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MINI REVIEW

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Status of treatment strategies for Hutchinson–Gilford progeria syndrome with a focus on prelamin: A posttranslational modification

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Abstract

Hutchinson–Gilford progeria syndrome (HGPS) is a rare genetic disorder characterized by premature ageing and early death at a mean age of 14.7 years. At the molecular level, HGPS is caused by a de novo heterozygous mutation in *LMNA*, the gene encoding A-type lamins (mainly lamin A and C) and nuclear proteins, which have important cellular functions related to structure of the nuclear envelope. The *LMNA* mutation leads to the synthesis of a truncated prelamin A protein (called progerin), which cannot undergo normal processing to mature lamin A. In normal cells, prelamin A processing involves four posttranslational processing steps catalysed by four different enzymes. In HGPS cells, progerin accumulates as a farnesylated and methylated intermediate in the nuclear envelope where it is toxic and causes nuclear shape abnormalities and senescence. Numerous efforts have been made to target and reduce the toxicity of progerin, eliminate its synthesis and enhance its degradation, but as of today, only the use of farnesyltransferase inhibitors is approved for clinical use in HGPS patients. Here, we review the main current strategies that are being evaluated for treating HGPS, and we focus on efforts to target the posttranslational processing of progerin.

KEYWORDS
HGPS, HGPS therapy, ICMT, posttranslational processing, progerin

1 | INTRODUCTION

Hutchinson–Gilford progeria syndrome (HGPS) is an exceedingly rare disease that occurs in one per 20 million newborns.[1,2] HGPS is associated with a median lifespan of 14.7 years. During the first year of life, children with HGPS are usually indistinguishable from unaffected children; disease symptoms then appear gradually, and their severity usually correlates with the accumulation of progerin. Common HGPS symptoms are alopecia, malformation of the skull and face, short stature, growth retardation, bone defects, metabolic disorders, endocrine problems and cardiovascular disease, which is the predominant cause of death.[3]

HGPS is a non-heritable genetic syndrome caused by a de novo point mutation at nucleotide 1824 (c.1824C>T) in the coding region of the *LMNA* gene.[4,5] *LMNA* in normal cells encodes mainly lamin C and lamin A, the latter of which is synthetized as a precursor called prelamin A. Prelamin A is a so-called *CAAX* protein that undergoes three posttranslational modifications at a carboxyl-terminal cysteine residue: Firstly, the cysteine residue is farnesylated by farnesyltransferase (FTase) in the cytosol. Secondly, the last three amino acids are cleaved off by RAS converting enzyme 1 (RCE1) or by Zinc metalloproteinase Ste24 homologue (ZMPSTE24). Thirdly, the newly exposed farnesylcysteine residue is methylated by isoprenylcysteine carboxyl methyltransferase (ICMT).[6] Prelamin A is unique among *CAAX* proteins in that it undergoes a fourth processing step where the last 15 amino acids, including the farnesylated and methylated cysteine residue, are cleaved off by ZMPSTE24. Mature lamin A is then incorporated into the nuclear lamina filament meshwork, where it interacts with many proteins important for nuclear structure integrity, including Emerin, UBC9, LAP2α, LAP1β, LMNB1 and RBBP7. Some of them, including LAP2β and Emerin, interfere with the synthesis and degradation of other proteins[7] such as progerin, while others, including lamins B1 and B2, become part of the nuclear envelope[8] and influence interactions with and the function of chromatin and the centrosome.[9]

The changes in net charge on the carboxyl-terminal domain of progerin and prelamin A following farnesylation and carboxyl methylation is an important issue that has not been carefully evaluated. Whereas farnesylation changes the molecular mass of prelamin A/progerin by hundreds of daltons, methylation only adds 14 Da. Thus, blocking farnesylation is expected to cause more changes to the structure and hydrophocity of prelamin A/progerin compared with blocking methylation. Nevertheless, it is important to note that blocking methylation leaves a negatively charged carboxylate anion on the farnesylcysteine residue, which clearly has the capacity to disrupt the interaction of prelamin A/progerin with the nuclear membrane.

