Pharmacotherapy to Gene Editing: Potential Therapeutic Approaches for Hutchinson-Gilford Progeria Syndrome

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Table S1: Potential treatment strategies for HGPS and their assessment in different disease models.

Abbreviations: 1,25 D, 1α, 25-dihydroxy vitamin D3; AFC, N-acetyl-S-farnesyl-l-cysteine; AMPK, adenosine monophosphate-activated protein kinase; ATM, ataxia-telangiectasia-mutated); ATRA, all-trans retinoic acid; CK2, Casein kinase 2; COL3, Collagen type III; CRISPR, clustered regularly interspaced short palindromic repeats; CRM1, Chromosomal region maintenance 1; DOT1L, Disruptor of telomeric silencing 1-like; DSB, double strand break; ECM, Extracellular Matrix; ER, endoplasmic reticulum; FDPS, farnesyl diphosphate synthase; FTI, farnesyl transferase inhibitors; GH, growth hormone; H3K27me3, histone H3 trimethylated on lysine 27; HSCs, hematopoietic stem cells; ICMT, Isoprenylcysteine carboxyl methyltransferase; IGF-1, insulin-like growth factor-1; IKK complex, IκB kinase complex; iPSC, induced pluripotent cell; iPSC-EVs, extracellular vesicles derived from induced pluripotent cells; MAF: mouse adult fibroblast; MDSPCs, muscle-derived stem/progenitor cells; MEF, mouse embryonic fibroblast; MIAMI cells, marrow isolated adult multilineage inducible cells; MMP, mitochondrial membrane potential; mono-AP, mono-aminopyrimidines; MRTF-A, myocardin related transcription factorA; MSC, mesenchymal stem cells; MSC-EVs, Extracellular vesicles derived from healthy mesenchymal stem cells; mTOR, mammalian target of rapamycin; NAT10, N-acetyltransferase 10; NRF-2, Nuclear factor erythroid 2–related factor 2; OSKM: *Oct4*, *Sox2, Klf4*, and *c-Myc*; ROS, reactive oxygen species; ROCK, Rho-associated protein kinase; SASP, senescence-associated secretory phenotype; SIRT1 and 6, sirtuin-1 and -6; SRF, serum response factor; SRSF-1 and -5, serine/arginine-rich splicing factor-1 and -5; UTR, untranslated region; VSMC, vascular smooth muscle cells.

Therapeutic approach / Treatment	Target molecule/function	Affected pathway	Therapeutic effects	Model of study	Reference
Drug based therapeutic approaches					
FTI	Inhibitor of farnesyl transferase enzyme	Prelamin A processing	Ameliorated nuclear shape defects, mis-localization of prelamin A away from nuclear rim, improved chromosome positioning and tethering of telomeres to the nucleoskeleton	Skin fibroblast from HGPS patient, *Zmpste24*$^{-/-}$ MEF, *Lmna*$^{HG/HG}$ and *Lmna*$^{HG/+}$ MEF	(Bikkul et al. 2018; Capell et al. 2005; Glynn and Glover 2005; Toth et al. 2005; Yang et al. 2005)
			Improved ATP synthesis and COX/CS ratio	Mouse adult fibroblast (MAF) from *Zmpste24*$^{-/-}$ and *Lmna*$^{G609G/G609G}$ mice	(Rivera-Torres et al. 2013)

			Improved self-renewal capacity, increased cell migration, decreased cell stiffness	Marrow Isolated Adult Multilineage Inducible (MIAMI) cells	(Pacheco et al. 2014)
			Extended life span, increased body weight, improved muscle and bone strength	*Zmpste24*$^{-/-}$ mice	(Fong et al. 2006a)
			Extended life span, increased body weight, improved bone mineralization and cortical thickness, elevated adipose tissue mass	*Lmna*$^{HG/+}$ mice	(Yang et al. 2006; Yang et al. 2008b)

