Review Article

Current Pathophysiological and Therapeutic Options for Children withHutchinson-Gilford Syndrome

Abstract
Hutchinson-Gilford-Progeria syndrome (HGPS) cannot, to date, be treated causally. Therapy for affected children focus on alleviating the symptoms, treating secondary diseases and preventing complications such as strokes or heart attacks. Various medications and physiotherapeutic methods are primarily available for this extremely rare pediatric genetic disease. Lonafarnib, a farnesyltransferase inhibitor, has been used for the treatment of progeria in children since 2022, which can extend the life of children with HGPSup to 4 years. Farnesyltransferase inhibitors are able to block an enzyme that is involved in progerin processing. Progerin is the altered protein that occurs in HGPS due to the spelling mistake in the lamin A gene and accumulates within the cell nucleus envelope. As a result, the envelope is weakened and the cell nucleus becomes deformed. The spectrum of therapies includes progerin-targeting strategies on one hand and on therapies to alleviate the tremendous effects by progerin. Research focus on different new targets in the managementof HGPS-like the farnesyltransferase inhibitor lonafarnib, Acetyltransferase NAT10-inhibitors, KAT 6a/b and -7 inhibitors, paclitaxel, small molecule ICMT-inhibitors, exportin CRM-1 Inhibitors, progerin-lamin A binding inhibitors (Progerinin), Ghrelin, micro-RNA inhibitors, doxycycline and the regulation of rapamycin complex 1 (mTORC1). This manuscriptanalyses these new therapeutic targets and pathophysiological aspects in a review manuscript.

Key Words
Progeria-HGPS-senescence-premature aging-child

Introduction
Progeria, also known as progeria and premature ageing, in the narrower sense HGPS, also known as progeria infantilis, belongs to the segmental progeroid syndromes or progeria syndromesand is a symptom of various hereditary diseases that are associated with premature ageing in children. The first description was published in 1886 by Jonathan Hutchinson and later in 1904 by Hastings Gilford (1,2). 200-250 cases worldwide were found with classical and non-classical forms of HGPS. HGPS has a prevalence of 1 case per 4-8 million live births (3).The most striking feature is the premature ageing of affected children (1-71).From cellular aspect, different features of aging have been described, instability of genome, telomere lengths changes, epigenetic impairment, disturbances in proteostasis, senescence of cells, disturbances of mitochondrial functions, changes in intercellular communication, stem cell depletion and deregulated nutrient sensing (3,24,72).One cause of progeria is a dominant de novo mutation within exon 11 of codon 608 on chromosome 1q22 on the LMNA gene, which induces the synthesis of progerin, a mutant form of lamin A (4,5,7). It is a silent mutation with a cryptic splicing site (4,5). Children affected by this disease are born without any abnormalities and develop their first symptoms at the age of six to twelve months. Lifespan includes a range between 6 and 20 years (3).The most common causes of death are heart attacks and strokes, which occur most often around age 13 (3).Lamin A is a key element of the structure of the nuclear envelope, playing an important role in gene expression regulation (6,71). Prelamin Aundergoes post-translational. changes and cleavage by ZMPSTE24 to form lamin A (6). Mature lamin A originates from a pre-lamin A precursor protein (6). Pre-lamin A includes a CaaX-box at the carboxyl-terminus, which then will be farnesylated at a cysteine residue in the process of production of the enzyme farnesyltransferase (6). After concluded reaction, 3 last three amino acids of pre-lamin A (aaX), will be removed and methylation of a farnesylated cysteine will take place (6). Pre-lamin A then passes the endoplasmatic reticulum to inner nuclear membrane, where it undergoes a final cleavage reaction with a zinc metalloprotease Zmptse24. This metalloprotease then removes the last 15 amino acids including farnesylated cysteine from the carboxyl-terminus (6). Progerin influences relevant cellular and molecular mechanism (6). Important mechanism are energy generation by oxidative phosphorylation, regulation of apoptosis, calcium homeostasis and cellular senescence (6). Mitochondria play an important role in diseases like cancer, metabolic and neurological diseases or natural and premature aging (8-14). In HGPS cells, diminished mitochondrial activity with accumulation of reactive oxygen species (ROS) and lower ATP levels have been described in former studies (3,8-14). Mitochondrial production is disturbed due to low expression of peroxysome proliferator-activated receptor-gamma coactivator-1 alpha. It is an important transcriptional modulator of hemostasis in mitochondria (3). High progerin levels in 3T3L1 preadipocytes show the changes in mitochondria of HGPS cell cultures (3). A higher activity of complex I of the respiratory chain and an accumulation of ROS were described (3). The decrease in cell proliferation and adipogenic capacity mirrors the lipodystrophy realized in HGPS (3). The ectopic progerin expression in rat nucleus pulposus cell cultures lead to abnormal mitochondrial structure and disturbed mitochondrial membrane potential, contributing to intervertebral

disc structural changes commonly seen in aging. This fact has not been studied in patients with HGPS (3,8-14).Mitochondrial function is normally regulated by two opposing ways: mitochondrial biogenesis, which creates new mitochondria, and mitophagy, which eliminates damaged mitochondria through autophagy (3). Disrupted mitophagy accounts for mitochondrial dysfunction in HGPS (3,8-14).Elevated parkin levels were described in HGPS cells showing enriched mitophagy (15,75).Telomere lengths is a hallmark of aging by replicative senescence (16,17). Human telomeres consist of a repeated DNA sequence (5'-TTAGGG-3') located at the ends of chromosomes (16). They help maintain chromosomal integrity by preventing damaged DNA recognition through the shelterin protein complex (17). Telomeres shorten with each cell division, leading to cellular events triggering apoptosis (17). Accelerated telomere attrition refers to progerin's negative role on cell physiology. Progerin induces replication fork collapse, DNA destructive response, and cell cycle stop. It also influences redox imbalance, leading to telomere shortening (16,17). Progerin disturbes interactions between lamin A, TRF2, and LAP2a, disturbing telomeric homeostasis (17). HGPS-cell cultures show a change in replication time and elongation of replication forks, diminishing dNTP availability (18,19).Changes in nucleocytoplasmic trafficking of proteins plays also an important role in HGPS cell cultures (3). The movement of proteins into and out of the nucleus through the nuclear pore complex (NPC) is controlled by nuclear receptors, importins and exportins, with a focus on specific sequence motifs on cargo proteins, such as nuclear localization signal and nuclear export signal (20).Cellular changes in HGPS cells are the structural defects of the nuclear envelope due to the accumulation of progerin (20-22). Intensive clustering of nuclear pore complexes (NPC) have also been described, suggesting a potential change in nucleocytoplasmic protein trafficking in HGPS cells (20-22). Further studies revealed reduced nuclear transport of high molecular weight proteins E2-conjugating enzyme Ubc9 and the translocated promoter region, nucleoporin TPR, in fibroblasts of HGPS cells,resulting to an imbalance in Ran-GTPase gradient critical for import/export complex structuring (21).Progerin influencesthe non-classical nuclear import pathway mediated by Transportin-1 (TNPO-1), resulting to cytoplasmic sequestration of TNPO-1 by the microtubule network and hindering nuclear translocation of client proteins like nucleoporin Nup 153 (23). The CRM1-driven nuclear protein export pathway is hyperactive in human HGPS fibroblasts due to CRM1 overexpression, impacting protein distribution between the nucleus and cytoplasm and potentially contributing to HGPS pathophysiology (12).CRM1overexpression in normal fibroblasts can influence the HGPS phenotype (12).These results underline the importance ofnucleocytoplasmic protein transport in HGPS and suggest that interventions targeting this pathway could have therapeutic benefits for HGPS (12,20-23).

