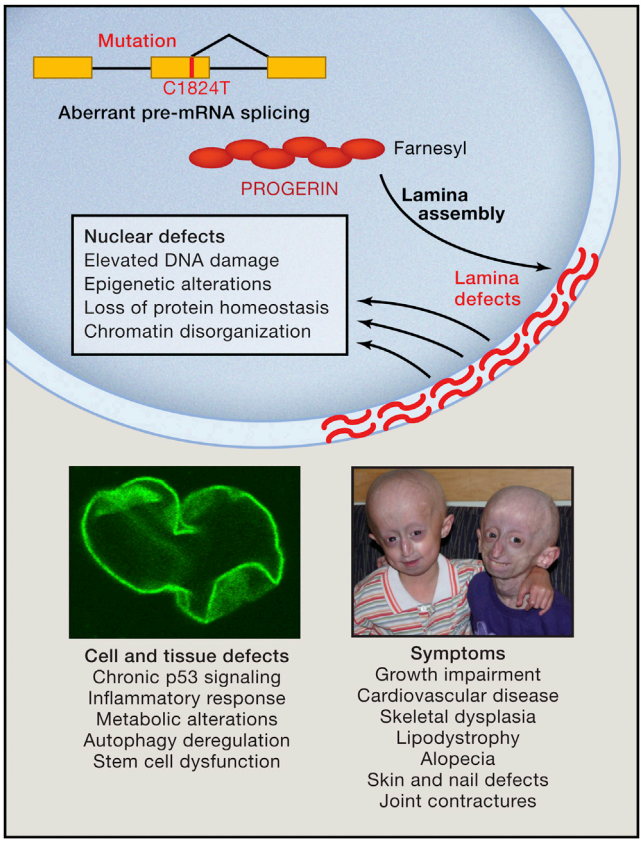

Figure 1. HGPS: From Genetics to Symptoms

HGPS is caused by a spontaneous point mutation in the *LMNA* gene, coding for the nuclear intermediate filament proteins lamin A and C. The disease mutation activates an alternative pre-mRNA splice site in exon 11 that results in removal of 150 nt from the 3′ end of this exon and creates an internal deletion of 50 aa in the translated lamin A protein. The mutant protein (red), referred to as progerin, is permanently farnesylated as the 50 aa deletion includes an endoproteolytic cleavage site, which normally removes the farnesylated C terminus from the wild-type protein. The farnesyl group is believed to facilitate the association of the protein to the nuclear membrane, resulting in its accumulation at the nuclear periphery. Association of progerin with the lamina interferes with normal lamina function and triggers, via yet unknown mechanisms, many of the commonly observed nuclear defects. HGPS cells also exhibit nonnuclear defects, including altered signaling and metabolic properties. It is assumed that these cellular defects and particularly the loss of stem cell function contribute to the prominent overt patient symptoms. (Left) Fluorescently tagged progerin (green) accumulates at the periphery of patient nuclei and alters nuclear morphology. (Right) Two progeria patients. Image reproduced with permission, courtesy of The Progeria Research Foundation.

DNA and Chromosome Function

Two other notable cellular defects in HGPS patient cells are widespread alterations of chromatin structure, such as the loss of heterochromatin domains, and changes in epigenetic markers. Using HGPS cells as a model system, the nucleosome-remodeling and deacetylase complex NURD has been identified as a mediator of both higher-order chromatin structure and maintenance of genomic integrity (Pegoraro et al., 2009). Using genome-wide studies in which the physical interactions of lamins with the genome are comparatively mapped in wild-type and patient cells, HGPS also provides an opportunity to probe lamin-genome interactions, which are increasingly recognized as key drivers of overall genome organization (McCord et al., 2013). HGPS patient cells also suffer DNA repair defects due to both reduced recruitment of DNA damage response (DDR) factors to sites of damage and slowed repair kinetics (Benson et al., 2010; Musich and Zou, 2009). On the other hand, the xeroderma pigmentosum group A (XPA) protein appears aberrantly recruited to replication forks, promoting replication fork stalling and activation of the DDR (Liu et al., 2006). Progerin also appears to modulate telomere function and to induce DDR signaling from telomeres via activation of p53 and Rb pathways (Benson et al., 2010). Interestingly, telomere dysfunction during senescence appears to feed back and promote progerin expression (Cao et al., 2011a). These studies have begun to uncover the elusive mechanisms that link nuclear structure and genomic instability.

