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EDITORIAL

Progeria: a perspective on potential drug targets and treatment strategies

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1. Introduction to Hutchinson-Gilford progeria syndrome (HGPS)

HGPS is an ultra-rare genetic disease (prevalence 1 in 18 million people) characterized by accelerated aging and premature death at an average age of 14.6 years (www.progeriaresearch.org). Most HGPS patients are heterozygous carriers of a de novo synonymous mutation (c.1824C>T) in the *LMNA* gene [1,2], which encodes the nuclear lamina proteins lamin A and C, generated by alternative splicing. In normal cells, lamin A maturation includes the farnesylation, methylation, and subsequent cleavage of its C-terminus by the zinc metalloprotease ZMPSTE24. The HGPS mutation activates the use of a cryptic splice donor site in exon 11, generating an aberrant lamin A variant called progerin that lacks 50 amino acids spanning the ZMPSTE24 cleavage site and therefore remains permanently farnesylated and methylated [3] (Figure 1).

Progerin exerts a dominant-negative effect, inducing multiple cellular and organismal alterations. HGPS patients appear normal at birth, and the first disease symptoms are growth failure and alopecia, typically appearing in the first or second year of life. Over time, additional symptoms develop and worsen, including dermal and bone abnormalities, joint contractures, and lipodystrophy. Although patients typically lack most traditional cardiovascular risk factors, their main medical problem is severe cardiovascular disease, including generalized atherosclerosis and vascular calcification and stiffness, which can ultimately provoke fatal myocardial infarction, stroke, or heart failure [3].

There is no cure for HGPS. Nevertheless, since the discovery of the HGPS mutation in 2003 [1,2], multiple preclinical studies have continually yielded improvements in the understanding of progerin-dependent cellular and organismal alterations, paving the way for the development of new therapeutic approaches. Numerous drug-based strategies ameliorate progerin-induced alterations in cultured cells (reviewed in [4,5]), but only some have proved beneficial in HGPS mouse models with ubiquitous progerin expression. These include modulating inflammation by targeting NF-κB [6] and IL6 [7], decreasing progerin-lamin A/C interaction by JH4 and progerinin treatment [8,9], inducing progerin

clearance by MG132 administration [10], and inhibiting N-acetyltransferase 10 (NAT10) using remodelin [11], although remodelin´s ability to specifically inhibit NAT10-catalyzed RNA acetylation has been recently questioned [12]. Additional molecules have been shown to reduce HGPS-associated cardiovascular alterations, such as tauroursodeoxycholic acid (an endoplasmic reticulum stress inhibitor) [13], β-aminopropionitrile (a lysyl oxidase inhibitor) [14], batimastat (a metalloprotease inhibitor) [15], and paclitaxel (a chemotherapeutic agent that stabilizes microtubules) [16]. Other therapeutic strategies shown to extend the lifespan and/or improve the progeroid phenotype of progerin-expressing mice include pyrophosphate treatment [17] and ATP-based therapy [18], dietary supplementation with sodium nitrite [19] and magnesium [20], dietary methionine restriction [21], and fecal microbiota transplantation from healthy animals [22]. Here, we discuss current and potential treatment options for HGPS based on drugs targeting progerin posttranslational modifications and genetic approaches to correct the HGPS-causing *LMNA* mutation and aberrant splicing.

2. Drugs to treat HGPS: targeting progerin posttranslational modifications

Several pharmacological strategies have been tested in cell and animal models for their ability to target the production, degradation, and downstream effects of progerin [4,5]. Here, we discuss the treatment of progeria with farnesyltransferase inhibitors (FTIs). We also review the potential for treating HGPS by targeting the enzyme isoprenylcysteine carboxyl methyltransferase (ICMT), another enzyme that posttranslationally modifies progerin, and discuss the pros and cons of both strategies.