			Delayed onset and progression of cardiovascular disease	BAC *Lmna*^{G608G} mice	(Capell et al. 2008)
Combined treatment of Amino bisphosphonate + Statin	Amino bisphosphonate inhibits farnesyl pyrophosphate synthase and isopentenyl pyrophosphate isomerase. Statins are HMG-CoA reductase inhibitor.	Prelamin A processing	Ameliorated nuclear morphological defects, inhibition of formation lamin A/C nucleoplasmic aggregates, partial rescue of DNA damage	Skin fibroblast from HGPS patient, Zmpste24-deficient cells	(Varela et al. 2008)
			Extended life span, increased size and body weight, improved bone mineralization and cortical thickness, reduced nuclear abnormalities	*Zmpste24*$^{-/-}$ mice	(Varela et al. 2008)

			Improved ATP synthesis and COX/CS ratio	Mouse adult fibroblast (MAF) from *Zmpste24*$^{-/-}$ and *Lmna*$^{G609G/G609G}$ mice	(Rivera-Torres et al. 2013)
Rapamycin and its analogs	mTOR signaling inhibitor	Autophagy	Delayed senescence, rescued nuclear blebbing, reduced progerin level	Skin fibroblast from HGPS patient	(Cao et al. 2011)
			Reduced progerin level, restored nuclear integrity and chromatin organization	Skin fibroblast from HGPS patient	(Cenni et al. 2011)
			Increased progerin clearance, restored nuclear shape, increase cell growth, partially rescued DNA damage	Skin fibroblast from HGPS patient	(Gabriel et al. 2016)

			Improved cell proliferation, decreased nuclear lobulation, reduced senescence.	Skin fibroblast from HGPS patient	(DuBose et al. 2018)
			Reduced DNA damage	Skin fibroblast from HGPS patient	(Bikkul et al. 2018)
			Reduced senescence & apoptosis, improved myogenic and chondrogenic differentiation potential, decreased adipogenic differentiation ability	MDSPCs from *Zmpste24*$^{-/-}$ mice	(Kawakami et al. 2019)
AFC	Competitive ICMT inhibitor	Prelamin A processing	Increased cell proliferation	Skin fibroblast from HGPS patient	(Ibrahim et al. 2013)

Mono-AP	Inhibitor of Farnesyl pyrophosphate synthase and farnesyl transferase	Prelamin A farnesylation and prenylation	Rescued nuclear defects, ameliorated premature differentiation of HGPS-MSC into osteoblastic lineage.	Mesenchymal stem cells (MSC) derived from HGPS-iPSCs, HGPS patient dermal fibroblast	(Blondel et al. 2016)
All-trans retinoic acid (ATRA)	Retinoic acid responsive element,	Autophagy	Reduced progerin as well as lamin A accumulation, decreased DNA damage, restored nuclear structure, enhanced cell proliferation (Synergistic action with rapamycin)	Skin fibroblast from HGPS patient	(Pellegrini et al. 2015)
Sulforaphane	Inducer of antioxidant enzymes	Oxidative stress, autophagy	Reduced nuclear blebbing, decreased ROS and DNA damage, increased cell proliferation rate, increased progerin clearance, increase in intracellular ATP	Skin fibroblast from HGPS patient	(Gabriel et al. 2015; Gabriel et al. 2017)

MG132	Proteasome inhibitor, Regulates SRSF-1 and SRSF-5	Autophagy, Aberrant splicing of *LMNA*	Decreased progerin level, reduced abnormal nuclei, delayed senescence, increased cell proliferation, lowered DNA damage and heterochromatin loss.	Skin fibroblast from HGPS patient	(Harhouri et al. 2017)
			Increased progerin clearance	HGPS iPSC-derived MSC and VSMC, *Lmna*$^{G609G/G609G}$ mice	(Harhouri et al. 2017)
Metformin	Regulates SRSF-1, Activates AMPK	Aberrant splicing of *LMNA*, AMPK cell signaling pathway	Decreased SRSF-1 and progerin expression, reduced abnormal nuclei, lowered premature osteogenic differentiation of HGPS-MSCs, reduced ROS and DNA damage, retarded senescence,	Mouse *Lmna*$^{G609G/G606G}$ fibroblast, HGPS-MSCs, Skin fibroblast from HGPS patient	(Egesipe et al. 2016; Park and Shin 2017)