On one hand, farnesylation is believed to target prelamin A to the nuclear membrane where proteolysis and methylation take place before the protein is firmly anchored on the inner surface of the nuclear envelope.[10] On the other hand, prelamin A in cells from mice that exclusively express a non-farnesylated prelamin A mutant is localized at the nuclear rim, like wildtype lamin A, suggesting that farnesylation is not required for nuclear membrane targeting.[11] Farnesylated prelamin A and progerin cause misshapen nuclei, and blocking farnesylation corrects this phenotype.[12] Regarding methylation, prelamin A in ICMT-deficient cells is partly mislocalized into the nucleoplasm, suggesting that methylation is required but not essential for proper membrane localization of prelamin A. Farnesylation and methylation are also important for protein–protein interactions.[13]

In most patients, the HGPS mutation in *LMNA* exon 11 results in the conversion of a cytosine residue to thymine,[4,5] which activates a cryptic splice site that causes aberrant splicing of the pre-mRNA resulting in an internal deletion in the prelamin A carboxyl terminus which eliminates the ZMPSTE24 cleavage site (Figure 1). As a result, prelamin A in HGPS cells cannot be cleaved by ZMPSTE24, which causes the accumulation of a permanently farnesylated and methylated truncated prelamin A variant called progerin. Progerin accumulation in the nuclear membrane triggers nuclear shape abnormalities and alters protein–protein interactions, protein stability and chromatin binding and transcription. Progerin thus causes senescence and is responsible for all clinical HGPS phenotypes.

Since the identification of the HGPS mutation and the involvement of progerin in disease initiation and progression almost 20 years ago,[4,5] much effort has been geared toward targeting this protein as a strategy to treat the disorder (Figure 1). Briefly, the efforts can be categorized into gene therapy approaches that are designed to correct the *LMNA* mutation with CRISPR/Cas9 and adenosine base editor techniques, reduce progerin mRNA expression with antisense strategies targeting abnormal splicing, stimulate progerin degradation and inhibit the enzymes that posttranslationally modify prelamin A and progerin. Most of the latter efforts have focused on targeting FTase, but recent studies have identified ICMT as a potential enzymatic drug target. These approaches are briefly described below.