Regulatory and Stress Response

Functional studies using animal and cellular models of HGPS have facilitated the identification of regulatory and stress-response pathways involved in HGPS development. Of special interest is the hyperactivation of p53 signaling in HGPS cells and in mouse models of HGPS (Kudlow et al., 2008; Liu et al., 2006; Varela et al., 2005). However, the fact that phenotype alterations in these progeroid mice are not completely rescued in a p53 null background indicates that other pathways contribute to the generation of the observed defects.

These additional pathways may include the attrition of adult stem cells (Espada et al., 2008; Rosengardten et al., 2011; Scaffidi and Misteli, 2008), the dysregulation of the somatotrophic axis and several miRNA-controlled circuits (Mariño et al., 2010; Ugalde et al., 2011), the generation of profound changes in glucose and lipid metabolism (Mariño et al., 2008), and the ATM-dependent activation of NF-κB signaling that links nuclear lamina defects to the systemic inflammation observed in two different progeroid murine models (Osorio et al., 2012).

Induced Pluripotent Stem Cells and Their Potential

As in many diseases, tissue-specific cell lines from HGPS patients are not easily obtainable due to the difficulty of performing biopsies on frail patients. The development of patient-derived induced pluripotent stem (iPS) cells provides powerful tools to study differentiation pathways of tissues affected by the disease. HGPS iPS cells have been successfully generated and differentiated along multiple lineages, including the particularly disease-relevant vascular smooth muscle cells (VSMCs) and mesenchymal stem cells (Zhang et al., 2011). Early experiments using these cells revealed heightened sensitivity of HGPS mesenchymal stem cells to stress and aberrant differentiation of HGPS VMSCs (Zhang et al., 2011). Patient-derived iPS cells have also already been used to develop strategies that can successfully correct the HGPS mutation (Liu et al., 2011), and, as with many other diseases, they will also be invaluable in screening approaches to identify possibly tissue-specific drugs. Finally, normal and gene-corrected HGPS iPS-derived tissue-specific cells may in the future provide a foundation for cell replacement therapy approaches to HGPS.

What Progeria May or May Not Teach Us about Normal Aging

Rare diseases often reflect highly prevalent pathological events and provide a unique opportunity to study physiological processes. In the case of HGPS, the obvious question is whether the disease provides insights into normal aging and, because cardiovascular failure is the source of significant morbidity and mortality, into aging-related cardiovascular disease.

The similarities between HGPS and normal aging extend to all levels, from shared molecular features to similarities in symptoms (Burtner and Kennedy, 2010; López-Otín et al., 2013). Notably, progerin is produced in normally aging individuals as well as in HGPS patients. This is because the classic HGPS mutation is a pre-mRNA splicing mutation, which activates a weak, yet sporadically used, intronic splice site that is present in wild-type individuals (Rodriguez et al., 2009; Scaffidi and Misteli, 2006). Progerin RNA and protein are detected in tissues from healthy individuals, even before the teenage years, albeit at levels ~50-fold lower than in HGPS cells. However, given the dominant-negative nature of progerin, these levels are likely sufficient to elicit limited cellular damage. In addition, there is histological evidence that progerin levels may increase with age and may be responsible for some of the cellular defects associated with aging, which are reminiscent of those seen in HGPS patients (McClintock et al., 2007). In support of a potential dosage effect of progerin, nonclassical progeria mutations that induce less frequent use of the internal splice site and thus lower cellular levels of progerin also cause a much milder form of disease but still eventually produce atherosclerosis (Hisama et al., 2011). The extent to which lower levels of progerin relative to HGPS can affect health and aging is undetermined, but evidence is accumulating to suggest a role of progerin in many aspects of generalized aging and cardiovascular health. Notably, the atherosclerotic plaques in HGPS are similar to those found in aging individuals (Olive et al., 2010). Additionally, vascular stiffening in progeria is much like that seen over a lifetime of aging reflected in each population by increased pulse wave velocity (Gerhard-Herman et al., 2012).