Different Pre-Aging Diseases

Different pre-aging diseases do exist. Progeroid laminoathies will be divided into 4 groups, whereas Hutchinson-Gilford syndrome is placed into group 4. The autosomal recessive mandibuloacral dysplasia (MAD) is divided based on the underlying mutations in LMNA (MADA) or ZMPSTE24 in (MADB), both of which cause an accumulation of prelamin A and thus impair chromatin physiology due to insufficient lamin A.In addition to thepostnatal progeroid symptoms, local osteolyses ,with hypoplasia of the mandible, clavicles, fingers, and receding chin, and osteoporosis are characteristic. The main difference between the two subgroups lies in the partial lipodystrophy in the extremities and fat deposits in the neck and facial area in Type A and a more generalized lipodystrophy in MADB.The "Néstor-Guillermo progeria syndrome" (NGPS) caused by mutations in BANF1 ("barrier to autointegration factor 1") is characterized by a longer life expectancy and a slower clinical course. BANF plays a role in the assembly and disassembly of the nuclear lamina during mitosis, but also interacts with LMNA. However, the clinical presentation is very similar to the previously mentioned MAD syndromes. There is growth retardation, progressive lipoatrophy, and the progeroid symptoms mentioned above. Despite the striking skeletal changes, there were no cardiovascular complications, which are common in HGPS. Restrictive dermopathy, also known as "lethal hyperkeratosis-contractures syndrome," is mostly caused by mutations in the ZMPSTE24 gene, but can also be caused by heterozygous de novo mutations in the LMNA gene. Due to intrauterine growth retardation, there is fetal akinesia and polyhydramnios, leading to premature birth. Affected individuals have a typical appearance with tight, thin skin with hyperkeratosis, erosions, scales, and protruding nipples. There is a characteristic facies with an O-shaped mouth, protruding inner corners of the eyes, a small nose, and low-set ears. Bone deformities include oversized long bones, dysplastic clavicles, and contractures. Due to the fetal akinesia deformation sequence, there is pulmonary hypoplasia, leading to death within the first week of life for the children.Cockayne syndrome (CS) is primarily caused by mutations in the CSA (ERCC8) or CSB (ERCC6) genes. CSB (ERCC6 gene locus 10q11) is also referred to in the literature as DeSanctis-Cacchione syndrome. Both genes encode proteins involved in TC-NER. Clinically, symptoms can vary inter-familially even in homozygous variants. However, the disease is characterized by progressive neurodegeneration similar to TTD, especially compared to XP. Microcephaly and growth retardation are cardinal symptoms. In addition to ataxia, tremor, and dystonia, patients may also exhibit growth retardation, intellectual disability, microcephaly, light sensitivity, hearing loss, and retinal degeneration. The overall life expectancy is approximately 8 to 9 years.Neurodegeneration, microcephaly, and growth retardation are cardinal symptoms of Cockayne syndrome.

New Therapeutic Options

Farnesyltransferase Inhibitor (Lonafarnib)

Since 2020 in the US and 2022 in the EU, the drug lonafarnib, a farnesyltransferase inhibitor, has been approved for the treatment from the age of 12 months (25-29,30,31). Lonafarnib seems to slow down the progression of the disease with an increasing life expectancy of 2.5 and 4.3 years (3,25-29,30,31). By inhibiting the enzyme farnesyltransferase, lonafarnib prevents truncated or aberrant prelamin A from being farnelyzed in the first place and consequently reduces the accumulation of aberrant progerin and progerin-like proteins in the inner nuclear membrane (3,20-23,25,29,30). This leads to the maintenance of cell integrity and normal function. Lonafarnib is a non-hygroscopic powder that is practically insoluble in water and sparingly soluble in ethyl acetate and tetrahydrofuran. The drug is indicated for the treatment of patients aged12 months and older withgenetically confirmed diagnosis of Hutchinson-Gilford progeria syndrome and in progeroid laminopathy with processing defects associated with a heterozygous LMNA mutation with progeria-like protein accumulation or a homozygous or compound heterozygous ZMPSTE24 mutation.Based on this knowledge, the hypothesis was proposed that farnesyltransferase inhibitors would block the accumulation of progerin and reduce the amount of this abnormal protein, potentially improving the disease status in HGPS and progeroid laminopathies.Lonafarnib is intended for oral administration and should be swallowed whole as a capsule. Lonafarnib is a non-peptidic, selective farnesyltransferase inhibitor that prevents the farnesylation and subsequent accumulation of progerin and progerin-like proteins in the cell nucleus and cellular cytoskeleton. For all indications, the recommended initial dose is 115 mg/m2 twice daily. After 4 months of treatment with the initial dose of 115 mg/m2 twice daily, the dose should be increased to the maintenance dose of 150 mg/m2 twice daily.The most commonly reported side effects of Lonafarnib that occurred in clinical studieswere vomiting (86%), diarrhea (78%), increased aspartate aminotransferase (64%), increased alanine aminotransferase (50%), loss of appetite (41%), nausea (38%), abdominal pain (35%), fatigue (29%), weight loss (27%), constipation (18%) and upper respiratory tract infection (11%) (25-29, 30,31). Most side effects occurred within the first 4 weeks of starting treatment and generally decreased with continued treatment.The most serious side effectswere increased alanine aminotransferase (3.6%), increased aspartate aminotransferase (3.6%), cerebral ischemia (3.2%), fever (1.6%), and dehydration (1.6%) (25-29, 30,31).In vitro studies have shown that Lonafarnib is mainly metabolized by CYP3A and to a lesser extent by CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1.Therefore, the use ofLonafarnib with strong or moderate CYP3A inhibitors, strong or moderate CYP3A inducers, selected HMG-CoA reductase inhibitors (statins), and midazolam is contraindicated.Concomitant use ofLonafarnib with CYP2C9 inhibitors, weak CYP3A4 inhibitors, CYP2C19 substrates, or sensitive CYP3A4 substrates should be avoided. If concurrent use is unavoidable, dose reduction of Lonafarnib and/or monitoring of patients for side effects may be necessary.When Lonafarnib is used together with P-glycoprotein substrates with a narrow therapeutic range, patients should be monitored for side effects, and the dose of the P-glycoprotein substrate should be reduced accordingly.Furthermore, in vitro data have shown thatLonafarnib is a MATE1/MATE2-K inhibitor, so the drug should not be used simultaneously with metformin, the only known MATE1/MATE2-K substrate (36).Lonafarnib should not be used in patients with hypersensitivity to the active substance or farnesyltransferases, use of strong CYP3A inhibitors, use of drugs primarily metabolized by CYP3A4 such as midazolam, atorvastatin, lovastatin, and simvastatin. There are no or very limited experiences with the use of Lonafarnib in pregnant women. Animal studies have shown reproductive toxicity, so the use during pregnancy and in women of childbearing potential not using contraception is not recommended.Lonafarnib is the only approved drug for the treatment of progeria.