2.1. Inhibiting progerin prenylation

In the years following the identification of the HGPS mutation in *LMNA* and the role of ZMPSTE24 in prelamin A maturation, several groups proposed that the farnesyl lipid that remains permanently attached to progerin might contribute to its toxic
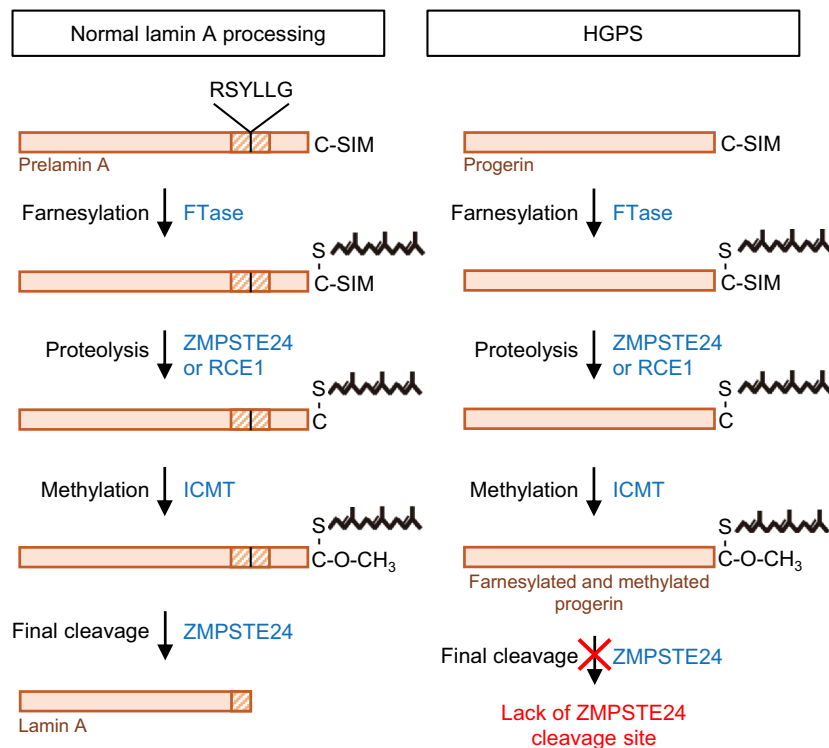
Figure 1. Post-translational processing of prelamin A and progerin. In normal cells, prelamin A C-terminus (CAAX motif, CSIM in prelamin A) is sequentially farnesylated by FTase, cleaved by ZMPSTE24 or RCE-1 to remove the last three residues, and methylated by ICMT. In a final step, prelamin A C-terminus is cleaved by ZMPSTE24 resulting in mature non-farnesylated, non-methylated lamin A. In HGPS cells, progerin lacks a 50 amino acid region that contains the ZMPSTE24 cleavage site (RSYLLG), and therefore remains permanently farnesylated and methylated at its C-terminus. FTase, farnesyltransferase; ZMPSTE24, zinc metallopeptidase STE24; RCE-1, Ras-converting CAAX endopeptidase 1; ICMT, isoprenylcysteine carboxyl methyltransferase.

effects (Figure 1). This led to attempts to inhibit farnesylation with FTIs previously developed to block RAS-driven cancer. Several studies on progeroid cells demonstrated the ability of FTIs to reduce the frequency of progerin-induced nuclear shape abnormalities (reviewed in [4,5]), but few of them investigated whether blocking farnesylation influences the senescence phenotype of cells or improves their proliferation.

The first in vivo experiments with FTIs evaluated the impact of ABT-100 supplied in drinking water on the disease phenotypes of progeroid *Zmpste24*-deficient and *Lmna*$^{HG/+}$ mice (which accumulate prelamin A and progerin, respectively). The results revealed that FTI administration attenuates most premature aging phenotypes [23]. Likewise, the FTI tipifarnib (R115777, Zarnestra) significantly delayed the onset of cardiovascular problems and attenuated existing cardiovascular disease in progerin-expressing *Lmna*^{G609G} mice [24]. However, all FTI-treated mice eventually died from progeria, suggesting that FTIs can delay but not cure symptoms. This may be in part related to the reported anti-proliferative effects of FTIs or to detrimental effects arising from the blocked farnesylation of substrates other than progerin.

