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Current Therapeutic Approaches for Hutchinson-Gilford Progeria Syndrome

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Hutchinson-Gilford Progeria Syndrome (HGPS; OMIM #176670) is a rare genetic disorder characterized by accelerated aging beginning in infancy. It is primarily caused by a *de novo* point mutation in the *LMNA* gene (c.1824C>T; p.G608G), which results in the production of progerin that disrupts nuclear integrity and promotes cellular senescence. The identification of LMNA gene has led to significant advances in targeted therapeutic research in the past 20 years. In this review, we will outline the pathophysiology of HGPS, and discuss the mechanism based therapeutic strategies, including recently approved drug, lonafarnib. We also address the multidisciplinary approach in the comprehensive management of patients with progeria.

Key words: Progeria, Therapeutics, Progerin, Lamin A, Rare disease

REVIEW ARTICLE

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INTRODUCTION

Hutchinson-Gilford Progeria Syndrome (HGPS; OMIM #176670), also known as Progeria, is an ultra-rare genetic disorder characterized by fatal, rapidly progressive aging. The estimated prevalence is 1 in 20 million. Classic HGPS is caused by a *de novo* mutation in the *LMNA* gene (c.1824C>T; p.G608G), which leads to production of mutant lamin A, progerin. Affected infants appear normal at birth, but clinical features such as skin changes, growth failure, distinctive facial features and joint contracture, begin shortly after birth and progress over time. Average life expectancy is 14 years, primarily due to myocardial infarction and stroke resulting from rapidly progressing atherosclerosis [1-3]. Although HGPS was first described in 1886, management remained limited to symptomatic care until the early 2000s. The identification of the *LMNA* mutation and understanding of progerin's role have opened new avenues for targeted therapeutic research [4]. In this article, we review current and emerging treatment strategies, with a focus on their mechanisms of action and therapeutic potential.

PATHOPHYSIOLOGY OF HGPS: GENETIC MECHANISM, PROGERIN PRODUCTION, MOLECULAR MECHANISMS, RESEARCH MODEL

Classic HGPS is an autosomal dominant disorder mainly caused by *de novo* mutation in exon 11 of *LMNA* gene (c.1824C>T; p.G608G) located on chromosome 1q22 (Fig. 1A) [4]. The *LMNA* gene consists of 12 exons and encodes lamin A and lamin C, which are key structural components of the nuclear lamina [5]. Lamin A is initially synthesis as prelamin A and undergoes a series of post-transla-