			increased splenocyte proliferation, enhanced antioxidant expression		
JH4	Binding with C-terminal region of progerin	Lamin A-progerin interaction	Rescued cell cycle arrest, restored H3K9me3 level, alleviated nuclear defects in HGPS cells. Enhanced life span of mice, improved body weight, increased muscle strength, raised cell density, restored tissue growth morphology in thymus and spleen etc.	*Lmna*$^{+/G609G}$ and *Lmna*$^{G609G/G609G}$ mutant mice	(Lee et al. 2016b)
N-acetyl cysteine	ROS scavenger	Oxidative stress	Depletion of DNA DSB load, improved cell proliferation rate	Skin fibroblast from HGPS patient	(Richards et al. 2011)
Methylene blue	Improves mitochondrial function	Mitochondrial biogenesis and oxidative stress	Induced cell proliferation, ameliorated nuclear blebbing, reduced ROS production, improved mitochondrial function, alleviated	Skin fibroblast from HGPS patient	(Xiong et al. 2016)

			senescence, decreased heterochromatin loss, corrected gene expression		
Oltipraz	NRF2 activator	Oxidative stress	Ameliorated the defects in certain lamina associated proteins and H3K27me3	Human skin fibroblast from HGPS patients	(Kubben et al. 2016)
			Decreased ROS production, increased NRF2 regulated antioxidant gene expression, reduced number of apoptotic cells	MSC derived from HGPS-iPSC implanted into *tibialis anterior* muscle of SCID mice	(Kubben et al. 2016)
Y-27632 and Fasudil	Inhibitor of Rho-associated protein kinase (ROCK) activity	Oxidative stress	Decreased ROS production, increased MMP, improved mitochondrial function, reduced DNA DSB and ameliorated nuclear	Skin fibroblast from HGPS patients	(Kang et al. 2017; Park et al. 2018)

			defects, increased cell proliferation, reduced senescence.		
KU-60019	ATM inhibitor	Metabolic reprogramming in mitochondria	improved mitochondrial function, decrease in ROS, reduced senescence associated markers	Skin fibroblast from HGPS patient	(Kuk et al. 2019)
Sodium salicylate	Inhibitor of the IKK complex	Blocking of NF-κB activation	Extended longevity, improved body weight, improved bone architecture, enhanced cell proliferation, increased subcutaneous fat layer thickness, raised normal hair follicles in the skin, inhibited thymic and spleen involution	*Lmna*$^{G609G/G609G}$ and Zmpste24-deficient mice	(Osorio et al. 2012)
Baricitinib	Inhibition of JAK-STAT Signaling	Inflammatory pathways belonging to SASP	Reduction of proinflammatory factors, activation of proteasomes and autophagy, lowered progerin expression, increased proliferation,	Skin fibroblast from HGPS patients	(Liu et al. 2019a)

			reduced senescence, decreased ROS level, restored cellular ATP levels		
Chloroquine	Increases ATM activity	DNA damage response and SIRT6 pathway	Decrease in DNA damage, retarded loss of body weight, enhanced running endurance, extended lifespan.	*Zmpste24*$^{-/-}$ mouse model	(Qian et al. 2018)
1,25D/calcitriol	vitamin D receptors	Correction of replicative stress and DNA damage	Ameliorated nuclear and DNA damage repair defects, improved cellular senescence	Skin fibroblast from HGPS patient	(Kreienkamp et al. 2016; Kreienkamp et al. 2018)
Remodelin	NAT10 inhibitor	Microtubular rearrangement	Improved nuclear morphology, restored normal nucleocytoplasmic transport, reduced DNA damage, enhanced cell proliferation, rebalanced gene expression in HGPS fibroblasts.	Skin fibroblast from HGPS patient	(Larrieu et al. 2014; Larrieu et al. 2018)