The cardiovascular system is of crucial importance in HGPS, as cardiovascular failure is the source of significant morbidity and almost all mortality. From a clinical perspective, HGPS is a primary vasculopathy, characterized by early and pervasive accelerated vascular stiffening followed by hypertension, vessel plaques, angina, cardiomegaly, metabolic syndrome, and congestive heart failure (Baker et al., 1981). Isolated from risk factors such as hypercholesterolemia and increased C-reactive protein (Gordon et al., 2005), early stage hypertension, and smoking, the study of HGPS could provide an opportunity to discover new elements that may influence the vascular disease component of aging. For example, the abnormally dense vascular adventitia observed in individuals with HGPS may contribute to their vessel stiffening, and the role of the adventitia in the pathobiology of generalized CVD during aging is just beginning to be explored (Havelka and Kibbe, 2011). Additionally, HGPS has shed light on mechanisms of vascular calcification in aging and atherosclerosis. Excess prelamin A or progerin results in calcium dysfunction (Ragnauth et al., 2010), and prelamin A promotes VSMC calcification and aging by inducing persistent DNA damage signaling (Liu et al., 2013). HGPS patients suffer from extraskeletal calcium phosphate deposition, which potentially acts as an important factor for vascular plaque development (Cleveland et al., 2012). These studies that show connections between cellular senescence, generalized calcium dysfunction, vascular calcification, and atherosclerotic plaque formation in both aging and HGPS represent emerging areas of cross-discovery in both basic and clinical research arenas (Mackenzie and MacRae, 2011).

Much like in normal aging, tissue stem cell functions appear to be compromised in HGPS (Espada et al., 2008; Rosengardten et al., 2011; Scaffidi and Misteli, 2008). In a progeroid mouse model that lacks the prelamin A endoprotease ZMPSTE24 and recapitulates some phenotypes seen in HGPS, the proliferative potential of epidermal stem cells is greatly reduced (Espada et al., 2008). Furthermore, expression of progerin in human mesenchymal stem cells triggers premature expression of lineage markers, albeit in the absence of differentiation, but at the same time interferes with differentiation along defined lineages, including adipogenesis and osteogenesis (Scaffidi and Misteli, 2008).

Notably, some key aspects of aging are not recapitulated in HGPS. Most prominent among these are the absence of nervous system deterioration, including dementia, and the lack of detectable immune system deficits. Recent studies

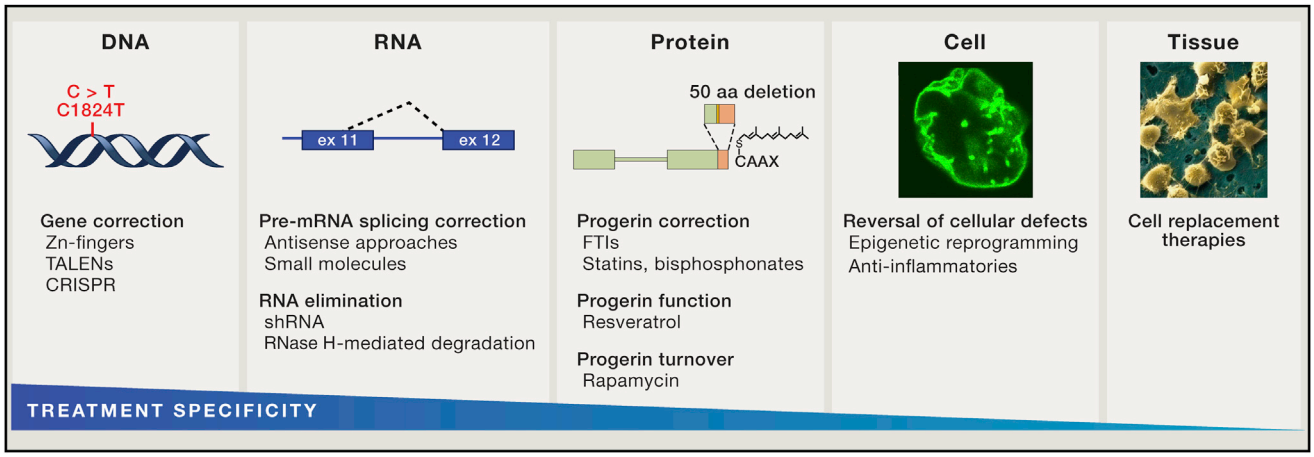

Figure 2. A Spectrum of Possible HGPS Therapies
HGPS is amenable to a wide spectrum of cutting-edge therapeutic strategies.

have shown that progerin levels in the brain are very low and that the microRNA miR-9 downregulates lamin A synthesis in the brain (Jung et al., 2012; Nissan et al., 2012). These results suggest that the lack of symptoms in the CNS of HGPS patients may be due to an absence of progerin in neural cells. This may also be the case for the absence of immune system deficiencies. Moreover, the paucity of reports on tumors or cancers in HGPS patients implies low susceptibility of their cells to malignant transformation, in contrast to the strong increase in tumor susceptibility during normal aging. The lack of tumors in HGPS patients is even more surprising, given the persistently high levels of DNA damage in HGPS cell lines. Interestingly, recent studies using ZMPSTE24 mosaic mice have revealed that prelamin A accumulation prevents cancer invasion and results in a decrease in the incidence of infiltrating carcinomas in association with altered extracellular matrix components (de la Rosa et al., 2013).

