Received: 27 October 2025 | Revised: 25 December 2025 | Accepted: 26 December 2025 | Published online: 29 December 2025

International Journal of Advance in Clinical Science Research, Volume 4 2025
https://h-tsp.com/
10.5281/zenodo.18149175

Therapeutic Restriction of the Fanconi Anemia Pathway to Limit Replication-Stress–Driven Genome Catastrophes in Hutchinson–Gilford Progeria Syndrome (HGPS)

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Abstract: ***Hutchinson–Gilford Progeria Syndrome (HGPS) arises from a dominant LMNA mutation that produces progerin, a toxic lamin A variant. Progerin undermines nuclear architecture and perturbs DNA replication, provoking chronic replication stress, micronucleus formation, and persistent DNA damage that drives p53-dependent senescence. Recent mechanistic work shows that the Fanconi anemia (FA) pathway—canonically protective at stalled replication forks— can, under specific conditions, induce large-scale nucleolytic cleavage that primes missegregated chromosomes for chromothripsis. This duality suggests a novel therapeutic approach for HGPS: conditional, transient restriction of FA-dependent nuclease activity at mitosis, preventing catastrophic chromosomal shattering while preserving sufficient fork protection during S phase. This paper synthesizes current cell and mouse evidence, evaluates risks by comparison to Fanconi anemia models, and proposes an experimentally tractable therapeutic strategy with an in-depth in vitro and in vivo testing roadmap.***

Keywords: Hutchinson–Gilford Progeria Syndrome (HGPS), progerin, replication stress, micronuclei, chromothripsis, Fanconi anemia pathway, SLX4–XPF, MUS81.

1. Introduction

Hutchinson–Gilford Progeria Syndrome (HGPS) is a devastating premature aging disorder marked by vascular disease, skin and bone abnormalities, and markedly shortened lifespan. The condition is caused most commonly by a silent LMNA point mutation (c.1824C>T) that activates a cryptic splice site and produces the truncated, farnesylated protein progerin. Progerin accumulates at the inner nuclear membrane and within the nucleoplasm, altering nuclear mechanics and displacing DNA replication and repair factors. A robust body of evidence demonstrates that progerin causes replication fork slowing and collapse, accumulation of γ-H2AX foci, and p53 activation leading to senescence. (See Keith Wheaton (2017) [8]; Ray Kreienkamp (2018) [6]).

Concurrently, the Fanconi anemia (FA) pathway has emerged as a major source of focal catastrophic genome rearrangements in cancer: lagging chromosomes trapped in micronuclei under-replicate,

rupture, and can be fragmented and reassembled in one cell cycle (Cheng-Zhong Zhang (2015) [9]; Maja Kneissig (2019) [4]). Very recently, mechanistic screens and genetic work indicate that the FA pathway (and specifically downstream recruitment of structure-selective nucleases such as SLX4–XPF and MUS81) can drive chromothripsis by nucleolytic cleavage of under-replicated micronuclear DNA (Justin Engel (2024) [2]; Anna Repczynska (2024) [7]). Thus, an ostensibly protective DNA repair pathway can, in the unique structural context of micronuclei and mitosis, convert stalled or under-replicated DNA into the substrate for chromosomal pulverization.

These findings pose both a threat and an opportunity for HGPS: on one hand, FA activity could exacerbate fragmentation if progerin-induced micronuclei are common; on the other hand, because HGPS patients retain intact p53 and rarely develop cancer, FA-driven chromothripsis may be suppressed in vivo by cell-intrinsic clearance. We propose, therefore, to explore transient, mitosis-focused restriction of FA-driven nucleolytic activity as a therapeutic axis: by preventing nuclease-mediated shattering at the most vulnerable time, we may reduce inflammatory DNA fragments and cytosolic DNA sensing while preserving S-phase fork protection. This paper reviews the mechanistic background, surveys mouse model evidence, contrasts risks using Fanconi anemia data, and lays out an experimental program to test FA-restriction therapeutics in vitro and in vivo.

2. Current Understanding

Multiple studies demonstrate that progerin perturbs replication directly. Progerin interacts abnormally with proliferating cell nuclear antigen (PCNA) and alters replication factor localization, slowing replication fork velocity and producing stalled forks that show single-stranded DNA markers (pRPA) and ATR activation (Keith Wheaton (2017) [8]; Ray Kreienkamp (2018) [6]). Replication fork slowing increases the probability of fork reversal, nucleolytic resection (e.g., MRE11 activity), and conversion to double-strand breaks when restarted improperly. In HGPS cells, these events are chronic rather than episodic, generating persistent γ-H2AX and 53BP1 foci and driving p53-mediated senescence.