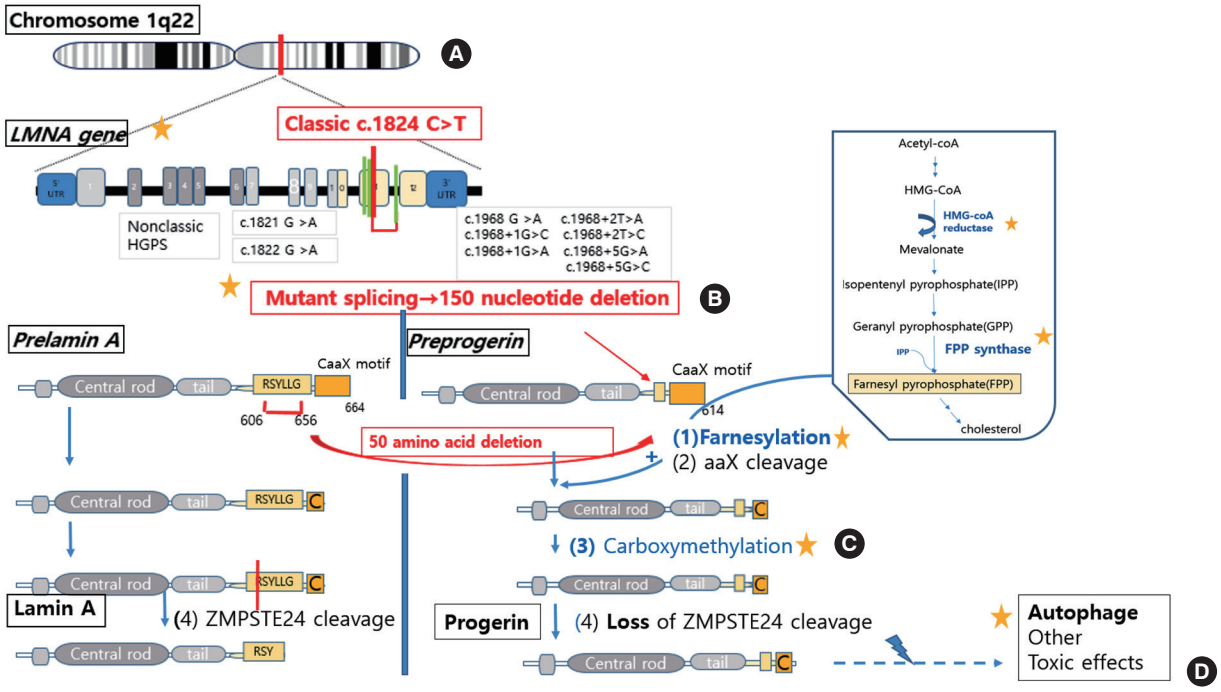


Fig. 1. Schematic illustration of the genetic and molecular mechanisms of progerin production in Hutchinson-Gilford Progeria Syndrome (HGPS). (A) *LMNA* gene is located on chromosome 1q22. (B) Classic HGPS is caused by a *de novo* c.1824C>T (p.G608G) mutation in exon 11, while non-classic HGPS is associated with other mutations in exon or intron 11. These mutations induce aberrant splicing, leading to a ~150 nucleotide deletion. (C) The deletion results in a truncated form of prelamin A, termed preprogerin, lacking 50 amino acids near the C-terminal region, including the ZMPSTE24 cleavage site. (D) Normally, prelamin A undergoes four sequential post-translational modifications: (1) Farnesylation of the C-terminal cysteine residue, (2) aaX cleavage by ZMPSTE24, (3) Carboxymethylation, and (4) final cleavage by ZMPSTE24 to generate mature lamin A. In HGPS, this final cleavage step is absent due to the loss of the cleavage site, resulting in the accumulation of permanently farnesylated progerin. Progerin accumulation leads to impaired autophagy and other toxic effects. Stars (*) indicate therapeutic targets designed to inhibit specific steps in the pathological process.

tional modifications to become mature lamin A (Fig. 1C):

1) Farnesylation: A farnesyl group is added to the cysteine residue within the C-terminal CaaX motif by farnesyltransferase.
2) -aaX Cleavage: The terminal three amino acids (-aaX) are cleaved off by the endoprotease ZMPSTE24.
3) Carboxymethylation: The exposed farnesylated cysteine residue is methylated by isoprenylcystein carboxylmethyltransferase (ICMT).
4) Cleavage of the farnesylated Tail: ZMPSTE24 removes the remaining 15 amino acids, including the farnesylated cysteine, producing mature lamin A. These modifications are crucial for the proper function and localization of lamin A within the nuclear lamina.

In classic HGPS, a mutation in exon 11 (c.1824C>T) induces aberrant splicing, results in the deletion of 50 amino acids nearby C-terminal region of prelamin A, producing a truncated protein known as preprogerin. Since the deleted region includes ZMPSTE24 cleavage site, final cleavage does not occur, leading to the accumulation of permanently farnesylated protein, progerin (Fig. 1D). Non-classic HGPS is associated with other *LMNA* pathogenic variants in exon 11 or intron 11 that results in production of progerin (Fig. 1B). Progerin accumulation disrupts nuclear organization and leads to epigenetic alterations, accelerated telomere shortening, mitochondrial dysfunction, defects in DNA damage response, altered p53 activation and autophagic degradation. These changes contribute to cellular aging and premature senescence. HGPS serve as a compelling model for studying genetic disorders, cellular senescence, clinical research, and regenerative medicine.

Progeria research models enhance understanding of its pathophysiology and developing of targeted therapies. Cellular models include HGPS patient-derived fibroblasts, iPSC-derived cells, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9-engineered gene edited models expressing progerin normal cells. Recently, organoid blood vessel