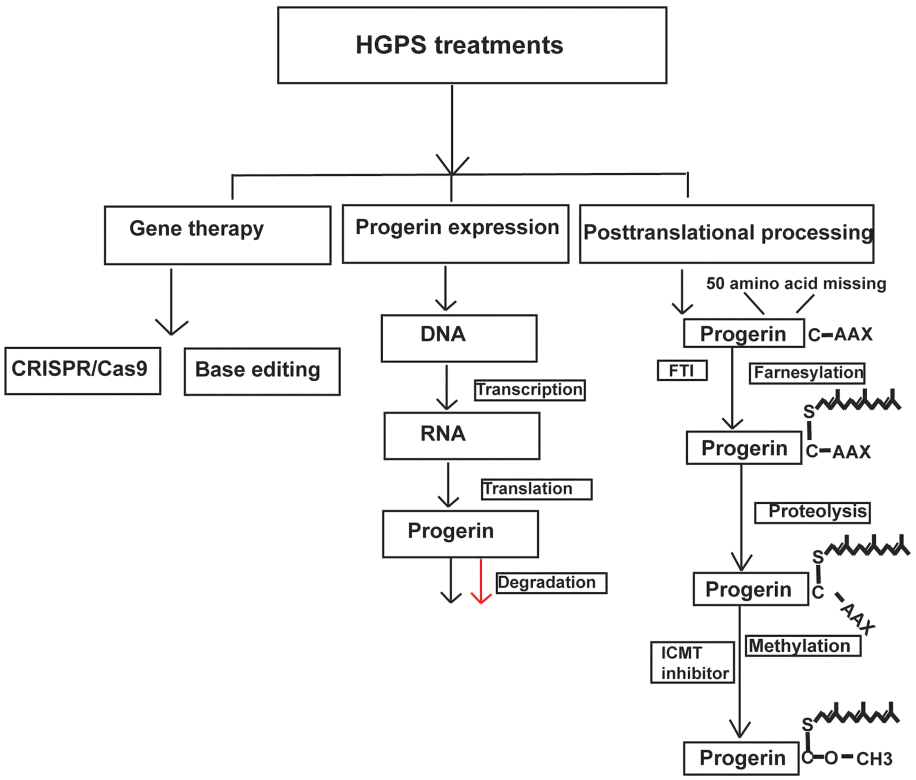

FIGURE 1 Overview of potential Hutchinson–Gilford progeria syndrome (HGPS) treatment strategies

2 | GENETIC APPROACHES

Progerin is toxic and causes all the disease phenotypes of HGPS patients, and the strategy of correcting the mutation and preventing progerin synthesis is highly attractive. Since mice that lack lamin A but retain lamin C expression are viable and one copy of this 'lamin A-specific' knockout allele prevents progeria in *Zmpste24*-deficient mice,[14] reducing progerin expression by knocking out wildtype prelamin A expression could also provide therapeutic benefit. This has been confirmed in two recent studies that implemented an in vivo CRISPR/Cas9-based strategy where guide (g)RNAs targeting lamin A/progerin downstream of lamin C reduced the expression of progerin and lamin A without disturbing lamin C expression.[15,16] This intervention alleviated cardiovascular symptoms and increased overall survival of progerin-expressing mice by 25% (median survival increased from 127 to 160 days in treated mice). Although promising, this strategy did not offer a cure likely due to low gene targeting efficiency. Thus, more work is required to increase the efficiency of this strategy.

A major limitation of CRISPR/Cas9-based strategies is that off-target effects may generate unwanted mutations in important protein coding genes. To avoid this limitation, adenosine base editors (ABE) developed in David Liu's laboratory that repair the *LMNA* c.1824C>T back to C have been tested.[17] The group used a CRISPR-Cas9 system coupled with ABE and converted a single adenosine to inosine—a nucleoside that could take the place of the standard guanosine. Application of this approach in asymptomatic progerin-expressing mice alleviated several HGPS phenotypes and markedly increased the lifespan. However, it remains to be determined whether ABE can reverse already established phenotypes. Another limitation of ABE is that the adeno-associated virus systems used in this strategy raise questions about safety including long-term effects in proliferative tissues, which could potentially drive cancer initiation. Moreover, as opposed to antisense therapy, the mutation only needs to be corrected once in each cell, which makes integration of the editing system redundant and potentially harmful. An attractive alternative would be to test non-integrative lentiviral systems.

Whisenant and co-workers recently used chimeric bacteriophage-lentivirus particles to correct the HGPS mutation in mice expressing progerin in the skin.[18] The mutation-correction rate was around 4% 3 weeks after administration, and after 4 weeks, reduced numbers of progerin-expressing cells were documented, and progerin-negative clusters of cells were detected in several layers of the epidermis. The latter result was particularly important as it demonstrates mutation correction in progenitor cells. One important advantage of this approach is that the particles do not integrate into the genome and are likely to be associated with fewer long-term side effects.

The use of gene therapy for treating HGPS is in its infancy but has generated tremendous interest. But ethical issues and problems with efficiency and off-target effects indicate that the clinical use of ABE and CRISPR-Cas9 approaches for HGPS therapy is a few years off.

3 | MANIPULATING PROGERIN LEVELS

Several groups have reported that RNA-based therapies can be used to reduce the accumulation of progerin by blocking its production at the mRNA level using antisense and morpholino oligonucleotides.[19–21] These oligonucleotides reduce progerin mRNA levels in cultured cells in vitro and in tissues in vivo, have the capacity to improve phenotypes in the aorta and heart and extend survival in several progerin-expressing mouse models. These strategies are worth pursuing further although several questions remain regarding specificity and long-term in vivo effects. Another problem is that the compounds need to be administered continuously as opposed to DNA editing approaches.