Acetyltransferase NAT10 inhibitor (Remodelin)

Remodelin hydrobromide is a compound that acts as a selective inhibitor of the acetyltransferase NAT10 (32,33,34). It has been shown to inhibit NAT10 activity, leading to a slowdown in DNA replication and a suppression of the growth of prostate cancer cells (32). Remodelin hydrobromide has demonstrated the ability to inhibit the growth of prostate cancer and hepatocellular carcinoma in xenograft models (33). Remodelin hydrobromide has been shown to inhibit Acetyltransferase NAT10 activity and cell proliferation in both androgen receptor (AR)-positive and (AR)-negative prostate cancer cells in a dose-dependent manner (33). It has been found to slow DNA replication in prostate cancer cells in xenograft model and decrease nuclear shape defects while increasing genomic stability in fibroblasts (33).Remodelin hydrobromide may have potential therapeutic applications in the treatment of prostate cancer and other related conditions like osteosarcoma (32,35). Furthermore, it has been found to enhance the healthspan in a mouse model of Hutchinson-Gilford progeria syndrome (32). In this mice model, an oral administrationwas started daily at 3 weeks of age. As a result, improved age-related weight loss and cardiac pathology was found (32). Moreover, significantly reducedadventitial fibrosis in the aorta, in preserved vascular smooth muscle cells, and maintained levels of smooth muscle actin in both the aorta and coronary arteries in HGPS mice were found (32).Chemical inhibition of NAT10 seem to reduce defects of laminopathic cells (34). Down-regulation and mutations of the nuclear-architecture proteins lamin A and C result in misshapen nuclei and altered chromatin organization, which are associated with cancer and laminopathies. In a study published in Science, Remodelinimproved nuclear architecture, chromatin organization, and cellular fitness in human

cells lacking lamin A/C and in cells derived from HGPS patients (34). Additionally, Remodelin reduced markers of DNA damage in these cells (34). Through a combination of chemical, cellular, and genetic techniques, acetyl-transferase protein NAT10 inhibitor Remodelinwas responsible for rescuing nuclear shape in laminopathic cells by reorganizing microtubules (34). These findings shed light on the role of NAT10 in nuclear architecture and propose new approaches for treating laminopathies and age-related conditions (34). Human NAT10 acetylates the N4 position of cytidine in RNA, primarily on rRNA and tRNA, to aid in ribosome formation and protein synthesis. NAT10 is being explored as a potential target for cancer treatment and age-related conditions like Hutchinson-Gilford Progeria Syndrome (HGPS)(74). The 120 kDa NAT10 protein utilizes its acetyl-CoA-dependent acetyltransferase, ATP-dependent helicase, and RNA binding domains to carry out RNA-specific N4-cytidine acetylation. While the enzymatic function of NAT10 is well understood, the molecular mechanisms underlying eukaryotic RNA acetylation are not fully defined. To gain insights into this process, we analyzed the cryo-EM structures of Chaetomium thermophilum NAT10 (Ct NAT10) bound to a bisubstrate cytidine-CoA probe with and without ADP. These structures reveal a symmetrical dimeric structure of NAT10 with key functional domains surrounding the acetyltransferase active sites containing the cytidine-CoA probe. Mutagenesis studies and in vitro analysis of mutants support the importance of specific active site residues (His548 and Tyr549 in Ct NAT10) and basic patches for RNA-specific acetylation. Functional assays in yeast and human cells further confirm the role of NAT10 in thermoadaptation and cellular senescence. A comparison of the NAT10 structure with other acetyltransferases suggests a unique open active site tailored for RNA recognition and cytidine-specific acetylation (74).

KAT6 a/b and KAT 7-Inhibitors

KAT6 a/b inhibition could play a major role in progeria (33,37,38). Inhibitors of histone acetyltransferases KAT6A/B seem to induce senescence (33,38). KAT7, also known as MYST2/HBO1, is a lysine acetyltransferase that belongs to the MYST KAT family. It plays a role in controlling cell survival, DNA replication, and transcription. KAT7 has been shown to interact with the origin of replication and is involved in various replication-associated processes by interacting with replication factors (33,37). Deletion of KAT7 in cell lines has been found to stall DNA replication. Inactivation of KAT7 leads to a global loss of H3K14ac and decreased expression of a broad range of genes, including patterning genes required for normal development. Aberrant expression of KAT7 has been associated with oncogenesis in various cancers, including gastric cancer, acute myeloid leukemias, bladder cancer, and ovarian cancer. KAT7 can form various MYST complexes subunits and has been localized in the promoter and intragenic region of target genes, playing an essential functional role at these sites. It acetylates histone H3K14, H3K23, H4K5, H4K8, and H4K12 (33,37). Suppression of KAT7 leads to H3K14ac reduction in mouse embryos and fetal liver erythroblasts (33). However, the mechanisms by which KAT7 regulates oncogenesis and radioresistance in breast cancer are not yet fully understood and require further investigation.Acetylation of histones by lysine acetyltransferases (KATs) is crucial for chromatin organization and function (37). The MYST family of KATs includes the oncogenes KAT6A (also known as MOZ) and KAT6B (also known as MORF and QKF) (37). KAT6A plays essential roles in normal hematopoietic stem cells and is involved in recurrent chromosomal translocations that lead to acute myeloid leukemia. Similarly, chromosomal translocations involving KAT6B have been found in various cancers. KAT6A suppresses cellular senescence by regulating suppressors of the CDKN2A locus, a function dependent on its KAT activity (37). Inhibiting KAT6A and KAT6B may have therapeutic benefits in cancer treatment. Biochemical and structural studies show that these compounds competitively inhibit acetyl coenzyme A and block MYST-catalyzed histone acetylation (37). Histone acetyltransferases KAT induce cell cycle arrest and cellular senescence without causing DNA damage (38). Senescence is INK4A/ARF-dependent and leads to gene expression changes characteristic of KAT6A loss (37). These inhibitors are expected to aid in the development of therapeutics targeting gene transcription regulated by histone acetylation (37,38).