Table 1. Comprehensive overview of progeria therapeutic strategies

Therapy target		Drug	Mechanism
Genome editing		CRISPR-Cas9, ABE	Gene correction
Aberrant RNA splicing		ASO	Block aberrant splicing
Posttranslational modification	Mevalonate pathway	Statin, Bisphosphonate	Reduce progerin prenylation
: progerin production	Farnesylation	Lonafarnib (Zokinvy)	1st FDA approval drug
			Farnesyltransferase inhibitor
	Carboxymethylation	ICMT inhibitor	Block final maturation of progerin
Progerin clearance	Autophage activation	Everolimus, Rapamycin, temsirolims	mToR inhibitor
		Sulforaphane	Antioxidant
		Metformin, MG132	AMPK activation
	Mitochondrial dysfunction	Methylen blue	Antioxidant
Hazardous effects of progerin	Nuclear abnormalities	Progerinin (JH4 analogue)	Inhibit laminA /progerin binding
		Resveratrol, Leptomycin B, selinexor	CRM1 inhibitor- restore chromatin structure
			Normalize nuclear export
		Doxycycline	Alleviates the abnormal nuclear envelope
	DNA damage response	ATM inhibitor (KU-60019), methylene blue	DNA repair enhancement
		TERT circRNA(26)	Telomerase elongation
	Inflammation	Baricitinib, Vitexin	JAK-STAT inhibitor
		Dapansutrile (NLRP inhibitor),	Suppresses proinflammatory cytokines
		Tocilizumab (IL-6R inhibitor)	
	Endothelial dysfunction	Angiopoietin-2	Increase vascular health
		Vertepofin (YAP/TAZ inhibitor)	
	Stem cell depletion	Stem cell therapy	Replace damaged stem cells
	Senolytic	Dasatinib, Quercetin	Remove senescent cells

The therapies are categorized based on their mechanism of action, including genome editing, progerin production, progerin clearance, and reducing hazardous effecs of progerin. Bold text with line indicated that clinical trial has been conducted.
CRISRP/Cas, clustered regularly interspaced short palindromic repeats/CRISPR- associated protein 9; ABE, adenine base editing; ASO, antisense oligonucleotides; ICMT, isoprenylcystein carboxyl methyltransferase; ATM, ataxia-telangiectasia mutated.

models have also been utilized. *In vivo* models, *Lmna*$^{G609G/G609G}$ (HGPS Mouse Model) and *Zmpste24*$^{-/-}$ mice, which mimic laminopathy-related premature aging, tissue specific progerin producing model (progerin^{ecTg}, progerin^{VSMCTg}, etc.) as well as ApoE$^{-/-}$ mice further facilitate investigations into disease mechanism and therapeutic strategies (Table 1).

CURRENT THERAPEUTIC APPROACHES OF HGPS

Following the identification of *LMNA* mutations in 2003, therapeutic strategies for HGPS have progressed through several phases:

2003-2010: Drug repurposing

During this period, researchers focused on repurposing existing drugs to target progerin production and accumulation. Notably, farnesyltransferase inhibitor (FTIs), initially developed for cancer treatment, were employed to inhibit the farnesylation of progerin, aiming to reduce its deleterious effects.

2010-2020: Combination therapies and enhancement of cellular clearance mechanisms.

The therapeutic approach evolved to include combination therapies that not only targeted progerin modification but also enhanced its clearance. For instance, combining FTIs with statins and aminobisphosphonates aimed to prevent alternative prenylation pathways. Additionally, agents like rapamycin were investigated for their potential to promote autophagic degradation of progerin.

2020-Present: Gene-based and regenerative approaches, aiming for disease reversal.

Recent advancements have shifted towards gene-based therapies, including CRISPR/Cas9-mediated correction of the LMNA mutation, offering the potential for disease reversal. These approaches aim to directly address the underlying genetic defect responsible for HGPS.

These evolving strategies reflect a comprehensive effort to mitigate the effects of HGPS, ranging from modifying post-translational processing of progerin to correcting the genetic mutations at their source.

1. FTI (Fig. 1C-(1), farnesylation*)

FTIs were originally developed as anticancer agents. These compounds to bind to the farnesyltransferase CAAX motif on progerin, preventing its farnesylation and subsequent progerin accumulation. By inhibiting this post-translational modification, FTIs mitigate the toxic effects of progerin in HGPS.

Lonafarnib (Zokinvy) is the first FDA approval drug for HGPS and progeroid laminopathy at 2020 [6]. A phase 2 clinical trial (NCT 00425607) enrolled 25 patients over 2 years to access efficacy compared to an untreated HGPS cohort. The study demonstrated that Lonafarnib extended mean survival by 2.5 years over an 11-year follow-up period. Additional benefits observed in treated patient included improvements in weight gain, bone density, arterial functions, and hearing. However, gastrointestinal side effects such as nausea and diarrhea were reported in up to 80% of patients [7]. Lonafarnib is administered orally and is approved for patients ≥ 12 months old with body surface area (BSA) of ≥ 0.39 m^2.