Progerin levels can also be reduced by accelerating its degradation rate. Rapamycin—an inhibitor of mTOR signalling pathway[22]—was found to reduce the characteristic nuclear shape abnormalities and delay senescence of HGPS cells in vitro.[23,24] The effect was linked to increased progerin clearance. A clinical trial (NCT02579044) where everolimus, a rapamycin derivative, was given together with lonafarnib (i.e. the standard FTI therapy) was initiated to evaluate its efficiency in treating HGPS and other progeroid laminopathies.[25] However, no results have yet been released from this trial. A potential limitation of this strategy is that rapamycin inhibits proliferation of human and mouse HGPS cells and worsens the senescence phenotype, at least in cultured cells.[26]

4 | TARGETING PROGERIN POSTTRANSLATIONAL MODIFICATIONS

The most well-studied strategy to alleviate the HGPS symptoms is to reduce progerin toxicity by targeting the enzymatic posttranslational processing steps of prelamin A/progerin, most importantly the farnesylation step. FTIs were originally developed to treat oncogenic RAS-induced cancer. However, most RAS proteins can undergo geranylgeranylation by geranylgeranyltransferase type I (GGTase-I) and escape the effects of FTI therapy. Prelamin A and progerin are not readily substrates for GGTase-I, and FTIs were tested early on as a strategy to treat HGPS. FTIs were found to markedly reduce the nuclear shape abnormalities and achieve significant success in alleviating HGPS symptoms.[12] In other studies, treatment with FTIs reduced clinical signs of HGPS in progeroid *Zmpste24*-deficient mice and in $Lmna^{HG/+}$ and $LMNA^{G608G}$ knock-in mice.[12,27,28] These promising preclinical studies stimulated clinical trials using lonafarnib and a triple combination clinical trial with lonafarnib, pravastatin and zoledronate (to inhibit both progerin farnesylation and geranylgeranylation).[28–30] FTI administration alone increased mean survival by 1.6 years and attenuated some progeria-associated symptoms, including bone mineral density and heart phenotypes. However, the combinations produced little, if any, synergy. In short, clinical trials showed that FTIs can ameliorate key HGPS phenotypes, but they cannot cure the disease. In November 2020, lonafarnib (Zokinvy) became the first drug to be approved by the FDA for treating HGPS.[31]

Some studies have revealed that FTIs have potent anti-proliferative effects. FTase has dozens of substrates, including RAS, lamin B and RHEB, whose activities depend on farnesylation. Children with HGPS would benefit from a therapy that can overcome senescence and that is compatible with sustained cell proliferation and growth.

The second step in prelamin A/progerin posttranslational processing is the proteolytic removal of the last three amino acids, catalysed by RCE1 and ZMPSTE24. We found that knockout of *Rce1* rescues key progeria phenotypes and extends survival of *Zmpste24*-deficient mice, suggesting that RCE1 inhibitors might be useful in progeria induced by ZMPSTE24 inactivating mutations. However, these disorders are even rarer than HGPS and include mandibuloacral dysplasia (MAD) and atypical HGPS.[32,33] Importantly, RCE1 inhibition cannot help HGPS patients[34] since ZMPSTE24 can also perform the carboxyl-terminal cleavage.

The third step in the posttranslational processing of prelamin A/progerin is mediated by ICMT, which methylates the newly exposed farnesylcysteine residue after the RCE1/ZMPSTE24 cleavage. We hypothesized that lowering ICMT levels might inhibit prelamin A/progerin methylation and thereby reduce the toxicity of the disease-causing protein.[26] Indeed, knockout or knockdown of *Icmt* prevents prelamin A methylation and mislocalizes the protein away from the nuclear envelope, which delays senescence and increases proliferation of human HGPS cells and mouse *Zmpste24*-knockout cells. Further studies revealed that knockout of *Icmt* in vivo increases body weight and grip strength, completely restores the bone fracture phenotype and osteoporosis

and extends the lifespan of *Zmpste24*-deficient mice. However, this study raised two important new questions: Firstly, would *Icmt* inactivation inhibit disease in mice expressing progerin rather than prelamin A? And secondly, would ICMT inhibitors be useful in HGPS therapy?