The results of these and other preclinical studies were sufficiently convincing to justify testing FTIs in children with HGPS. Clinical trials in HGPS are exceedingly difficult to perform due to the low numbers of patients, their fragility, and the distance some of them must travel to participate. It is also difficult or even impossible to use a placebo-controlled regimen. Nevertheless, clinical trials with FTIs were started and produced several clear outcomes.

A phase II clinical trial in which 25 children with HGPS received lonafarnib for at least 2 years provided preliminary evidence that this FTI may ameliorate arterial stiffness, bone alterations, and audiological status [25]. In another study comparing treated versus age- and sex-matched untreated HGPS cohorts, lonafarnib was estimated to increase mean survival by 1.6 years [26]. Recently, the Food and Drug Administration (FDA) approved the use of lonafarnib (Zokinvy) for the treatment of HGPS and other progeroid laminopathies [27]. Future clinical trials are likely to evaluate the efficacy of lonafarnib in combination with new candidate therapies.

Additional strategies to treat progeria were based on the idea that progerin and prelamin A, like K-RAS, might undergo alternative prenylation by protein geranylgeranyltransferase type I (GGTase-I) when FTase is inhibited by FTIs [4]. In line with this idea, bone density was partially preserved, and survival increased in progeroid *Zmpste24*$^{-/-}$ mice upon treatment with statins and aminobisphosphonates, which inhibit both the farnesylation and the geranylgeranylation of progerin/prelamin A [28]. However, the results of a single-arm triple therapy trial revealed no additional benefit of combining lonafarnib with pravastatin and zoledronate compared with lonafarnib monotherapy [29]. The idea that statins and bisphosphonates inhibit prenylation is based on the exposure of cultured cells to high drug doses, which reduce and even block prenylation of certain substrates in this setting. However, there is little or no robust evidence that these classes of drugs inhibit either farnesylation or

geranylgeranylation in human tissues in vivo. It is also possible that progerin contributes to HGPS pathogenesis due in part to the lack of 50 amino acids in its C-terminus compared to normal lamin A, an alteration that is not expected to be corrected by FTIs and geranylgeranylation inhibitors.

2.2. Inhibiting progerin methylation

Oncogenic RAS mutations are found in roughly one-third of all cancers. All RAS proteins are methylated by ICMT following farnesylation and removal of the last three amino acids (the – AAX residues of the carboxyl-terminal CAAX motif). Knockout of Icmt in mice mislocalizes RAS proteins away from the plasma membrane and inhibits RAS-mediated cell transformation [30]. Prelamin A and progerin are both methylated by ICMT following farnesylation and – AAX proteolysis (Figure 1), leading Ibrahim and colleagues to propose that inhibiting ICMT might reduce progerin and prelamin A toxicity. Their experimental analysis confirmed this idea and revealed that knockout or knockdown of Icmt mislocalized progerin and prelamin A away from the nuclear rim, markedly delayed senescence, and increased proliferation of human HGPS cells and mouse Zmpste24-knockout cells [31]. In vivo, Icmt deficiency in progeroid Zmpste24-knockout mice increased body weight and grip strength, prevented the osteoporosis and bone fracture phenotypes, and extended lifespan [31]. Icmt inactivation also improved phenotypes and extended survival in progerin-expressing heterozygous and homozygous $Lmna^{G609G}$ mice, although it surprisingly did not improve nuclear shape alterations [32]. These results suggest that the nuclear shape abnormalities in progeria require farnesylation but not methylation, and that progeroid phenotypes can be improved despite the continuing abundance of nuclear shape defects.

These studies suggested the potential of ICMT inhibitors in HGPS therapy. Two groups produced the ICMT inhibitors C75 and UCM-13207 and showed that they have a therapeutic benefit similar to that of ICMT genetic inactivation, reducing the levels of multiple senescence markers and increasing viability and proliferation of mouse and human HGPS cells without affecting nuclear shape [32,33]. Conversely, in side-by-side experiments, the FTI lonafarnib dose-dependently normalized nuclear shape abnormalities but reduced proliferation of HGPS cells [32], underscoring the different consequences of inhibiting progerin farnesylation and methylation. Furthermore, treatment of progerin-expressing $Lmna^{G609G/G609G}$ mice with UCM-13207 improved some vascular alterations, increased body weight and grip strength, and extended survival by ≈30% [33].