Paclitaxel

Paclitaxel works by interfering with the mitosis (39,40). It therefore belongs to the family of cytoskeletal inhibitors (39,40). It binds to ß-tubulin and disrupts the breakdown of microtubules, which are part of the essential mitotic spindle during mitosis. In contrast to colchicine, vinblastine and nocodazole, which directly inhibit the formation of microtubules, paclitaxel inhibits their degradation. It therefore acts on all dividing cells and can cause corresponding side effects. However, as cancer cells divide rapidly compared to healthy cells, they are more severely affected. Improved pharmacokinetics are achieved by formulating paclitaxel as paclitaxel-albumin nanoparticles. Paclitaxel is poorly soluble in water and must be brought into solution with suitable solubilizers such as ethanol and macrogol glycerol ricinoleate to achieve the therapeutically required concentrations. Macrogol glycerol ricinoleate often leads to hypersensitivity reactions. Alternative, macrogolglycerol ricinoleate-free dosage forms are nanoparticulate formulations such as paclitaxel bound to human albumin or encapsulated in liposomes. In nab-paclitaxel, nanoparticle albumin bound paclitaxel, paclitaxel is bound to albumin nanoparticles with an average size of approximately 130 nanometers. The powder, which is formulated as a lyophilizate (trade name Abraxane), approved throughout the EU in January 2008, is mixed with isotonic alcohol immediately before use.Chemotherapy-induced cognitive impairment, also known as "chemobrain," is a common side effect in cancer survivors who have been treated with paclitaxel (PTX) (39). The exact mechanisms behind PTX-induced cognitive impairment are not well

understood, and there are currently no effective treatments or prevention methods. In this study, we hypothesized that PTX causes endothelial senescence, leading to impaired microvascular function and contributing to cognitive decline (39). Experiments were performedin transgenic p16-3MR mice, which allow for the detection and elimination of senescent cells (39). The mice were treated with PTX (5 mg/kg/day, 2 cycles; 5 days/cycle), and their spatial memory performance, neurovascular coupling (NVC) responses, microvascular density, blood-brain barrier (BBB) permeability, and presence of senescent endothelial cells were assessed 6 months after treatment (39). PTX treatment induced senescence in endothelial cells, which was associated with microvascular rarefaction, NVC dysfunction, BBB disruption, neuroinflammation, and impaired cognitive performance (39). To investigate the link between PTX-induced senescence and impaired microvascular function, senescent cells were eliminated from PTX-treated animals using genetic (ganciclovir) or pharmacological (ABT263/Navitoclax) methods at 3 months post-treatment (39). Both treatments effectively removed senescent endothelial cells, restored NVC responses and BBB integrity, increased capillarization, and improved cognitive performance in PTX-treated mice (39). These results suggest that senolytic treatments could be a promising approach to prevent chemotherapy-induced cognitive impairment.In another study in heart tissue from progerin-expressing LmnaG609G/G609G (G609G) miceincluding microscopy, intracellular calcium dynamics, patch-clamping, in vivo magnetic resonance imaging, and electrocardiography was revealed and analyzed (40). G609G mouse cardiomyocytes showed tubulin-cytoskeleton disorganization, t-tubular system disruption, sarcomere shortening, altered excitation-contraction coupling, and reductions in ventricular thickening and cardiac index (40). G609G mice exhibited severe bradycardia, and significant alterations of atrio-ventricular conduction and repolarization. Most importantly, 50% of G609G mice had altered heart rate variability, and sinoatrial block, both significant signs of premature cardiac aging (40). G609G cardiomyocytes had electrophysiological alterations, which resulted in an elevated action potential plateau and early afterdepolarization bursting, reflecting slower sodium current inactivation and long Ca+2 transient duration, which may also help explain the mild QT prolongation in some HGPS patients (40). Chronic treatment with low-dose paclitaxel ameliorated structural and functional alterations in G609G hearts (40).The studydemonstrated that tubulin-cytoskeleton disorganization in progerin-expressing cardiomyocytes causes structural, cardiac conduction, and excitation-contraction coupling defects, all of which can be partially corrected by chronic treatment with low dose paclitaxel (40).

Small Molecule ICMT-Inhibitors (Isoprenylcysteine Carboxyl Methyltransferase Inhibitor)

ICMT-Inhibitors are cell-permeable indoleacetamides, that act as a substrate-competitive and AdoMet-noncompetitive isoprenylcysteine carboxyl methyltransferase (ICMT) inhibitor, which has no activity against FTase, Gernaylgeranyltransferase type I, CaaX protease Rce1, AdoMet-dependent DNA methyltransferase, SssI DNA methyltransferase or PCMT1 protein methyltransferase (41,42). Cysmethynil (25 μ;M) induces G1 cell cycle arrest and autophagy-mediated, but not apoptotic, cell death in PC3 prostate cancer cells with concomitant blockade of PI 3-K/Akt and mTOR signaling, consistent with inhibition of ICMT-mediated activation of the GTPases Ras and Rheb (41,42). PC3 xenograft studies in mice show limited in vivo efficacy. Cell-permeable indoleacetamide compound that inhibits ICMT, isoprenylcysteine carboxyl methyltransferase activity in an acceptor substrate-isoprenylated, cysteine-competitive and donor substrate AdoMet non-competitive manner, showing no activity against FTase, Gernaylgeranyltransferase type I, CaaX protease Rce1, AdoMet-dependent DNA methyltransferase, SssI DNA methyltransferase or PCMT1 protein methyltransferase (41). It has been shown to inhibit the proliferation of non-cancerous MEF cells and prevent anchorage-independent growth of colon cancer DKOB8 in a dose- and ICMT-dependent manner.Cysmethynil induces G1 cell cycle arrest and autophagy-mediated, but not apoptotic, cell death in PC3 prostate cancer cells with concomitant blockade of PI 3-K/Akt and mTOR signaling, consistent with inhibition of ICMT-mediated activation of GTPases Ras and Rheb. Blocking progerin methylation by disabling the isoprenylcysteine carboxylmethyltransferase (ICMT) gene promotes the growth of HGPS cells and enhances the survival of Zmpste24-deficient mice (42). However, it is unclear whether Icmt inactivation can improve symptoms in an actual HGPS mouse model (42). Additionally, the tolerance of cells to pharmacological targeting of ICMT and the potential cellular effects of such targeting compared to genetic inactivation are unknown (41,42). The study demonstrated that Icmt knockout extends the lifespan of HGPS mice and restores the number of vascular smooth muscle cells in the aorta. Furthermore, a potent ICMT inhibitor named C75 was developed, which delays senescence and boosts the growth of late-passage HGPS cells and Zmpste24-deficient mouse fibroblasts (41). Importantly, C75 has no impact on the growth of normal human cells or Zmpste24-deficient mouse cells lacking Icmt, indicating its specificity (41). These findings suggest that ICMT inhibitors could hold promise for the treatment of children with HGPS (41,42).Several progeroid disorders, such as Hutchinson-Gilford progeria syndrome and restrictive dermopathy (ZMPSTE24 deficiency), occur due to the accumulation of a farnesylated and methylated form of prelamin A at the nuclear envelope. In a studywas demonstrated,that a hypomorphic allele of isoprenylcysteine carboxyl methyltransferase led to increased body weight, improved grip strength, and prevented bone fractures and death in Zmpste24-deficient mice (42). The decreased ICMT activity resulted in mislocalization of prelamin A within the nucleus, leading to activation of AKT-mammalian target of rapamycin (mTOR) signaling, which prevented premature senescence in Zmpste24-deficient fibroblasts (42). Inhibition of ICMT increased AKT-mTOR signaling and proliferation, delaying senescence in human HGPS fibroblasts without reducing misshapen nuclei levels in mouse and human cells. Therefore, targeting ICMT could be a potential