2. Statin and Bisphosphonate* (Fig. 1, ▯ box)

Statin, and bisphosphonate inhibit progerin prenylation, by reducing production of protein required for farnesylation. Preclinical studies demonstrate improved bone and vascular function, however clinical trials showed no superiority compared to lonafarnib monotherapy. These treatments can be considered selectively for patients with severe osteoporosis or high cholesterol, but potential for side effects like myopathy and bone pain.

3. ICMT* inhibitor (Fig. 1C-(3))

ICMT inhibitors target the carboxymethylation step, post-translational modification of progerin. *In vitro* studies have shown that ICMT inhibitors delocalized progerin from the nuclear membrane, reduced DNA damage, and increased cellular viability. *In vivo* mouse model, it extended lifespan, improved grip strength, and reduced tissue senescence without notable toxicity [8]. Further studies are warranted to validate its safety and efficacy.

4. mTOR inhibitor and other drugs enhance autophagy* to progerin removal

mTOR inhibitor enhance autophagy-mediated progerin clearance, reducing nuclear abnormalities, senescence, and DNA damage levels in HGPS fibroblasts [9-11]. Among them, Everolimus, rapamycin, temsirolimus have been investigated for progeria. Everolimus is preferred due to its superior tissue penetration, ease of control owing to its short half-life, and relatively mild side effect profile [12,13]. Common side effects of mTOR inhibitors include an increased risk of infection due to immunosuppression, peripheral edema, dyslipidemia, hyperglycemia and delayed wound healing. A Phase I/II clinical trial on everolimus and lonafarnib combination therapy for HGPS has been conducted to evaluate everolimus and lonafarnib combination therapy in HGP.

Sulforaphane is an antioxidant derived from cruciferous vegetable and stimulates proteasome activity and autophagy studied in *in vivo* therapy. Methylene blue improves mitochondrial dysfunction and increases autophagy *in vitro*. MG132 is a proteasome inhibitor, induce macroautophagy and, also act on reducing progerin production through splicing regulation by downregulate splicing factors. Metformin induces activation of AMP-activated protein kinase (AMPK) and mTOR inhibition.

5. Antisense oligonucleotide (ASO) therapy

ASO therapy corrects the LMNA splicing error and reduces progerin production at the mRNA level. The study in mice shows a 50-60% increase in lifespan and human trials are forthcoming [14]. However, ASO therapy faces limitations, including a lack of improvement in cardiovascular pathology, the need for repeated administration, and the possibility of off-target effects.

6. Gene editing (CRISPR and base editing)

CRISPR/Cas 9 and adenine base editing (ABE) correct the *LMNA* mutation at DNA level and offers a potential one-time cure. In progeria mouse models, base editing doubled lifespan, demonstrating curative potential [15,16]. It is still experimental in humans. It may induce immunogenicity and requires safe and effective delivery methods. Off-target genetic modifications remain a concern.

7. Therapies for other toxic effects of progerin

JH4 is a small molecule—a low-molecular-weight compound capable of modulating intracellular interactions—that acts as a progerin and lamin A binding inhibitor. Progerinin is an orally administered analog of JH4, developed to improve the pharmacokinetic and therapeutic properties. It reduces progerin levels and prevents progerin from damaging the nuclear lamina. In a study in mice, progerinin improved aging phenotype and cardiac dysfunction. It also extended the lifespan by approximately 50%, demonstrating better results than

lonafarnib [17,18]. A clinical trial for combination therapy with lonafarnib is planned (NCT06775041). Other drugs that target nuclear abnormalities include Chromosomal Region Maintenance 1 CRM1 (CRM1) inhibitor such as leptomycin, resveratrol, selinexor [19], and doxycycline [20]. CRM1 inhibitor normalize the nucleocytoplasmic partitioning of proteins, modulate chromatin accessibility, and decrease progerin levels. Additionally, doxycycline has been explored for its potential role in nuclear homeostasis.

Progerin accumulation exacerbates inflammation in progeria. JAK-STAT inhibitor (Baricitinib, Vitexin) [21], NLRP inhibitors (dapansutrile) [22], anti-IL6R inhibitory Antibodies (Tocilizumab) [23] have been studied. These drugs modulate proinflammatory cytokines and impact on senescence *in vitro* and *in vivo* models. Progerin accumulation also disrupts normal DNA repair mechanisms, accelerated telomere shortening, and increases genomic instability. Therapies targeting DNA damage repair include ATM inhibitors (e.g., KU-600196) [24], methylene blue [25], and TERT circRNA [26].