When unresolved replication intermediates or structural chromosome lesions persist into mitosis, cells commonly produce lagging fragments that are excluded into micronuclei. Micronuclei often lack complete nuclear lamins (notably low lamin B1), replicate asynchronously, and are subject to nuclear envelope rupture and cytosolic exposure. Live-cell and single-cell genomic studies show that micronuclear chromosomes under-replicate, accumulate strand breaks, and— upon entry into mitosis or premature condensation— can be pulverized (Cheng-Zhong Zhang (2015) [9]; Maja Kneissig (2019) [4]). In a progeroid context, nuclear fragility and mitotic errors are more frequent, making micronucleus formation a plausible downstream outcome of progerin-driven replication stress.

Chromothripsis is defined by clustered breakpoints and oscillating copy-number states restricted to one or a few chromosomes. Mechanistically, chromothripsis arises when an isolated chromosome (e.g., in a micronucleus) experiences extensive fragmentation and random rejoining within a single cell cycle. Experiments that force micronucleus formation produce chromothripsis-like rearrangements, establishing the pathway from missegregation → micronucleus → fragmentation → reassembly. Collapsed replication forks (one-ended DSBs) that are processed incorrectly can also seed complex rearrangements. Experimental evidence now indicates that the fate of under-replicated or missegregated DNA, repair/recovery versus fragmentation, depends heavily on which repair complexes are engaged and on cell-cycle timing.

The FA pathway normally senses stalled forks and interstrand crosslinks and orchestrates repair through monoubiquitination of FANCI–FANCD2, recruitment of nucleases (SLX4–XPF, MUS81), and cooperation with homologous recombination factors. Under canonical conditions, this action preserves

genome integrity. However, CRISPR screens and mechanistic studies have revealed a non-canonical, pro-fragmentation role: when FA factors engage persistent replication intermediates inside micronuclei, their recruitment of structure-selective nucleases can create clustered cleavages that catalyze chromothripsis (Justin Engel (2024) [2]; Anna Repczynska (2024) [7]). Crucially, in cell lines where FA core components were genetically disabled, chromothripsis frequency fell, implying that FA activity is necessary for cleavage-driven shattering in some contexts. Yet FA deficiency itself causes hallmark phenotypes (bone marrow failure, cancer predisposition), so chronic inactivation is not a viable blanket therapy.

Multiple genetically engineered mouse models (notably LmnaG609G knock-in mice and Zmpste24–/– mice) faithfully recapitulate key features of human HGPS: vascular smooth muscle cell (VSMC) loss, adventitial fibrosis, cutaneous thinning, alopecia, growth retardation, and shortened lifespan. Studies of these mice provide crucial in vivo insight into where FA-restriction therapeutics could act and what safety constraints apply.

The LmnaG609G mouse carries the human-equivalent cryptic splice mutation and develops progeroid features with severity dependent on zygosity (LmnaG609G/G609G more severe than heterozygotes). These mice show early VSMC loss in the aorta, frequent nuclear membrane ruptures in aortic SMCs, and increased collagen deposition leading to arterial stiffening and heart dysfunction (Magda Hamczyk (2019) [3]; Lara Del Campo (2019) [1]). Importantly, studies demonstrate that nuclear membrane ruptures in vivo precede SMC loss, supporting a model in which progerin-driven nuclear fragility leads to replication/mitotic errors, cytosolic DNA exposure, inflammation, and cell death.

Mouse genetics shows that p53 activity modulates aging phenotypes broadly. In HGPS cell models p53 activation drives senescence, and experimental p53 depletion in vitro can delay senescence caused by progerin (allowing cells to continue cycling despite damage). In mice, p53 pathway manipulation yields complex results across progeroid models; in some accelerated-aging strains, reducing p53 ameliorates tissue degeneration but increases cancer risk. These data highlight that p53 preserves tissue integrity at the population level by clearing dangerously damaged cells— an effect that must be carefully respected in any therapy aimed at preserving genomic integrity.

Gene-editing rescue of HGPS in mice provides a benchmark for curative potential. In vivo adenine base editing (ABEmax-VRQR delivered by dual AAV9) corrected the LMNA splice mutation in LmnaG609G mice, restored VSMC counts, reduced adventitial fibrosis, and dramatically extended median lifespan (from ~215 to ~510 days) (Luke Koblan (2021) [5]). These results demonstrate that correcting the root mutation in mice is feasible and highly effective, and also define a "ceiling" of benefit against which other interventions must be measured.