Like any premature aging syndrome, HGPS is only a partial representation of the multifactorial process of normal aging. However, rather than using discrepancies as an argument to diminish the potential of HGPS to provide insight into normal aging, a more productive approach may be to carefully elucidate the intersections and distinctions between HGPS and normal aging in order to gain new understanding within both fields.

Progeria as a Testbed for Therapeutic Strategies

The development of therapeutic strategies for HGPS benefited from the confluence of gene discovery and extensive prior knowledge of lamin A function at the time of the gene discovery. This made several therapeutic strategies immediately apparent. Remarkably, the time from gene discovery to the first human therapeutic trial for HGPS was just 5 years (Kieran et al., 2007). In the wake of initial therapeutic trials, exponential increases in our understanding of the disease mechanisms combined with technological advances have broadened the scope of both the potential therapeutic targets and approaches (Figure 2). All of the therapeutic strategies applied to HGPS are under consideration for many other diseases, and it is likely that experiences with HGPS will prove relevant to the larger medical community.

Drug Repurposing

Compared with developing any type of new medication, drug repurposing, which uses medications previously developed for other diseases, promises the shortest timeline from preclinical to clinical testing. Discovering that progerin is permanently farnesylated immediately opened the door for a candidate drug discovery approach using farnesyltransferase inhibitors (FTIs), which had previously been developed as potential anticancer drugs and had acceptable side effects in children. FTIs were quickly and successfully tested preclinically in cell culture (Capell et al., 2005; Glynn and Glover, 2005; Mallampalli et al., 2005; Toth et al., 2005; Yang et al., 2005) and animal models (Capell et al., 2008; Fong et al., 2006; Yang et al., 2008), which showed improvement of disease symptoms upon FTI treatment. A prospective single-arm clinical trial was initiated in 2007 with a cohort of 26 HGPS patients between 3 and 16 years of age. Administration of the FTI lonafarnib for a minimum of 2 years yielded improvements in weight gain, vascular stiffness, and bone structure in some patients (Gordon et al., 2012) and provided evidence for decreased headaches and strokes (King and Heyer, 2013; Ullrich et al., 2013), though the extent of improvements varied among patients.

Subsequent to initiation of the first clinical trial, it was reported that progerin was partially modified in cultured HGPS fibroblasts by geranylgeranylation after FTI treatment (Varela et al., 2008). This alternate modification could be blocked by statins and aminobisphosphonates that prevent the production of both farnesyl and geranylgeranyl precursors (Varela et al., 2008). This result offered one possible explanation for why FTI treatment only modestly lengthened lifespan in a mouse model (Yang et al., 2008) and prompted several currently ongoing therapeutic trials in which FTIs are combined with pravastatin (a statin) and zoledronic acid (an aminobisphosphonate). The development of combination therapies reflects a potentially powerful iterative approach between basic and clinical

sciences toward improving and optimizing therapeutic strategies.

The drug-repurposing approach for HGPS is still ongoing. One rationale is that treatments with putative prolongevity effects may also benefit children with HGPS. For example, the macrolide antibiotic rapamycin, which extends lifespan and improves stroke volume in several model organisms, including aging mice (Choi et al., 2012; Ramos et al., 2012), has been shown to abolish nuclear structure defects and postpone senescence in HGPS fibroblasts in cell culture by enhancing progerin clearance through autophagy (Cao et al., 2011b; Cenni et al., 2011). Another compound of interest is resveratrol, a SIRT1 activator that interacts with lamin A (Liu et al., 2012). In the presence of progerin, SIRT1 exhibits reduced association with the nuclear matrix and decreased deacetylase activity, leading to rapid depletion of adult stem cells in an HGPS model mouse. Treatment with resveratrol improved cellular phenotypes and extended lifespan in this mouse model (Liu et al., 2012). Other repurposed drug candidates are likely to emerge, for example, non-steroidal anti-inflammatory drugs, which may be useful for blocking the NF-κB-signaling hyperactivation observed in progeroid cells and mouse models (Osorio et al., 2012).