Endothelial dysfunction is the main pathogenesis of progeria-associated atherosclerosis. Therapeutic approaches targeting this mechanism include Verteporfin (YAP/TAZ inhibitor) *in vitro* study [27], and angiopoietin-2 in mouse models [28]. From a regenerative medicine perspective, progeria is characterized by premature stem cell exhaustion and chronic inflammation. Consequently, stem cell-based therapies are under investigation and have demonstrated improvements in body composition, arterial elasticity, and systemic inflammatory markers in patients [29,30]. Senolytic therapies such as Dasatinib, Quercetin are also explored as potential treatment for cellular senescence.

8. Combination therapies with lonafarnib

1) Zoledronate+Pravastatin (ZOPRA)+Lonafarnib (NCT00916747)

A clinical trial involving 37 patients evaluated the combination therapy with statins and bisphosphonates targeting the mevalonate pathway to prevent farnesylation. The study found that, aside from an increase in bone mineral density, this combination therapy did not demonstrate superior efficacy compared to monotherapy [31]. Additionally, an increased amount of abnormal donut-shaped nuclei was observed in patients receiving the combination therapy [32].

2) Everolimus+Lonafarnib (NCT02579044)

Improved endothelial function and vascular stiffness *in vitro* 3D blood vessel model [13] and currently combination clinical trial is ongoing state.

3) Progerinin+Lonafarnib (NCT06775041)

A phase 2 clinical trial of combination therapy is recruiting now. Progerinin is a JH4 analog that inhibits the binding of progerin to lamin A. In the *in vivo* model, progerinin was more effective than lonafarnib alone or in combination [18].

4) Other research with Lonafarnib in vitro and in vivo

Additional combination therapies with barcitinib, dapansutrile, and sulforaphane has been studied to improve efficacy. Baricitinib (JAK-STAT inhibitor) reduce toxicity of FTI, and improve nuclear morphology, restoring proteostasis and alleviating inflammation and senescence in HGPS fibroblasts [33]. Dapansutrile (NLRP3 inhibitor) with lonafarnib reduced progerin accumulation, inflammation, and senescence, leading to extended survival and improved phenotypes compared to lonafarnib alone in animal model [22]. Sulforaphane is antioxidant and increases autophagy. Not concomitant, cross repeated administration with lonafarnib improves cellular homeostasis [34].

9. Multidisciplinary clinical approach

Multidisciplinary care is central to improving the quality of life for patients with HGPS. Cardiac care includes regular monitoring of blood pressure, lipid profile, EKG and echocardiography performed at least annually. If possible, pulse wave velocity and carotid intima media thickness should also be considered. An immediate brain MRI with angiography is required when symptoms like headache, seizures or muscle weakness occur. To prevent stroke, low dose aspirin and adequate hydration (1-1.5 L/day) are recommended. Annual ophthalmologic and audiologic exams are also essential. Supportive strategies including a high-caloric diet, rehabilitation therapy, and use of shoe inserts can help maintain daily function [35].

CONCLUSION

Over the past two decades, our understanding of HGPS has deepened with uncovering LMNA gene mutation and elucidation of progerin production and its pathologic effects. This progression led to active research by repurposing drug targeted mechanisms. One major breakthrough came with the FDA approval of lonafarnib, a farnesyltransferase inhibitor, which prolongs the lives of patients with HGPS. However, it has lim-

ited efficacy in some aspects, such as dermatologic and joint contractures, and does not halt disease progression. Because of these shortcomings, the research trends have shifted toward combination therapies that target multiple mechanisms. Also, many innovative treatments, such as genetic, regenerative approaches, are currently under investigation. Genome-editing technologies, such as CRISPR-Cas9 and ABE, present promising avenue as potential one-time curative options. Clinical trials of stem cell therapies in HGPS patients are also ongoing. Still, further research is required to evaluate the long-term safety and efficacy, and to carefully assess the limitations of real-world clinical use. Our goal for HGPS treatment should be to refine combination treatment and translate preclinical advances into clinical practice. Additionally, comprehensive management with a multidisciplinary approach will improve treatment outcomes. Continued commitment to this work could lead to safer, more effective ways to manage HGPS in the future.

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