Recently, our group demonstrated that a small molecule ICMT inhibitor can potentially be useful in HGPS therapy.[35] In this study, we first documented that *Icmt* inactivation improves HGPS phenotypes and extends survival of progerin-expressing $Lmna^{G609G/G609G}$ mice. Indeed, the *Icmt* inactivation (accomplished with a mouse model that expresses 10%–15% of normal ICMT activity) rescued several phenotypes of $Lmna^{G609G/G609G}$ mice, increased their body weight and extended survival by nearly 30%. Importantly, reducing the expression of ICMT normalized the vascular phenotype of $Lmna^{G609G/G609G}$ mice, a particularly important result as cardiovascular complications are the main cause of death in children with HGPS. In this study, we also synthesized compound C75, a potent ICMT inhibitor (IC50 = 0.5 μM). We found that C75 administration to HGPS cell lines inhibits ICMT activity and prelamin A/progerin methylation and markedly delays senescence and stimulates proliferation. Consistent with these observations, C75 stimulated cell cycle progression and reduced expression of senescence markers in HGPS cells, including senescence-associated (SA)-βgal staining and expression of p16INK4A and interleukin-6 (IL-6). Although C75 prevents the ability of prelamin A and progerin to cause several progeria-associated phenotypes, it does not influence the nuclear shape phenotype, in line with previous experiments with genetic ICMT inactivation. Thus, it is possible to improve HGPS phenotypes and allow progerin-expressing cells to proliferate in the presence of the hallmark nuclear shape abnormalities. A downside with C75 is that although potent, it is not suitable for in vivo administration; thus, other compounds will be required for in vivo studies.

Recently, Marcos-Ramiro and co-workers synthesized another ICMT inhibitor (UCM-13207) and found similar effects as we found with C75. Importantly, UCM-13207 was also tested in progerin-expressing mice in vivo where it was found to increase body weight and grip strength and reduce senescence markers in organs. Moreover, the drug reduces progerin levels in the aortic wall and increases the number of vascular smooth muscle cells and increases survival by 20%.[36]

In summary, targeting posttranslational processing of progerin has produced promising results, and currently, FTIs represent the only approved therapy. However, FTIs produce limited clinical benefits, and there is a need for more research on more strategies. Regarding ICMT, we need to determine whether more efficient ICMT inhibitors with acceptable pharmacological properties can be produced. We also need to determine whether ICMT inhibition can be combined with other therapies. However, at least in theory, it would not be advisable to combine FTIs with ICMT inhibitors because progerin will only be methylated if it is first farnesylated. Thus, blocking farnesylation with an FTI will render the ICMT step irrelevant.

The only approved therapy for HGPS, FTIs, have demonstrated a maximum survival benefit of 1–2 years. Consequently, all the potential therapeutic approaches described in this minireview should be pursued in parallel to maximize the chances of obtaining an effective therapy for current and future children with HGPS, and ideally, this therapy should both improve quality of life and extend lifespan.

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CONFLICT OF INTERESTS

All authors confirm that there is no conflict of interests.

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REFERENCES

1. Young SG, Fong LG, Michaelis S, Prelamin A. Zmpste24, misshapen cell nuclei, and progeria—new evidence suggesting that protein farnesylation could be important for disease pathogenesis. *J Lipid Res*. 2005;46(12):2531-2558. doi:10.1194/jlr.R500011-JLR200
2. Kieran MW, Gordon L, Kleinman M. New approaches to progeria. *Pediatrics*. 2007;120:834-841. doi:10.1542/peds.2007-1356
3. Hennekam RCM. Hutchinson–Gilford progeria syndrome: review of the phenotype. *Am J Med Genet A*. 2006;140a:2603-2624.
4. Eriksson M, Brown WT, Gordon LB, et al. Recurrent de novo point mutations in lamin A cause Hutchinson–Gilford