New Drug Discovery Strategies

The HGPS etiology offers several points of entry for drug discovery (Figure 2). One potential avenue is the identification of small molecular inhibitors of the aberrant pre-mRNA splicing event in HGPS. But this is a challenging undertaking, as no specifically acting small molecular regulators of pre-mRNA splicing have ever been reported. As a complementary approach, imaging-based high-content screens may be able to identify small molecules that prevent the formation, or promote the reversion, of HGPS cellular phenotypes. Aberrant nuclear morphology, DNA damage, or elimination of the progerin protein may serve as readouts for these cell-based approaches in drug discovery. HGPS patient-derived iPS cells should prove a particularly useful tool for such screens. New candidate molecules from several such screens are likely to be forthcoming shortly.

Similar to the farnesylation inhibitor treatment strategy, another potential treatment avenue is based on our understanding of lamin A posttranslational modifications. After farnesylation, the last three amino acids of prelamin A and progerin are cleaved, and the farnesylcysteine is methylated. Inhibition of the posttranslational methylation step was recently reported to improve HGPS cellular senescence in vitro and ameliorated disease and early death in a progeroid mouse model (Ibrahim et al., 2013).

RNA Therapy

Because the HGPS mutation results from the activation of an alternative pre-mRNA splice site, HGPS is a prime candidate for an RNA therapy approach via inhibition or elimination of this site. Reversal of phenotype by inhibition of the altered splice site was first achieved in HGPS fibroblasts by treatment with a morpholino antisense oligonucleotide targeted to the activated splice site (Scaffidi and Misteli, 2005). This strategy was successfully applied to a knockin HGPS mouse model, resulting in improved body weight, extended lifespan, and correction of several mutant phenotypes (Osorio et al., 2011). An alternative approach is to eliminate the progerin mRNA using siRNA-based methods (Huang et al., 2005). Although systemic delivery of oligonucleotides and siRNAs remains a challenge to these therapeutic approaches, the availability of an appropriate animal model, an extensively clinically characterized patient population, and a clearly defined primary target tissue (the vasculature) may make HGPS an attractive case study for the development of high-efficiency delivery methods for these types of agents (Kole et al., 2012).

Stem Cell Treatment

Many of the alterations seen in HGPS are consistent with stem cell dysfunction (Halaschek-Wiener and Brooks-Wilson, 2007; Wenzel et al., 2012). In vitro, progerin affects the multipotency and differentiation of human mesenchymal stem cells (Scaffidi and Misteli, 2008), and HGPS patient-derived iPS cells exhibit differentiation defects (Zhang et al., 2011). Furthermore, in a HGPS-related cellular model, the proliferative potential of epidermal stem cells was reduced (Espada et al., 2008), and in an inducible HGPS mouse model that specifically expresses progerin in skin, the epidermal population of adult stem cells was depleted and wound healing impaired (Rosengardten et al., 2011). This involvement of tissue-stem cells in the HGPS phenotype opens the possibility of cell-based replacement therapies using either matching wild-type cells or tissue-stem cells generated from genetically corrected HGPS iPS cells. Cell replacement approaches face many challenges, particularly in systemic diseases such as HGPS. However, the prominence of the vascular defects in HGPS may provide an interesting model system to explore the effectiveness of tissue-targeted approaches in systemic diseases.

Gene Therapy Approaches

As the progerin protein acts in a dominant fashion and its effects cannot be compensated by introduction of wild-type lamin A, gene therapy for HGPS focuses on targeted gene correction. For example, zinc-finger, TALEN, or CRISPR-based approaches, in which the *LMNA* is repaired ex vivo and corrected cells are re-introduced into patients, is a possibility, albeit a technically challenging one. As proof of principle for the feasibility of this approach, correction of the genetic defect in HGPS patient-derived iPS cells and their subsequent differentiation has been achieved (Liu et al., 2011).