Several lines of evidence suggest that a key mediator of the positive effects of reduced ICMT activity in progeroid cells is the activation of AKT, which interacts with prelamin A in cultured fibroblasts derived from $Zmpste24^{-/-}$ mice and with progerin in fibroblasts from HGPS patients; this interaction is disrupted by ICMT genetic inactivation or pharmacological inhibition, and both strategies stimulate the AKT signaling pathway [31–33]. Pharmacological inhibition of AKT signaling prevents the increased proliferation of $Zmpste24^{-/-}$ fibroblasts after ICMT inactivation [31], strongly suggesting that AKT signaling is an important mediator of the effects of ICMT deficiency.
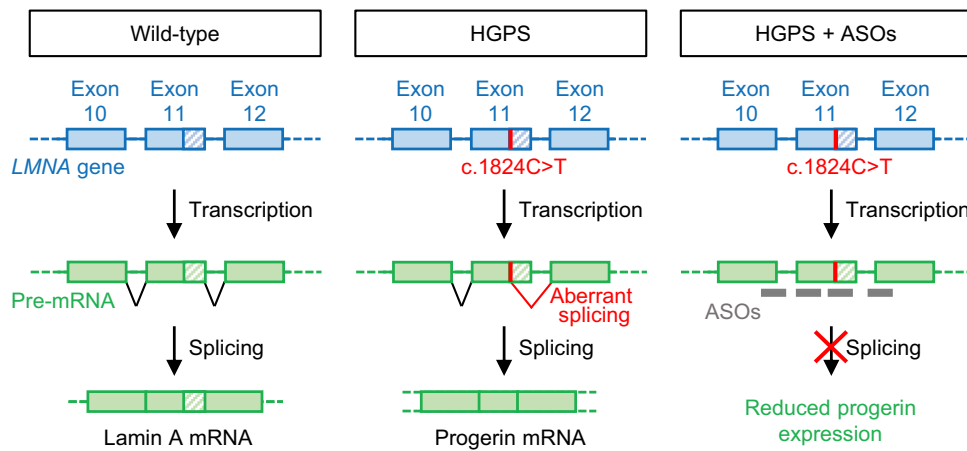
3. Genetic approaches to treat HGPS

Significant efforts have focused on the development of therapeutic approaches in preclinical models to correct the underlying genetic cause of HGPS. Several groups have used antisense oligonucleotide (ASO) technology in attempts to reduce progerin expression by inhibiting the aberrant splicing of the LMNA gene induced in exon 11 by the HGPS-causing mutation (Figure 2). More recently, with the advent of gene-editing technologies, the aim has become even more ambitious: to correct the disease-causing mutation (Figure 3). In this section, we summarize the progress and achievements of these lines of research.