therapeutic approach for prelamin A-associated progeroid disorders like Hutchinson-Gilford syndrome in children (41,42).

Exportin CRM-1 Inhibitors

Selinexor, trade name *Nexpovio*, an exportin CRM-1-inhibitor, has been approved for the treatment of multiple myeloma since march 2021. In patients who have already received at least four therapies, it is only used with dexamethasone. Multiple myeloma is a rare cancer in which abnormally altered plasma cells in the bone marrow multiply uncontrollably. This destroys the bone and prevents normal blood formation. This can lead to bone pain and fractures as well as anemia. Multiple myeloma weakens the immune system and is life-threatening. The disease can progress for years without any noticeable symptoms. If symptoms occur, the disease is usually at an advanced stage. The nuclear protein export mechanism driven by CRM1 is abnormally increased in HGPS fibroblasts because Exportin-1 (XPO1), also known as chromosomal region maintenance 1 (CRM1), is overexpressed (3,43-45). CRM1 is the primary transport receptor responsible for exporting proteins across the nuclear pore complex (NPC) to the cytoplasm by recognizing the hydrophobic-rich nuclear export signals (NES) present in cargo molecules (3,44). CRM-1-inhibitors could play a role in HGPS (43-45). Interestingly, many important cellular processes that are altered in HGPS cells are regulated by CRM1-target proteins. For example, SIRT2 is involved in heterochromatin organization, B23 is important for nucleoli function, and dystrophin Dp71, ß-dystrobrevin, and ß-dystroglycan are implicated in nuclear envelope function. Additionally, p53 plays a critical role in cellular senescence (46). Therefore, the use of CRM1 inhibitors could help preserve the nuclear fraction of these and other NES-contained proteins, leading to an improvement in overall cellular physiology (43). Further research using omics technologies is needed to fully understand the metabolic and molecular pathways underlying the therapeutic effects of CRM1 inhibitors on aging (43-45).An abnormal increase in nuclear protein export is an early event in the development of cardiac hypertrophy, as HDAC5 is shuttled out of the cardiomyocyte nucleus in a CRM1-dependent manner in response to hypertrophy signaling (3,43-45). Treatment of cardiomyocytes with a CRM1 inhibitor has been shown to repress pathological gene expression and linked hypertrophy, suggesting that pharmacological attenuation of CRM1 activity could prevent or delay cardiac hypertrophy associated with both HGPS and normal aging (34).In conclusion, thepharmacological modulation of the CRM1-mediated nuclear export pathway offers a promising therapy against HGPS and other aging-related diseases (43-45). The development of synthetic selective inhibitors of CRM1 with superior pharmacological properties to LMB, such as selinexor/KPT-330, which have been well-tolerated in cancer clinical trials, would facilitate the preclinical evaluation of this therapy in HGPS animal studies.

Progerin-Lamin A binding inhibitors

Progerinin is a Progerin-Lamin A binding inhibitor, which shows progerin clearance in a significant manner (47). Progerinin has the potential to be used as a therapy to improve cardiovascular dysfunction and histological defects in individuals with HGPS (47). The findings indicate that Progerinin may be effective in treating the cardiovascular disease associated with HGPS (47,48). Additionally, Progerinin has positive effects on cardiac function and phenotypes, and in previous studies that it is less toxic and more effective than lonafarnib, the only drug currently approved for HGPS treatment (47,48). These results suggest that Progerinin treatments could be more effective in reducing the risk of premature death in individuals with HGPS. Overall, our findings support the potential of Progerinin as a therapeutic approach for the cardiovascular system in individuals with HGPS. A Phase I study of Progerinin in healthy adult volunteers, conducted by PRG Science & Technology Co., Ltd, was recently initiated (49). The study aimed to assess the safety, tolerability, pharmacokinetics, and pharmacodynamic profile of Progerinin in healthy volunteers. Progerinin is being developed for the treatment of Hutchinson-Gilford Progeria Syndrome (HGPS) and Werner Syndrome (WS). The study will consist of a single ascending dose (SAD) phase and a multiple scending dose (MAD) phase (49). The estimated enrollment is approximately 56 healthy volunteers, with 40 subjects for the SAD phase and 16 subjects for the MAD phase at a single site in the USA. The study will evaluate the safety and tolerability of Progerinin after single and multiple doses and assess its pharmacokinetics(49).

Ghrelin

Ghrelin is an appetite-stimulating peptide that is produced in the stomach lining and pancreas. In addition to stimulating appetite, the hormone has a number of other effects. Ghrelin is mainly produced in the parietal cells in the epithelium of the gastric fundus, but also by the ε-cells of the pancreas as well as in a precursor in the hypothalamus and the pituitary gland and converted into the active form by splitting off some amino acids. Ghrelin is a peptide hormone consisting of 28 amino acids, which is formed by post-translational modification from the precursor protein preproghrelin, which contains 117 amino acids.
At the same time, a molecule of obestatin is formed. The third amino acid serine of ghrelin is esterified with octanoic acid. This modification is essential for the effect of the hormone. Ghrelin is a hormone that regulates food intake and the secretion of growth hormone. Ghrelin levels in the blood rise during periods of hunger and fall after eating. Treatment with the hormone ghrelin increases autophagy, reduces progerin levels, and improves other cellular markers of premature aging in human HGPS fibroblasts (50). In a HGPS mouse model (LmnaG609G/G609G mice), ghrelin administration effectively reverses molecular and

histopathological progeroid features, prevents progressive weight loss in later stages, reverses the lipodystrophic phenotype, and extends the lifespan of these short-lived mice (50). These findings suggest that modulating ghrelin signaling could be a promising approach for treating HGPS and other age-related conditions, potentially improving patient outcomes and quality of life (50,51).The orexigenic hormone ghrelin plays various roles in health and disease (53,54). Previous research has shown that deleting the ghrelin receptor, growth hormone secretagogue receptor (GHS-R), can protect against metabolic dysfunction in aging adipose tissues (53). Overall, the authors of the study suggested that GHS-R negatively impacts the metabolism of aging muscle (53).