progeria syndrome. *Nature*. 2003;423(6937):293-298. doi:10.1038/nature01629
5. De Sandre-Giovannoli A, Bernard R, Cau P, et al. Lamin A truncation in Hutchinson–Gilford progeria. *Science*. 2003;300(5628):2055. doi:10.1126/science.1084125
6. Davies BS, Fong LG, Yang SH, Coffinier C, Young SG. The posttranslational processing of prelamin A and disease. *Annu Rev Genomics Hum Genet*. 2009;10:153-174. doi:10.1146/annurev-genom-082908-150150
7. Muchir A, Massart C, van Engelen BG, Lammens M, Bonne G, Worman HJ. Proteasome-mediated degradation of integral inner nuclear membrane protein emerin in fibroblasts lacking A-type lamins. *Biochem Biophys Res Commun*. 2006;351:1011-1017. doi:10.1016/j.bbrc.2006.10.147
8. Dechat T, Pfleghaar K, Sengupta K, et al. Nuclear lamins: major factors in the structural organization and function of the nucleus and chromatin. *Genes Dev*. 2008;22(7):832-853. doi:10.1101/gad.1652708
9. Bronshtein I, Kepten E, Kanter I, et al. Loss of lamin A function increases chromatin dynamics in the nuclear interior. *Nat Commun*. 2015;6(1):8044. doi:10.1038/ncomms9044
10. Young SG, Fong LG, Michaelis S. Prelamin A, Zmpste24, misshapen cell nuclei, and progeria—new evidence suggesting that protein farnesylation could be important for disease pathogenesis. *J Lipid Res*. 2005;46(12):2531-2558. doi:10.1194/jlr.R500011-JLR200
11. Davies BSJ, Barnes RH, Tu YP, et al. An accumulation of non-farnesylated prelamin A causes cardiomyopathy but not progeria. *Hum Mol Genet*. 2010;19(13):2682-2694. doi:10.1093/hmg/ddq158
12. Capell BC, Erdos MR, Madigan JP, et al. Inhibiting farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson–Gilford progeria syndrome. *Proc Natl Acad Sci U S A*. 2005;102(36):12879-12884. doi:10.1073/pnas.0506001102
13. Ibrahim MX, Sayin VI, Akula MK, et al. Targeting isoprenylcysteine methylation ameliorates disease in a mouse model of progeria. *Science*. 2013;340(6138):1330-1333. doi:10.1126/science.1238880
14. Fong LG, Ng JK, Lammerding J, et al. Prelamin A and lamin A appear to be dispensable in the nuclear lamina. *J Clin Investig*. 2006;116(3):743-752. doi:10.1172/JCI27125
15. Beyret E, Liao HK, Yamamoto M, et al. Single-dose CRISPR-Cas9 therapy extends lifespan of mice with Hutchinson–Gilford progeria syndrome. *Nat Med*. 2019;25(3):419-422. doi:10.1038/s41591-019-0343-4
16. Santiago-Fernandez O, Osorio FG, Quesada V, et al. Development of a CRISPR/Cas9-based therapy for Hutchinson–Gilford progeria syndrome. *Nat Med*. 2019;25(3):423-426. doi:10.1038/s41591-018-0338-6
17. Gaudelli NM, Komor AC, Rees HA, et al. Programmable base editing of A. T to G. C in genomic DNA without DNA cleavage. *Nature*. 2017;551(7681):464-471. doi:10.1038/nature24644
18. Whisenant D, Lim K, Revêchon G, et al. Transient expression of an adenine base editor corrects the Hutchinson-Gilford progeria syndrome mutation and improves the skin phenotype in mice. *Nat Commun*. 2022;13(1):3068.
19. Puttaraju M, Jackson M, Klein S, et al. Systematic screening identifies therapeutic antisense oligonucleotides for Hutchinson–Gilford progeria syndrome. *Nat Med*. 2021;27(3):526-535. doi:10.1038/s41591-021-01262-4
20. Erdos MR, Cabral WA, Tavarez UL, et al. A targeted antisense therapeutic approach for Hutchinson-Gilford progeria syndrome. *Nat Med*. 2021;27(3):536-545. doi:10.1038/s41591-021-01274-0