			Increased life span, reduced loss of body weight, improved cardiac function in progeroid mouse model	Homo- and hetero-zygous *Lmna*^{G609G} progeroid mouse model	(Balmus et al. 2018)
Quercetin	Multiple including NRF2	Multiple pathways, majorly of cell cycle, nuclear division, NRF2 antioxidant and chromosome segregation pathways	Reduced cellular senescence, improved cell proliferation (synergistic effect with vitamin C)	Human HGPS-hMSC	(Geng et al. 2018)
Vitamin C	Multiple	Multiple pathways including oxidative stress, telomere attrition, inflammation, nuclear lamina and	reduced cellular senescence, improved cell proliferation (synergistic effect with quercetin)	Human HGPS-MSC	(Geng et al. 2018)

		heterochromatin reorganization			
Resveratrol	SIRT1 activator	Deacetylase activity	Decreased adult stem cell depletion, reduced body weight loss, improves bone structure and mineral density, extended life span	*Zmpste24* $^{-/-}$ mouse model	(Liu et al. 2012)
MS-275 (entinostat)	Class I HDAC inhibitor	Lamin A/C-HDAC2 interaction	Improved histone acetylation status of the cell	Skin fibroblast from HGPS patient	(Mattioli et al. 2019)
Spermidine	Activation of CK2	Multiple pathways *viz.* cell proliferation, cell survival, cell differentiation and development, apoptosis, DNA repair *etc.*	Increased CK2 activity, reduced p16^{Ink4a} expression & SA-β-gal activity (reduced senescence), decreased DNA damage marker level, improved DDR and repair.	*Zmpste24* $^{-/-}$ MEFs	(Ao et al. 2019)

			Increased body weight, extended life span, lesser rib fractures, increased bone density	*Zmpste24*$^{-/-}$ mice	(Ao et al. 2019)
S-adenosyl-methionine	Alternative source of purine	AMP production	Increased proliferative capacity and reduced senescence associated markers	Skin fibroblast from HGPS patient	(Mateos et al. 2018)
Recombinant human IGF-1	Balance between IGF-1 and growth hormone	Somatotroph signaling	Increased life span, improved body weight, increase in the amount of subcutaneous fat, reduced level of kyphosis, and alopecia.	*Zmpste24*$^{-/-}$ mice	(Mariño et al. 2010)
ABT-737	Inhibitor of anti-apoptotic proteins BCL-W and BCL-XL	Apoptosis	Decrease in senescent cells, lowering of molecular markers of senescence, reduced inflammation, increased life span	*Lmna*$^{+/G609G}$ progeroid mice	(Ovadya et al. 2018)
0.1% cholic acid	Bile acid metabolism	Lipid metabolism	Increased life span, retarded hindlimb stiffness, enhanced daily	*Zmpste24*$^{-/-}$ mice	(Bárcena et al. 2018)

			movement, bigger size, milder loss of weight, reduced loss of hair, lowered cervicothoracic lordokyphosis, decreased loss of body weight		
Tauroursodeoxycholic acid	Improves protein folding	ER stress	Extended life span, ameliorated vascular pathology	*Apoe*$^{-/-}$ *Lmna*$^{LCS/LCS}$*SM22αCre* mice	(Hamczyk et al. 2019)
Pamidronate	Inhibitor of FDPS	Progerin/PLA2R1/p53/ FDPS prosenescent axis	Reduced senescence, increased cell proliferation, improved nuclear morphology	Primary culture of human dermal fibroblasts from HGPS patients	(Griveau et al. 2018)
Exogenous pyrophosphate	Inhibition of calcium phosphate deposition	Pyrophosphate homeostasis	Reduced aortic calcification	*Lmna*$^{G609G/G609G}$ mice	(Villa-Bellosta et al. 2013)
Leptomycin B	CRM1 inhibitor	Nuclear export	Decreased nuclear blebbing, improved lamin B1 expression, reduced cellular senescence,	Primary culture of human dermal fibroblasts	(García-Aguirre et al. 2019)

			lowered heterochromatin loss, alleviated expansion of nucleoli.		
BRL37344	β_3-adrenergic receptor (β_3-AR) agonist	Bone marrow microenvironment	Restore lympho-myeloid skewing of HSCs, improved number of circulating granulocytes and lymphocytes, reestablished bone marrow neutrophils, partially restored bone marrow B cells, improved association of megakaryocytes to HSCs	*Lmna*$^{G609G/G609G}$ mice	(Ho et al. 2019)
Dietary interventions					
Methionine restriction in diet	Suppression of GH/IGF1 somatotrophic axis and mTOR pathway, enhances AMPK activity	Metabolic homeostasis	Increased life span, reduced DNA damage and inflammation, retardation in the appearance of lordokyphosis and loss of grooming, improvement in bone structure and	*Lmna*$^{G609G/G609G}$ mice	(Bárcena et al. 2018)