Micro-RNA-Inhibitors

One of the key mechanisms involved is chromatin remodeling, which drives changes in gene expression, including dysregulation of miRNAs. In an interesting study by Frankel et al. the expression profiles of miRNAs in HGPS and control fibroblasts were performed. An enrichment of overexpressed miRNAs from the 14q32.2-14q32.3 miRNA cluster was found (62). Using 3D FISH, the authors showed that the overexpression of these miRNAs was associated with chromatin remodeling at this specific locus in HGPS fibroblasts (62). The researchers focus on miR-376b-3p and miR-376a-3p, both of which are overexpressed in HGPS fibroblasts (62). The findings indicate that increasing their expression in control fibroblasts reduces cell proliferation and increases senescence, while inhibiting them in HGPS fibroblasts reverses proliferation defects, senescence, and reduces progerin accumulation (62). By targeting these key processes related to premature aging, these two miRNAs may have a significant impact on the development of HGPS. Overexpression of these micro-RNA could be treated by miR-376b-3p and miR-376a-3p inhibitorsin the future (63-66).In another interesting study, the two micro RNA`s miR-140-5p and miR-140-3p could be key actors in aging-related diseases and inhibition of these function could influence senescence (66).

Doycycline

In addition to its antimicrobial properties, doxycycline (DOX) has been shown to have a positive impact on longevity in nematodes, but its effects on mammals are not well understood. In mice study, a mouse model of Hutchinson-Gilford progeria syndrome (HGPS), Zmpste24 knockout (KO) mice was introduced, to investigate the anti-aging effects of DOX (73). Results demonstrate that DOX treatment extends the lifespan and improves various progeroid characteristics in Zmpste24 KO mice, such as decreased body and tissue weight, reduced exercise capacity, lower cortical bone density, and shortened colon length (73). DOX treatment also helps to normalize the abnormal nuclear envelope structure in multiple tissues and reduces cellular senescence and cell death in Zmpste24 KO and HGPS fibroblasts. Additionally, DOX decreases the levels of the proinflammatory cytokine IL6 in both serum and tissues. Furthermore, DOX treatment reverses the elevated acetylation of α-tubulin (K40) mediated by NAT10 in progeria, as observed in aorta tissues of Zmpste24 KO mice and fibroblasts. Overall, our findings suggest that DOX can slow down the aging process in progeria mice by inhibiting IL6 expression and NAT10-mediated acetylation of α-tubulin (73).

Rapamycin Complex 1 (mTORC1)

The mechanistic target of rapamycin complex 1 (mTORC1) plays a key role in controlling cell growth, metabolism, and autophagy (76). Various pathways influence mTORC1 activity in response to changes in nutrient levels. A recent study demonstrates that the movement of p300/EP300 between the nucleus and cytoplasm regulates mTORC1 activity in response to fluctuations in amino acid or glucose concentrations. When nutrients are depleted, p300 relocates from the cytoplasm to the nucleus, leading to reduced acetylation of the mTORC1 component raptor (76). This decrease in acetylation lowers mTORC1 activity and triggers autophagy. AMP-activated protein kinase phosphorylates p300 at serine 89, facilitating this process. Upon nutrient replenishment, protein phosphatase 2A dephosphorylates nuclear p300, allowing its export to the cytoplasm via CRM1 to reactivate mTORC1. This p300-mediated regulation of mTORC1 occurs in various cell types and tissues in mice in response to changes in nutrient availability. Notably, cells from individuals with Hutchinson-Gilford progeria syndrome exhibit altered p300 shuttling, leading to mTORC1 hyperactivation and impaired autophagy. These effects can be reversed by modulating p300 localization, highlighting the importance of p300 in nutrient-dependent mTORC1 regulation and its dysregulation in Hutchinson-Gilford progeria syndrome (76).

Conclusions

Different studies shed light on new research focus on different new targets in the treatment of Hutchinson-Gilford progeria like acetyltransferase NAT10 inhibitors, KAT-inhibitors, paclitaxel, small molecule ICMT-inhibitors, exportin CRM-1 inhibitors, progerin-lamin A binding inhibitors (Progerinin), Ghrelin, micro-RNA-inhibitors, doxycycline and the regulation of Rapamycin complex 1, which were extensively ruled out in detail above.To date, there are only few studies concentrating on this new targets. Further research is necessary to clearly define a curing potential in Hutchinson-Gilford syndrome. All these above mentioned new targets seem to have an important potential to ameliorate the progerin clearance, which is extensively found in Hutchinson-Gilford-syndrome patients.First in vivo base editing animal studies rescued Hutchinson-Gilford progeria syndrome in mice (67). CRISPR/Cas9-based treatments show great potential for addressing genetic diseases, with Hutchinson-Gilford progeria syndrome, linked to a LMNA gene mutation,

being a notable target (68-70). A recent study investigated the effectiveness of a CRISPR/Cas9 strategy in reversing various abnormalities in Hutchinson-Gilford progeria syndrome cells and mice through the introduction of frameshift mutations in the LMNA gene (68).

References

(1) Hutchinson J. Congenital Absence of Hair and Mammary Glands with Atrophic Condition of the Skin and its Appendages, in a Boy whose Mother had been almost wholly Bald from Alopecia Areata from the age of Six. Med Chir Trans. 1886;69:473-7. doi: 10.1177/095952878606900127. PMID: 20896687; PMCID: PMC2121576.

(2) Gilford H. Ateleiosis and progeria: continuous youth and premature old age. Brit Med J. 1904; 2:914–918.

(3) Cisneros B, García-Aguirre I, De Ita M, Arrieta-Cruz I, Rosas-Vargas H. Hutchinson-Gilford Progeria Syndrome: Cellular Mechanisms and Therapeutic Perspectives. Arch Med Res. 2023; Jul;54(5):102837. doi: 10.1016/j.arcmed.2023.06.002. Epub 2023 Jun 28. PMID: 37390702.

(4) Ahmed MS, Ikram S, Bibi N, Mir A. Hutchinson-Gilford Progeria Syndrome: A Premature Aging Disease. Mol Neurobiol. 2018; May;55(5):4417-4427. doi: 10.1007/s12035-017-0610-7. Epub 2017; Jun 28. PMID: 28660486.