Pharmacologic approaches in mice (e.g., lonafarnib) reduce progerin prenylation and partially improve vascular function; small molecules such as rapamycin or chaetocin analogs can stabilize lamina dynamics or promote progerin clearance, providing partial phenotype amelioration. These studies establish that mouse physiology can be rescued both genetically and pharmacologically, and that vascular tissues are readily assayable endpoints for therapeutic effect.

3. Therapeutic Hypothesis

Given the FA pathway's paradoxical role, we hypothesize that transiently restricting FA-driven nuclease recruitment during M phase, specifically limiting SLX4/XPF and MUS81 cleavage at mitotic entry, will reduce chromosomal pulverization of under-replicated micronuclear DNA and thereby

decrease the generation of cytosolic DNA fragments, micronucleus rupture events, cGAS–STING activation, and pro-inflammatory SASP signaling. By timing inhibition to the brief window when mitotic condensation and mitotic DNA synthesis (MiDAS) occur, we aim to spare FA's protective fork stabilization functions in S phase and thereby avoid the chronic repair deficiency that causes Fanconi anemia–like toxicity.

This is distinct from full FA pathway inhibition: it targets nuclease recruitment/activation in a cell-cycle– and context-specific manner, using transient pharmacologic inhibitors, inducible RNAi, or small molecules that block SLX4 scaffolding functions only during mitotic progression.

4. Proposed therapeutic modalities:

Mitotic window nuclease inhibitors: small molecules that inhibit SLX4 scaffolding interactions or the endonuclease activity of XPF or MUS81, delivered transiently or with pharmacokinetics that favor mitotic cells (e.g., nanoparticles taken up preferentially by proliferating tissue niches). No such highly selective clinical inhibitor currently exists for SLX4, but research compounds and peptide blockers could be optimized.

Inducible, tissue-targeted shRNA/CRISPRi: for preclinical testing, tetracycline-inducible shRNA or CRISPRi constructs directed against SLX4 or MUS81 delivered with adeno-associated virus (AAV) under vascular SMC promoters (e.g., SM22α) would permit temporally controlled downregulation in the most vulnerable tissues.

Combination strategy: pair limited mitosis-restricted nuclease inhibition with HR-supportive agents (e.g., RAD51 stabilizers) and ATR pathway enhancers to promote accurate fork restart in S phase while blocking catastrophic cleavage in M phase.

Adjunct p53-preserving measures: maintain p53 competence so heavily damaged cells still senesce or undergo apoptosis rather than tolerate chromothripsis; avoid any therapy that suppresses p53 globally. Complete FA deficiency causes bone marrow failure and cancer predisposition; clinical Fanconi anemia patients exhibit marrow aplasia and high leukemia risk. However, mice or cells with partial or conditional FA impairment sometimes tolerate reduced FA activity in a tissue-specific manner. By limiting FA-driven cleavage only to the brief mitotic phase and only in tissues where micronuclei formation and fragility are highest (e.g., VSMCs), we hypothesize an improved therapeutic index: decreased fragmentation and cytosolic DNA signaling without chronic accumulation of repair substrates.

5. Experimental framework

5.1 In vitro / cellular experiments

The in vitro experimental program will employ a range of cellular models to capture the principal contexts in which progerin-driven replication stress and FA-pathway activity interact. Primary dermal fibroblasts derived from HGPS patients and matched healthy controls will serve as a first-line, physiologically relevant substrate for interrogation. These primary cells will be complemented by isogenic human cell lines engineered for inducible progerin expression, enabling controlled comparison of progerin-on versus progerin-off states within an otherwise identical genetic background. To approximate disease-relevant vascular biology, the study will include established vascular smooth muscle cell (VSMC) lines and VSMCs differentiated from induced pluripotent stem cells (iPSCs) that

express progerin. Finally, targeted genetic perturbations will be implemented using CRISPR interference or siRNA constructs directed against SLX4, MUS81, and FANCD2 to dissect the role of FA-mediated nuclease recruitment and activity.

Experimental manipulations will be designed to isolate mitotic nuclease function from S-phase fork-protective roles. Inducible progerin expression will be combined with transient inhibition of SLX4 or MUS81, delivered either as available small molecules or via siRNA/CRISPRi, and timed using cell-cycle synchronization protocols to enrich for mitotic entry at the moment of inhibitor exposure. Parallel arms will deliver inhibitors selectively at S phase or continuously as controls to verify the importance of temporal restriction. Selected treatment arms will include co-administration of RAD51-stabilizing compounds or ATR-pathway enhancers to provide homologous-recombination (HR) support and mitigate fork collapse, permitting assessment of combination strategies intended to preserve S-phase repair while blocking mitotic cleavage.