			mineral density, augmented tissue architecture in muscle, modulation of respiration rates and energy expenditure, restoration of gene expression, escalates metabolism and lipid profile, increase in bile acid level in *LMNA*$^{G609G/G609G}$ mice.		
			Increased life span, decreased loss of hair, improved cervicothoracic lordokyphosis in *Zmpste24*$^{-/-}$ mice.	*Zmpste24*$^{-/-}$ mice	(Bárcena et al. 2018)
Sodium nitrite	Nitric oxide	Nitric oxide signaling	Ameliorated vascular stiffness and inward remodeling	*Lmna*$^{G609G/G609G}$ progeroid mice	(del Campo et al. 2019)
High-fat diet	Lipid metabolism	Multiple pathways related to metabolism	Nearly doubled life span, reduction in body weight loss, increase in body fat and adipocyte size,	*Lmna*$^{G609/G609G}$ progeroid mice	(Kreienkamp et al. 2019)

			ameliorated metabolic alterations, improved expression of genes associated with cachexia		
Oral supplementation of fecal microbiota obtained from healthy individuals	Intestinal dysbiosis	Bile acid metabolism (possible mechanism)	Increased body weight, improved body temperatures, ameliorated blood glucose level, extended life span	*Lmna*$^{G609G/G609G}$ mice and	(Bárcena et al. 2019b)
Oral supplementation of Verrucomicrobia *Akkermansia*	Intestinal dysbiosis	Bile acid metabolism (possible mechanism)	Extended life span, improved body weight and size, less pronounced cervicothoracic lordokyphosis, ameliorated hypoglycemia	*Zmpste24*$^{-/-}$ mice	(Bárcena et al. 2019b)

muciniphila			Increased expression of Reg3g in Ileum, thickened intestinal mucosa layer, enhanced expression of wound healing factor (*Tff3*) in the intestine, improvement metabolome profile in the ileum Improved life span and body weight	*Lmna*$^{G609G/G609G}$ mice *Zmpste24*$^{-/-}$ mice	(Bárcena et al. 2019b) (Bárcena et al. 2019b)
Other approaches					
Constitutively active NRF2 (caNRF2)	Reactivation of NRF2	Oxidative stress	Decreased ROS production, increased NRF2 regulated antioxidant gene expression, reduced progerin expression, improved expression of lamina associated proteins	Human skin fibroblast from HGPS patients	(Kubben et al. 2016)

			Enhanced expression levels of NRF2-controlled antioxidant genes, reduced ROS levels, improved nuclear architecture, lowered number of apoptotic cells	MSC derived from HGPS-iPSC implanted into tibialis anterior muscle of SCID mice	(Kubben et al. 2016)
Short hairpin (sh) RNA against ICMT	ICMT	Prelamin A processing	Delayed senescence, increased cell proliferation rate	Human skin fibroblast from HGPS patient	(Ibrahim et al. 2013)
Short hairpin (sh) RNA against *LMNA*	*LMNA* gene	Progerin expression	Amelioration of morphological defects in nucleus, increased cell proliferation, reduced numbers of senescent cells	Human skin fibroblast from HGPS patients	(Huang et al. 2005)
CK2α overexpression	Activation of CK2	Multiple pathways *viz.* cell proliferation, cell survival, cell	Reduced β-gal–positive cells & p16^{Ink4a} level (decreased senescence)	$Zmpste24^{-/-} CK2\alpha^{TG}$ MEFs	(Ao et al. 2019)

		differentiation and development, apoptosis, DNA repair *etc.*			
NANOG overexpression	Increases SMAD2/3 mediated COL3 synthesis	TGF-β1 pathway	Restoration of COL3 in ECM, reduced senescence, increased cell proliferation, decreased DNA damage	Human skin fibroblast from HGPS patient	(Rong et al. 2019)
	MRTF-A and SRF dependent gene expression	TGF-β1 and ROCK pathways	Induce actin polymerization and restore contractile activity	Human dermal fibroblast from HGPS patient	(Mistriotis et al. 2017)
CRISPR/Cas9 system	*LMNA* gene	Progerin expression	Extended life span, attenuated body weight loss, improved architecture of gastro-intestinal tissues, reduced epidermal thinning and dermal fat loss, decreased degeneration of VSMC of the aortic arch, lessened	$Lmna^{G609G/G609G}$ mouse	(Beyret et al. 2019)