(5) Gonzalo S, Kreienkamp R, Askjaer P. Hutchinson-Gilford Progeria Syndrome: A premature aging disease caused by LMNA gene mutations. Ageing Res Rev. 2017; Jan;33:18-29. doi: 10.1016/j.arr.2016.06.007. Epub 2016; Jun 29. PMID: 27374873; PMCID: PMC5195863.

(6) Casasola A, Scalzo D, Nandakumar V, Halow J, Recillas-Targa F, Groudine M, Rincón-Arano H. Prelamin A processing, accumulation and distribution in normal cells and laminopathy disorders. Nucleus. 2016; 7(1):84-102. doi: 10.1080/19491034.2016.1150397. PMID: 26900797; PMCID: PMC4916894.

(7) Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, Erdos MR, Robbins CM, Moses TY, Berglund P, Dutra A, Pak E, Durkin S, Csoka AB, Boehnke M, Glover TW, Collins FS. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. Nature. 2003, May 15;423(6937):293-8. doi: 10.1038/nature01629. Epub 2003; Apr 25. PMID: 12714972; PMCID: PMC10540076.

(8) Harrington JS, Ryter SW, Plataki M, Price DR, Choi AMK. Mitochondria in health, disease, and aging. Physiol Rev. 2023 Oct 1;103(4):2349-2422. doi: 10.1152/physrev.00058.2021. Epub 2023; Apr 6. PMID: 37021870; PMCID: PMC10393386.

(9) Lima T, Li TY, Mottis A, Auwerx J. Pleiotropic effects of mitochondria in aging. Nat Aging. 2022 Mar;2(3):199-213. doi: 10.1038/s43587-022-00191-2. Epub 2022; Mar 17. PMID: 37118378.

(10) Rivera-Torres J, Acín-Perez R, Cabezas-Sánchez P, Osorio FG, Gonzalez-Gómez C, Megias D, Cámara C, López-Otín C, Enríquez JA, Luque-García JL, Andrés V. Identification of mitochondrial dysfunction in Hutchinson-Gilford progeria syndrome through use of stable isotope labeling with amino acids in cell culture. J Proteomics. 2013; Oct 8;91:466-77. doi: 10.1016/j.jprot.2013.08.008. Epub 2013 Aug 20. PMID: 23969228.

(11) Mateos J, Landeira-Abia A, Fafián-Labora JA, Fernández-Pernas P, Lesende-Rodríguez I, Fernández-Puente P, Fernández-Moreno M, Delmiro A, Martín MA, Blanco FJ, Arufe MC. iTRAQ-based analysis of progerin expression reveals mitochondrial dysfunction, reactive oxygen species accumulation and altered proteostasis. Stem Cell Res Ther. 2015; Jun 12;6(1):119. doi: 10.1186/s13287-015-0110-5. PMID: 26066325; PMCID: PMC4487579.

(12) Monterrubio-Ledezma F, Navarro-García F, Massieu L, Mondragón-Flores R, Soto-Ponce LA, Magaña JJ, Cisneros B. Rescue of Mitochondrial Function in Hutchinson-Gilford Progeria Syndrome by the Pharmacological Modulation of Exportin CRM1. Cells. 2023; Jan 10;12(2):275. doi: 10.3390/cells12020275. PMID: 36672210; PMCID: PMC9856861.

(13) Xiong ZM, Choi JY, Wang K, Zhang H, Tariq Z, Wu D, Ko E, LaDana C, Sesaki H, Cao K. Methylene blue alleviates nuclear and mitochondrial abnormalities in progeria. Aging Cell. 2016 Apr;15(2):279-90. doi: 10.1111/acel.12434. Epub 2015; Dec 14. PMID: 26663466; PMCID: PMC4783354.

(14) Xu X, Wang D, Zheng C, Gao B, Fan J, Cheng P, Liu B, Yang L, Luo Z. Progerin accumulation in nucleus pulposus cells impairs mitochondrial function and induces intervertebral disc degeneration and therapeutic effects of sulforaphane. Theranostics. 2019; Apr 12;9(8):2252-2267. doi: 10.7150/thno.30658. PMID: 31149042; PMCID: PMC6531300.

(15) Aman Y, Schmauck-Medina T, Hansen M, Morimoto RI, Simon AK, Bjedov I, Palikaras K, Simonsen A, Johansen T, Tavernarakis N, Rubinsztein DC, Partridge L, Kroemer G, Labbadia J, Fang EF. Autophagy in healthy aging and disease. Nat Aging. 2021; Aug;1(8):634-650. doi: 10.1038/s43587-021-00098-4. Epub 2021 Aug 12. PMID: 34901876; PMCID: PMC8659158.

(16) Benson EK, Lee SW, Aaronson SA. Role of progerin-induced telomere dysfunction in HGPS premature cellular senescence. J Cell Sci. 2010; Aug 1;123(Pt 15):2605-12. doi: 10.1242/jcs.067306. Epub 2010 Jul 6. PMID: 20605919; PMCID: PMC2908049.

(17) Stroik S, Hendrickson EA. Telomere replication-When the going gets tough. DNA Repair (Amst). 2020 Oct;94:102875. doi: 10.1016/j.dnarep.2020.102875. Epub 2020; Jun 23. PMID: 32650286.

(18) Stewart M. Function of the Nuclear Transport Machinery in Maintaining the Distinctive Compositions of the Nucleus and Cytoplasm. Int J Mol Sci. 2022; Feb 25;23(5):2578. doi: 10.3390/ijms23052578. PMID: 35269721; PMCID: PMC8910404.

(19) Fragoso-Luna A, Askjaer P. The Nuclear Envelope in Ageing and Progeria. Subcell Biochem. 2023;102:53-75. doi: 10.1007/978-3-031-21410-3_3. PMID: 36600129.

(20) Snow CJ, Dar A, Dutta A, Kehlenbach RH, Paschal BM. Defective nuclear import of Tpr in Progeria reflects the Ran sensitivity of large cargo transport. J Cell Biol. 2013; May 13;201(4):541-57. doi: 10.1083/jcb.201212117. Epub 2013 May 6. PMID: 23649804; PMCID: PMC3653351.

(21) Kelley JB, Datta S, Snow CJ, Chatterjee M, Ni L, Spencer A, Yang CS, Cubeñas-Potts C, Matunis MJ, Paschal BM. The defective nuclear lamina in Hutchinson-gilford progeria syndrome disrupts the nucleocytoplasmic Ran gradient and inhibits nuclear localization of Ubc9. Mol Cell Biol. 2011; Aug;31(16):3378-95. doi: 10.1128/MCB.05087-11. Epub 2011 Jun 13. PMID: 21670151; PMCID: PMC3147792.

(22) Dworak N, Makosa D, Chatterjee M, Jividen K, Yang CS, Snow C, Simke WC, Johnson IG, Kelley JB, Paschal BM. A nuclear lamina-chromatin-Ran GTPase axis modulates nuclear import and DNA damage signaling. Aging Cell. 2019; Feb;18(1):e12851. doi: 10.1111/acel.12851. Epub 2018 Dec 19. PMID: 30565836; PMCID: PMC6351833.