3.1. ASO-mediated inhibition of aberrant LMNA splicing

ASOs are chemically synthesized oligonucleotides designed to bind and inactivate specific RNAs by steric blockade or the promotion of RNA degradation [34]. Their potential therapeutic use in HGPS was first tested in vitro by transfecting fibroblasts from HGPS patients with an ASO targeting the sequence containing the HGPS-causing mutation; this strategy reduced progerin expression and corrected the progerin-induced phenotype, including nuclear morphology alterations, nuclear protein mislocalization, and altered expression of selected genes [35]. In subsequent studies, various ASOs showed similar results in fibroblasts from HGPS patients [36,37], as well as in fibroblasts from HGPS-like patients harboring non-classical LMNA mutations that weaken the normal splicing site and also provoke progerin expression [38]. These studies revealed that progerin-targeting ASOs also reduce lamin A levels, raising concerns about the potential harm of lamin A depletion in vivo. However, $Lmna^{LCO/LCO}$ and $Lmna^{LCS/LCS}$ mice that lack lamin A but maintain lamin C expression showed no apparent phenotype and no alteration to lifespan compared with lamin A/C-expressing wild-type controls [36,39]. These results encouraged researchers to start testing the potential of ASOs to reduce progerin levels in vivo [36]. $Lmna^{G609G/G609G}$ mice were treated twice weekly starting at 6 weeks of age with a combination of two ASOs targeting different Lmna regions in order to inhibit the splicing events that induce lamin A and progerin expression. ASO treatment decreased progerin mRNA levels by ≈50% in liver, kidney, and heart, with a less pronounced reduction of protein expression. The treatment also reduced senescence markers in liver and kidney and partially restored normal serum glucose, subcutaneous fat layer thickness, and the size of the thymus and spleen. Importantly, ASO treatment increased lifespan by ≈40%, providing the first in vivo evidence of the potential of ASO technology to treat HGPS [36]. In another study, a ≈ 50% reduction in aortic progerin content was reported in $Lmna^{G609G/G609G}$ mice treated with an ASO selected from an in vitro screening approach that targeted a region 70 nucleotides upstream of the HGPS-causing mutation; the treatment also improved the HGPS-associated vascular phenotype, reducing loss of vascular smooth muscle cells (SMCs) and adventitial fibrosis, although longevity data were not reported [37].

More recently, two studies [40,41] confirmed the beneficial effects of ASO-dependent inhibition of progerin expression in homozygous G608G BAC mice, an HGPS mouse model which

Figure 2. Antisense oligonucleotide (ASO)-based approaches to treat HGPS. The HGPS mutation (c.1824C>T) activates the use of a cryptic splice donor site in *LMNA* exon 11, generating an aberrant lamin A variant called progerin. ASOs targeted to different regions of exons 10, 11, and/or 12 have been shown to impair the splicing events needed to generate mouse and human progerin mRNA, therefore reducing progerin expression [36,40,41].
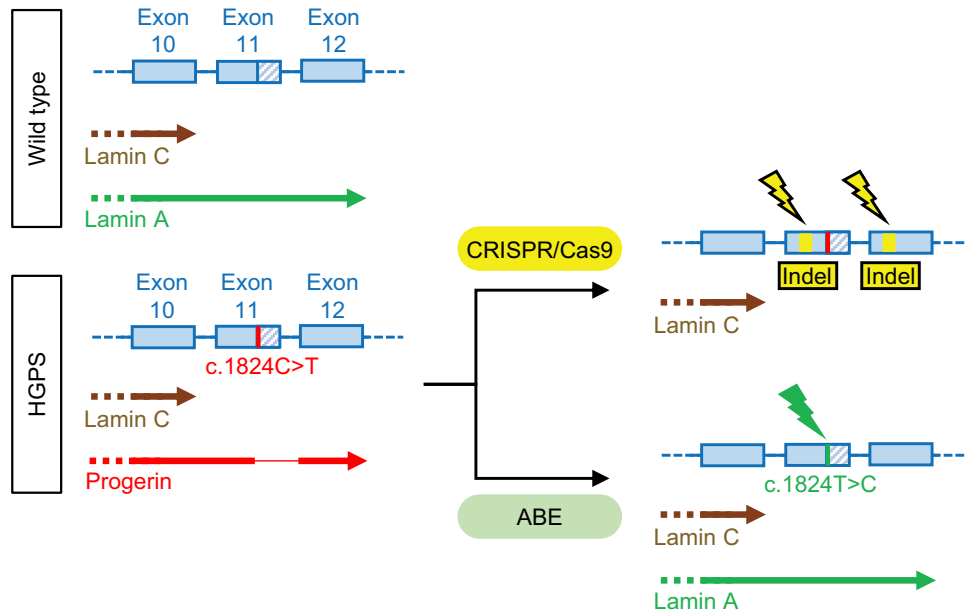
Figure 3. Gene editing by CRISPR/Cas9 and ABEs to treat HGPS. Alternative splicing of wild-type *LMNA* transcripts results in the expression of lamin A and C, whereas *LMNA* alleles containing the HGPS mutation (c.1824C>T) give rise to progerin and lamin C, and only residual levels of lamin A. The use of CRISPR/Cas9 to generate indels in *LMNA* exons 11 and 12 creates sequence frameshifts that abrogate lamin A and progerin expression without affecting lamin C levels [43,44]. An adenine base editor (ABE) targeted to the HGPS mutation converts the A•T base pair back into a wild-type G•C base pair and therefore suppresses the aberrant splice site in exon 11, eliminating progerin and restoring lamin A expression [45].