21. Osorio FG, Navarro CL, Cadinanos J, et al. Splicing-directed therapy in a new mouse model of human accelerated aging. *Sci Transl Med*. 2011;3(106):106ra107. doi:10.1126/scitranslmed.3002847
22. Hansen M, Taubert S, Crawford D, Libina N, Lee SJ, Kenyon C. Lifespan extension by conditions that inhibit translation in *Caenorhabditis elegans*. *Aging Cell*. 2007;6:95-110. doi:10.1111/j.1474-9726.2006.00267.x
23. Graziotto JJ, Cao K, Collins FS, Krainc D. Rapamycin activates autophagy in Hutchinson–Gilford progeria syndrome: implications for normal aging and age-dependent neurodegenerative disorders. *Autophagy*. 2012;8:147-151. doi:10.4161/auto.8.1.18331
24. Cao K, Graziotto JJ, Blair CD, et al. Rapamycin reverses cellular phenotypes and enhances mutant protein clearance in Hutchinson–Gilford progeria syndrome cells. *Sci Transl Med*. 2011;(89):3, 89ra58. doi:10.1126/scitranslmed.3002346
25. Kleinman ME. Phase I/II trial of everolimus in combination with lonafarnib in progeria. 2015. Accessed October 19, 2015. https://clinicaltrialsgov/ct2/show/record/NCT02579044?view%3Drecord
26. Ibrahim MX, Sayin VI, Akula MK, et al. Targeting isoprenylcysteine methylation ameliorates disease in a mouse model of progeria. *Science*. 2013;340(6138):1330-1333. doi:10.1126/science.1238880
27. Yang SH, Meta M, Qiao X, et al. A farnesyltransferase inhibitor improves disease phenotypes in mice with a Hutchinson–Gilford progeria syndrome mutation. *J Clin Investig*. 2006;116(8):2115-2121. doi:10.1172/JCI28968
28. Gordon LB, Kleinman ME, Miller DT, et al. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson–Gilford progeria syndrome. *Proc Natl Acad Sci U S A*. 2012;109(41):16666-16671. doi:10.1073/pnas.1202529109
29. Varela I, Pereira S, Ugalde AP, et al. Combined treatment with statins and aminobisphosphonates extends longevity in a mouse model of human premature aging. *Nat Med*. 2008;14:767-772. doi:10.1038/nm1786
30. Gordon LB, Kleinman ME, Massaro J, et al. Clinical trial of the protein farnesylation inhibitors lonafarnib, pravastatin, and zoledronic acid in children with Hutchinson–Gilford progeria syndrome. *Circulation*. 2016;134:114-125. doi:10.1161/CIRCULATIONAHA.116.022188
31. Voelker R. First progeria drug is approved. *JAMA*. 2021;325(1):20. doi:10.1001/jama.2020.24348
32. Morais P, Magina S, Ribeiro MD, et al. Restrictive dermopathy—a lethal congenital laminopathy. Case report and review of the literature. *Eur J Pediatr*. 2009;168(8):1007-1012. doi:10.1007/s00431-008-0868-x
33. Jameson JL, Groot LD, De Kretser DM. *Endocrinology: Adult and Pediatric*. Vol. 2. 7th ed. Elsevier/Saunders; 2016.
34. Yao HD, Chen X, Kashif M, et al. Targeting RAS-converting enzyme 1 overcomes senescence and improves progeria-like

phenotypes of ZMPSTE24 deficiency. *Aging Cell*. 2020;19(8). doi:10.1111/acel.13200

35. Chen X, Yao HD, Kashif M, et al. A small-molecule ICMT inhibitor delays senescence of Hutchinson–Gilford progeria syndrome cells. *elife*. 2021;10:e63284. doi:10.7554/eLife.63284
36. Marcos-Ramiro B, Gil-Ordonez A, Marin-Ramos NI, et al. Isoprenylcysteine carboxylmethyltransferase-based therapy for Hutchinson–Gilford progeria syndrome. *ACS Central Sci*. 2021;7(8):1300-1310. doi:10.1021/acscentsci.0c01698

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