A comprehensive suite of readouts will quantify genomic integrity, inflammatory signaling, replication dynamics, and cell fate. Micronucleus frequency will be measured by immunofluorescence with lamin B1 labeling to evaluate nuclear envelope integrity and missegregation events. DNA damage will be assessed by quantifying γ-H2AX and 53BP1 foci, and fork stability will be interrogated through DNA fiber assays. Single-cell whole-genome sequencing or shallow single-cell copy-number profiling will be used to detect chromothripsis-like signatures and to quantify complex rearrangements. Mitotic DNA synthesis (MiDAS) assays, together with POLD3 localization studies, will determine the extent and timing of late DNA synthesis events. Innate immune activation will be monitored by assaying cGAS localization and downstream interferon-stimulated gene expression, while senescence will be evaluated by SA-β-gal staining and measurement of p16 and p21 expression. Standard viability, proliferation, and apoptosis assays (including annexin V staining and caspase activation) will quantify cell fitness, and clonogenic assays will assess long-term survival and the potential outgrowth of damaged clones.

The working hypotheses are that transient restriction of FA-dependent nucleolytic activity specifically during mitosis will reduce the incidence of chromothripsis signatures and cytosolic DNA-mediated inflammatory signaling without measurably increasing the baseline burden of S-phase double-strand breaks, and that co-support of HR/ATR pathways will further decrease fork collapse and improve cellular survival and function.

5.2 Ex vivo organoid / tissue experiments

To bridge cellular findings and whole-organ physiology, the project will utilize ex vivo tissue systems that retain multicellular architecture and extracellular matrix context. Three-dimensional vascular tissue organoids derived from HGPS patient iPSCs will model vessel wall microenvironments in which VSMC loss and inflammatory signaling can be quantified in a tissue-relevant setting. Complementarily, aortic ring cultures harvested from LmnaG609G mice will provide an intact tissue explant system to examine VSMC integrity and responses to local interventions.

Manipulative approaches in these ex vivo systems will test local, intermittent delivery of mitotic-targeted nuclease inhibitors, for example via nanoparticle formulations that allow focal administration and controlled release. Endpoints will include histological and fluorescence-based evaluation of VSMC integrity, measurement of nuclear rupture events using reporters such as Nuc-tdTomato, and assessment of extracellular matrix remodeling and fibrosis. Genomic consequences will be probed by targeted sequencing panels to detect copy-number aberrations and other structural variants in organoid

cells, enabling direct comparison of chromothripsis-related outcomes between treated and control tissues.

5.3 In vivo mouse experiments (safety and efficacy)

The principal in vivo platform will be the LmnaG609G knock-in mouse, using both homozygous (LmnaG609G/G609G) and heterozygous (LmnaG609G/+) animals as appropriate; where tissue specificity is required, these mice will be crossed to inducible, tissue-specific Cre lines such as SM22α-CreER to permit VSMC-targeted interventions. Experimental arms will include three primary intervention strategies: first, adeno-associated virus (AAV)-mediated delivery of doxycycline-inducible shRNA constructs against SLX4 or MUS81 driven by a VSMC-specific promoter, with induction applied in short pulses timed to developmental windows or observed elevations in mitotic index; second, intermittent systemic or locally delivered small-molecule mitotic nuclease inhibitors, if appropriate candidates are available, administered with pharmacokinetics designed to concentrate activity during mitotic windows; and third, control and comparison arms consisting of AAV-control shRNA, low-dose global FA-pathway inhibitors, and a gene-editing rescue arm (ABE) as a positive-control benchmark, with additional combination arms pairing nuclease restriction with RAD51 stabilizers or ATR enhancers to evaluate synergistic benefit.

Primary efficacy outcomes will be anatomically and functionally focused. VSMC survival and number in the ascending aorta will be quantified by histology and immunostaining, while vascular function will be assessed with arterial stiffness measurements and echocardiography to capture physiologic improvement. Broader healthspan indices, including body weight trajectories, mobility assays, and bone densitometry, will be collected longitudinally, and overall lifespan will be recorded. Safety will be monitored rigorously through hematologic surveillance (complete blood counts) and bone marrow histology to detect cytopenias or hypocellularity, and tumor incidence will be recorded to detect any oncogenic consequences of the interventions.