expresses human progerin and lamin A/C in addition to endogenous mouse lamin A/C [42]. The main advantage of this model compared with $Lmna^{G609G/G609G}$ mice is that the candidate ASOs targeted the human (not mouse) *LMNA* gene, and therefore would have more translational potential. The authors screened ASOs with different chemical properties and targeted to a variety of regions within the *LMNA* gene. The best candidates were selected based on their ability to reduce progerin and lamin A levels without decreasing lamin C expression both in vitro and in vivo. Asymptomatic 2–6-week-old G608G BAC mice treated weekly with the selected ASOs showed a strong reduction in progerin mRNA levels in many tissues, with a less pronounced reduction in progerin protein [40,41], similar to the findings in $Lmna^{G609G/G609G}$ mice [36]. ASO treatment increased the lifespan of G608G BAC

mice by 35–60% [40,41], and one of the studies showed partial prevention of SMC loss and adventitial thickening in the ascending aorta [41], two main features of the HGPS vascular phenotype.

3.2. Using gene-editing technology to correct the HGPS-causing mutation

Gene editing has recently emerged as a very promising approach with the potential to eventually cure monogenic disorders such as HGPS. In 2019, two independent groups reported the use of CRISPR/Cas9-based technology to correct the HGPS-causing mutation in vivo in progeroid $Lmna^{G609G/G609G}$ mice [43,44]. Based on the normal phenotype and

lifespan of mice that express lamin C but lack lamin A [36,39], the rationale behind both studies was to generate DNA double-strand breaks in *Lmna* exon 11 and/or 12 that, after repair by non-homologous end-joining, would generate insertions and deletions (indels) that abrogate progerin and lamin A expression without affecting lamin C levels. The molecular machinery needed for gene editing was packaged into modified adeno-associated virus 9 (AAV9) particles, which were systemically administered to newborn *Lmna*$^{G609G/G609G}$ mice as a single injection either intraperitoneally [43] or via the facial vein [44]. Indels in the *Lmna* gene were readily detected in liver (≈15–35% genomic copies) and less frequently in heart, muscle, and lung (≈1–5%). A reduction in the number of progerin-positive cells was detected in liver, heart, and muscle, but not in aorta, kidney, or lung [43]. Despite the limited extent of *Lmna* editing, CRISPR/Cas9-based treatment increased lifespan by ≈25% and ameliorated several progeroid features, including failure to thrive, hypoglycemia, bradycardia, impaired skeletal muscle function, heart perivascular fibrosis, and loss of aortic SMCs [43,44].

It remains unknown whether lack of lamin A is as harmless in humans as it is in mice, and CRISPR/Cas9-based strategies involving lamin A depletion together with progerin suppression may be unsuitable for clinical practice. Koblan et al. [45] recently reported the benefit of a safer approach aimed at reverting the *LMNA* c.1824C>T mutation into a C, eliminating progerin and recovering normal lamin A expression, which constituted a major breakthrough for the HGPS and gene editing fields. The authors used an adenine base editor (ABE), an engineered molecular structure that can target a single A•T base pair in the entire genome and convert it into a G•C base pair. In ABE-treated fibroblasts derived from HGPS patients, ≈90% of genome copies were corrected, and progerin protein levels were reduced 15-fold, with no decreases in lamin A/C. Likewise, progerin protein levels were markedly reduced in many tissues 6 months after a single intravenous retro-orbital injection of AAV9-ABE into 14-day-old homozygous G608G BAC mice (reductions of >80% in liver and heart and ≈50% in aorta), and this treatment totally prevented aortic SMC loss and adventitial thickening and increased lifespan 2.4-fold compared with controls.