Challenges of Clinical Trials for Rare Diseases

Rare diseases pose particular challenges in designing and executing clinical trials. Given that there are more than 6,800 rare diseases—about 80% of them with a genetic basis—the lessons learned during the rapid journey in HGPS from gene identification to clinical trial may be of value to other disease populations. The very limited pool of patients with HGPS required worldwide recruitment and organized communication with patient families and their physicians through programs such as international patient registries, diagnostics programs, and continued outreach to the patient community. For optimal trial execution, these processes must precede clinical trials by several years. For HGPS, this recruitment was achieved through a patient advocacy organization (The Progeria Research Foundation), and the first clinical trial was fully enrolled in under 4 months. Hospital-based centers of excellence with similar programs can also be useful for recruiting patients to trials.

Due in part to the 100% fatality rate in HGPS and in part to the extremely small subject numbers (26 in the published clinical trial), all human trials to date have used open label design with no placebo control groups. In order to assess drug efficacy, primary outcome measures have relied upon a change in individual patient status using each patient as his or her own control (Gordon et al., 2012) (ClinicalTrials.gov identifier: NCT00425607). Designing appropriate outcome measures required intensive and ongoing natural history studies to establish robust baseline values for each clinical parameter in each individual patient. For any disease, investment into natural history clinical trials, with the aim of identifying longitudinal trends in disease-relevant and consistently evaluable clinical abnormalities for use as treatment trial outcome measures, is invaluable. In addition, natural history studies are remarkably insightful and powerful in uncovering disease characteristics. For example, some of the most relevant vascular defects in HGPS were discovered during baseline studies conducted as part of the first clinical trial (Gerhard-Herman et al., 2012; Gordon et al., 2011; Silvera et al., 2013), which precluded their inclusion as primary outcome measures for trial drug efficacy but led the way for improving detection of therapeutic efficacy in future trials. The constraints and approaches seen in the HGPS trials are not unlike those in oncology trials for rare, fatal pediatric cancers, wherein similar challenges apply and similar trial designs are used (Pui et al., 2011).

Future trials will need to grapple with how to reliably measure changes in disease status in the face of combination therapies whose implementation will also further amplify the challenge of recruiting sufficiently large patient populations for each treatment combination. Although treatment outcomes have been published for HGPS monotherapy using lonafarnib (Gordon et al., 2012; Ullrich et al., 2013), its effects on patient morbidity and mortality are not yet known and will require longer-term patient exposure. Given this, an important issue at hand is whether it will be ethical and statistically viable to conduct future trials using a control arm with farnesylation inhibitors and a treatment arm with farnesylation inhibitors plus a new treatment of interest.

Regulatory approval based on uncontrolled or small trials is a huge challenge, as the U.S. Food and Drug Administration (FDA) is responsible for evaluating safety and efficacy and for weighing the risk-to-benefit ratio with much less data than what is supplied for common diseases. Rare disease applications are the fastest growing area of pharmaceutical and biotechnical development. Unlike only 5 years ago, today there is an acute awareness of rare diseases within the FDA, which has identified the rare disease space as a priority area. As a result, the FDA has proactively created the Center for Drug Evaluation and Research specifically for Rare Diseases Drug Development. In addition, the FDA and European Medicines Agency Orphan Drug status is designed to fast track what is usually a very long process, without compromising the quality of the review process. Although increasing patient numbers may not be an option, there is now a regulatory body that can be consulted specifically on recommendations for rare disease treatment trials.

Looking Back and To the Future

Progress in the HGPS field has been remarkably rapid over the last decade, and if the most recent Progeria Research Foundation Workshop is any indication, there is no sign of slowdown. Many of the hot topics in the field have both a basic and translatable clinical component, and the basic-clinical connection will be driving much of the future work. A recurrent theme was the emergence of various candidate small molecules for consideration in clinical trials, which has been driven by our growing understanding of the molecular and cellular mechanisms affected in the disease.

Everyone wants to get to the finish line—to cure patients with fatal diseases and translate discoveries to the clinic. Looking back over the past 10 years in the progeria field, we see a roadmap for how to optimize our chances of tackling a disease once its molecular basis is uncovered. Key elements to success are a strong basic research foundation that creates a detailed knowledge base of the fundamental cellular disease process, access to patient populations, and intense crosstalk between basic and clinical investigators.

We have learned many important lessons from a very rare disease, and they will undoubtedly be applicable to many other diseases, especially as the rate with which disease-causing genes are being identified is growing exponentially due to the availability of powerful genomic methods. Perhaps most importantly, the story of HGPS is yet another example for how one can never predict how scientific research on basic and sometimes obscure-sounding topics, such as farnesylation of a precursor to a nuclear scaffold protein, may one day become the key to better health for many.

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