Secondary genomic endpoints will include whole-genome or targeted sequencing of aortic tissue and other organs to determine the frequency and distribution of chromothripsis signatures after treatment, microscopic quantification of tissue-level micronuclei, and measurement of systemic and tissue-specific cGAS-STING activation and senescence-associated secretory phenotype (SASP) markers in serum and tissue lysates.

Safety thresholds and decision points will be defined prospectively. Any evidence of bone marrow suppression, manifested as sustained declines in peripheral blood counts or marrow hypocellularity on histology, will trigger dose reduction or cessation of the investigational intervention. Likewise, a reproducible increase in tumor incidence in treatment cohorts will be considered an unacceptable risk and will necessitate termination of the corresponding arm. Finally, efficacy will be interpreted relative to outcomes achieved by ABE-mediated gene correction, using that intervention as a clinical and mechanistic benchmark to contextualize the therapeutic value and risk–benefit profile of mitosis-restricted FA-pathway modulation.

5.3.1 Fanconi anemia as an instructive counterexample

Fanconi anemia (FA) patients with biallelic loss of FA genes suffer marrow failure, developmental defects, and cancer predisposition. These clinical consequences reflect the essential role of FA factors in maintaining hematopoietic progenitor integrity and in repairing endogenous replication lesions. Any therapy that chronically disables FA function risks inducing similar outcomes. Our approach mitigates

this risk by (a) restricting inhibition temporally (brief mitotic windows), (b) localizing effect to vulnerable tissues (e.g., VSMCs via tissue-specific promoters), and (c) preserving S-phase protection by not inhibiting FA ubiquitination or fork-protective functions broadly.

5.3.2 Off-target and cell-nonautonomous effects

Transient nuclease inhibition could interfere with necessary resolution of recombination intermediates in proliferating tissues or impact fertility. Moreover, preventing fragmentation may inadvertently allow survival of cells with large unrepaired lesions; therefore, preserving p53 competency and monitoring for clonogenic survival of damaged cells is critical.

5.3.3 Pharmacologic tractability

Highly selective, reversible inhibitors of SLX4 scaffolding or MUS81 catalytic activity do not yet exist in clinical use; medicinal chemistry will be required to generate compounds with favorable mitosis-phased kinetics. Delivery options (AAV, lipid nanoparticles, or cell-penetrant peptides) present different trade-offs in duration and reversibility.

5.3.4 Discussion: balancing benefits and risks; translational prospects

Conditional FA-restriction offers a plausible, mechanistically grounded strategy to reduce catastrophic chromosome fragmentation in HGPS while avoiding the systemic toxicity of global FA loss. It targets a discrete mechanistic event, nuclease-mediated cleavage of under-replicated or micronuclear DNA during mitosis, that lies upstream of inflammatory cytosolic DNA sensing and downstream tissue degeneration. Experimental evidence that FA activity can drive chromothripsis in other contexts supports the approach, while HGPS mouse models demonstrate both the disease relevance of nuclear ruptures and the feasibility of tissue-targeted interventions.

Nevertheless, the translational pathway is nontrivial. The first priority is rigorous preclinical testing: verify in human HGPS cells and organoids that mitotic nuclease restriction reduces chromothripsis signatures without increasing S-phase DSBs. In mice, tissue specificity (VSMC vs marrow) must be demonstrated. Combining FA–restriction with HR–support and preserving p53-mediated clearance may create a safety buffer. Finally, the ABE gene-correction results show that curing the root mutation remains the gold standard (long-term efficacy and biomarker normalization). FA-restriction thus is most plausibly a complementary therapy — either as a bridge to definitive gene editing, as an adjunct to lamina stabilizers, or as a palliative strategy when genetic repair is not yet feasible.

6. Conclusion

Progerin-driven replication stress and micronucleus formation place HGPS cells at risk of catastrophic chromosome fragmentation. The FA pathway can paradoxically promote chromothripsis when it recruits nucleases to under-replicated or missegregated chromosomes. A carefully constrained therapeutic strategy that restricts nuclease activity during mitosis while preserving S-phase fork protection offers a novel route to reduce genome pulverization, downstream inflammatory signaling, and tissue degeneration. This strategy is deliberately conservative relative to global FA inhibition: it is temporal, context-dependent, and designed to preserve essential DNA repair functions. Robust in vitro and mouse testing (as laid out here) will be necessary to define therapeutic windows and safety margins. Ultimately, FA-restriction may serve as an adjunct to gene-corrective or lamina-stabilizing treatments, enhancing benefit while minimizing long-term risks.

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