			development of bradycardia, increased grip strength.		
			Reduced progerin expression, decreased number of aberrant nuclei	Human skin fibroblast from HGPS patient	(Santiago-Fernández et al. 2019)
			Reduced progerin expression, decreased nuclear alterations	*Lmna*$^{G609G/G609G}$ mouse fibroblast	(Santiago-Fernández et al. 2019)
			Reduced progerin expression, increased life span and maximum survival, decreased apoptosis, retarded loss of grooming,	*Lmna*$^{G609G/G609G}$ mice	(Santiago-Fernández et al. 2019)

			improved body weight and blood glucose levels, reduced gastric mucosa atrophy, lowered fibrosis in heart and muscle		
Stem cell transplantation	Cellular reprogramming	Stem cell regeneration capability	Extended life span, weight gain, delayed aging related symptoms, promoted neovascularization several tissues (*viz.* muscle, brain), reduced muscle atrophy	*Ercc1*$^{-/-}$ and *Ercc1*$^{-/\Delta}$ mice	(Lavasani et al. 2012)
Yamanaka transcription factors (*Oct4, Sox2, Klf4,* and *c-myc*)	Partial reprogramming of the cell	epigenetic alterations, cellular senescence pathways	Moderated spinal curvature, increase in median and maximum life span, augmented epidermal and dermal thickness, reduced keratinization of the skin, improved histological features of multiple organs (skin, spleen, kidneys, and	*Lmna*$^{G609G/G609G}$ (LAKI) mice crossed to mice carrying an OSKM polycystronic cassette (4F) and a rtTA trans-activator, thereby generating LAKI 4F mice	(Ocampo et al. 2016)

			gastrointestinal tract), decreased VSMC degeneration, rescued development of bradycardia, restored cell proliferation rate, reestablished histone modifications, reduced apoptosis, partial restoration of adult stem cell population		
			Reduced ROS and DNA damage, decreased senescence, lowered expression of senescence associated stress response genes, restored histone methylation, improved nuclear envelope architecture	LAKI 4F mice tail tip fibroblast culture	(Ocampo et al. 2016)

Morpholino antisense RNA	*LMNA* gene (Correction of aberrant splicing of *LMNA* gene)	Progerin expression	Restored nuclear structure and expression of misregulated genes, reduced lamin A expression	Human skin fibroblast from HGPS patient	(Scaffidi and Misteli 2005)
			Reduced progerin level, decreased loss of body weight, increased life span, lowered expression of senescence associated markers, thickened subcutaneous fat layer, heightened serum glucose level, a reduced involution of thymus and spleen.	$Lmna^{G609G/G609G}$ mice	(Osorio et al. 2011)
			Ameliorated nuclear shape abnormalities, increased lamin C but	Human skin fibroblast from HGPS patient	(Lee et al. 2016a)

			reduced lamin A/progerin expression, Reduced progerin, improved aortic pathology. Decreased progerin expression, reduced senescence, improved nuclear shape,	 *Lmna*$^{G609G/G609G}$mice Human skin fibroblast from HGPS patient	 (Lee et al. 2016a) (Harhouri et al. 2016)
miR-9 (micro RNA)	Lamin A RNA 3'-UTR	Progerin expression	Reduced lamin A/progerin, ameliorated nuclear abnormalities	HGPS-iPSC-MSC	(Nissan et al. 2012)
hTERT mRNA	Telomerase enzyme	Telomere length	Increased telomere length, partial restoration of telomere associated proteins, enhanced cell proliferation, reduced senescence, improved nuclear morphology,	HGPS cell line	(Li et al. 2019)

			rescued secretion of inflammatory cytokines		
Human MSC-EVs and iPSC-EVs	Peroxiredoxin antioxidant enzymes	Oxidative stress	Reduced senescence and increased cell proliferation	Progerin overexpressing MSCs	(Liu et al. 2019b)