4. Expert opinion

The recent FDA approval of lonafarnib as the first drug to treat HGPS was an important milestone, achieved after two decades of basic and clinical research and several clinical trials. Today, children with progeria can be treated with a drug that improves their vascular phenotype and extends their life expectancy. However, much work lies ahead to enhance the quality of life of HGPS patients, to further increase their lifespan, and eventually cure the disease.

Although targeting progerin farnesylation and methylation with chemical inhibitors ameliorates some progerin-induced alterations, many questions remain about the underlying mechanisms. Regarding ICMT inhibition, all tested strategies improved progeroid features; however, whereas genetic inactivation and C75 treatment tended to increase progerin levels in cells [32], UCM-13207 reduced progerin levels [33].

Moreover, the role of AKT-mTOR signaling as a downstream effector of ICMT inhibition awaits in vivo validation. The impact of mTOR signaling downstream of AKT also needs to be assessed. Given that mTOR haploinsufficiency extends lifespan of HGPS mice [46], additive positive effects might be expected by combining ICMT-targeting drugs with mTOR inhibitors such as everolimus, which is currently being tested in an HGPS clinical trial in combination with lonafarnib (ClinicalTrials.gov, NCT02579044). Although more studies are clearly needed to fully define the consequences of targeting ICMT, currently available data support further assessment of ICMT as a drug target in HGPS therapy.

A major drawback of blocking FTase and ICMT to treat HGPS is that these endogenous enzymes target many other proteins in addition to progerin. Alteration of homeostatic farnesylation and methylation after FTase and ICMT inhibition could therefore have detrimental side effects that partially counteract the positive outcomes of reducing progerin-induced disease. Several groups have developed treatment strategies that target progerin more specifically, for example with progerinin (a drug that disrupts the interaction between progerin and lamin A and increases lifespan of HGPS mice by ≈50%) [8,9], or using the ASO-mediated strategies outlined above. Because the FDA has already approved the use of ASOs to treat other diseases, including Duchenne muscular dystrophy and spinal muscular atrophy [34], it would not be surprising if ASOs were tested in HGPS patients in the near future. However, given the multiple candidate treatments uncovered by preclinical studies, as well as the extreme difficulty of carrying out clinical trials with HGPS patients, the strategies to be tested in humans must be chosen very carefully. Validation in large animal models such as pigs [47] or monkeys [48], which resemble human physiology more closely than other models, could aid in this decision-making process.

Although ASOs and other drug-based strategies have proved beneficial in HGPS mouse models, these approaches require continuous administration, do not correct the origin of the disease, and treated animals still die prematurely from HGPS. Therefore, over the long term, the ideal goal would appear to be a definitive cure based on a single intervention using gene editing technologies. In light of the currently available data, the use of ABEs seems more advantageous than CRISPR/Cas9-based approaches, since the ABE technology does not generate double-strand DNA breaks, does not involve lamin A suppression, efficiently corrects the HGPS-causing mutation without detectable off-target DNA or RNA editing, prevents the major features of HGPS-associated vascular phenotype, and extends lifespan more than any other tested treatment [45]. Nonetheless, before moving into clinical trials, more preclinical studies are needed to increase the safety and effectiveness of ABE-based treatment, by improving its efficiency, optimizing vectors, fine-tuning the dose, and establishing the optimal therapeutic window to achieve the best possible outcome in patients. In this regard, a recent study in the *HGPSrev* mouse model showed that progerin suppression and lamin A restoration in mildly symptomatic animals was much more beneficial than in severely ill animals [49], underscoring the importance of carefully selecting the best time window for therapeutic intervention. The same study reported prevention of major HGPS-associated vascular alterations and lifespan

normalization when progerin suppression and lamin A restoration were restricted to SMCs and cardiomyocytes [49]. Future gene-editing therapies may therefore yield good results by targeting only the cardiovascular system, which would probably require lower doses and facilitate delivery of the gene-editing machinery. Until the clinical use of gene-editing technology becomes available, treatment with lonafarnib and probably other compounds such as ICMT inhibitors and ASOs will improve quality of life and increase lifespan of children with HGPS.

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Declaration of interest

Reviewer disclosures

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