(23) Larrieu D, Viré E, Robson S, Breusegem SY, Kouzarides T, Jackson SP. Inhibition of the acetyltransferase NAT10 normalizes progeric and aging cells by rebalancing the Transportin-1 nuclear import pathway. Sci Signal. 2018; Jul 3;11(537):eaar5401. doi: 10.1126/scisignal.aar5401. PMID: 29970603; PMCID: PMC6331045.

(24) Gonzalo S, Kreienkamp R. DNA repair defects and genome instability in Hutchinson-Gilford Progeria Syndrome. Curr Opin Cell Biol. 2015; Jun34:75-83. doi: 10.1016/j.ceb.2015.05.007. Epub 2015 Jun 12. PMID: 26079711; PMCID: PMC4522337.

(25) Harhouri K, Frankel D, Bartoli C, Roll P, De Sandre-Giovannoli A, Lévy N. An overview of treatment strategies for Hutchinson-Gilford Progeria syndrome. Nucleus. 2018; Jan 1;9(1):246-257. doi: 10.1080/19491034.2018.1460045. PMID: 29619863; PMCID: PMC5973194.

(26) Guilbert SM, Cardoso D, Lévy N, Muchir A, Nissan X. Hutchinson-Gilford progeria syndrome: Rejuvenating old drugs to fight accelerated ageing. Methods. 2021; Jun;190:3-12. doi: 10.1016/j.ymeth.2020.04.005. Epub 2020 Apr 9. PMID: 32278808.

(27) Strandgren C, Revêchon G, Sola-Carvajal A, Eriksson M. Emerging candidate treatment strategies for Hutchinson-Gilford progeria syndrome. Biochem Soc Trans. 2017; Dec 15;45(6):1279-1293. doi: 10.1042/BST20170141. Epub 2017 Nov 10. PMID: 29127216

(28) Dhillon S. Lonafarnib: First Approval. Drugs. 2021 Feb;81(2):283-289. doi: 10.1007/s40265-020-01464-z. Erratum in: Drugs. 2021; Apr;81(5):619. PMID: 33590450; PMCID: PMC7985116.

(29) Hisama FM, Oshima J. Precision Medicine and Progress in the Treatment of Hutchinson-Gilford Progeria Syndrome. JAMA. 2018; Apr 24;319(16):1663-1664. doi: 10.1001/jama.2018.2199. PMID: 29710145; PMCID: PMC6368062.

(30) Suzuki M, Jeng LJB, Chefo S, Wang Y, Price D, Li X, Wang J, Li RJ, Ma L, Yang Y, Zhang X, Zheng N, Zhang K, Joseph DB, Shroff H, Doan J, Pacanowski M, Smpokou P, Donohue K, Joffe HV. FDA approval summary for lonafarnib (Zokinvy) for the treatment of Hutchinson-Gilford progeria syndrome and processing-deficient progeroid laminopathies. Genet Med. 2023; Feb;25(2):100335. doi: 10.1016/j.gim.2022.11.003. Epub 2022 Dec 12. PMID: 36507973.

(31) Odinammadu KO, Shilagardi K, Tuminelli K, Judge DP, Gordon LB, Michaelis S. The farnesyl transferase inhibitor (FTI) lonafarnib improves nuclear morphology in ZMPSTE24-deficient fibroblasts from patients with the progeroid disorder MAD-B. Nucleus. 2023; Dec;14(1):2288476. doi: 10.1080/19491034.2023.2288476. Epub 2023 Dec 5. PMID: 38050983; PMCID: PMC10730222.

(32) Balmus G, Larrieu D, Barros AC, Collins C, Abrudan M, Demir M, Geisler NJ, Lelliott CJ, White JK, Karp NA, Atkinson J, Kirton A, Jacobsen M, Clift D, Rodriguez R; Sanger Mouse Genetics Project; Adams DJ, Jackson SP. Targeting of NAT10 enhances healthspan in a mouse model of human accelerated aging syndrome. Nat Commun. 2018; Apr 27;9(1):1700. doi: 10.1038/s41467-018-03770-3. PMID: 29703891; PMCID: PMC5923383.

(33) Ma N, Liu H, Wu Y, Yao M, Zhang B. Inhibition of *N*-Acetyltransferase 10 Suppresses the Progression of Prostate Cancer through Regulation of DNA Replication. Int J Mol Sci. 2022; Jun 12;23(12):6573. doi: 10.3390/ijms23126573. PMID: 35743017; PMCID: PMC9223896.

(34) Larrieu D, Britton S, Demir M, Rodriguez R, Jackson SP. Chemical inhibition of NAT10 corrects defects of laminopathic cells. Science. 2014; May 2;344(6183):527-32. doi: 10.1126/science.1252651. PMID: 24786082; PMCID: PMC4246063.

(35) Gao J, Xu P, Wang F, Zhang W, Min M, Urba R, Fan L. Revealing the pharmacological effects of Remodelin against osteosarcoma based on network pharmacology, acRIP-seq and experimental validation. Sci Rep. 2024; Feb 13;14(1):3577. doi: 10.1038/s41598-024-54197-4. PMID: 38347067; PMCID: PMC10861577.

(36) Gessner A, König J, Fromm MF. Clinical Aspects of Transporter-Mediated Drug-Drug Interactions. Clin Pharmacol Ther. 2019; Jun;105(6):1386-1394. doi: 10.1002/cpt.1360. Epub 2019 Mar 18. PMID: 30648735.

(37) Baell JB, Leaver DJ, Hermans SJ, Kelly GL, Brennan MS, Downer NL, Nguyen N, Wichmann J, McRae HM, Yang Y, Cleary B, Lagiakos HR, Mieruszynski S, Pacini G, Vanyai HK, Bergamasco MI, May RE, Davey BK, Morgan KJ, Sealey AJ, Wang B, Zamudio N, Wilcox S, Garnham AL, Sheikh BN, Aubrey BJ, Doggett K, Chung MC, de Silva M, Bentley J, Pilling P, Hattarki M, Dolezal O, Dennis ML, Falk H, Ren B, Charman SA, White KL, Rautela J, Newbold A, Hawkins ED, Johnstone RW, Huntington ND, Peat TS, Heath JK, Strasser A, Parker MW, Smyth GK, Street IP, Monahan BJ, Voss AK, Thomas T. Inhibitors of histone acetyltransferases KAT6A/B induce senescence and arrest tumour growth. Nature. 2018; Aug;560(7717):253-257. doi: 10.1038/s41586-018-0387-5. Epub 2018 Aug 1. PMID: 30069049.

(38) Wang W, Zheng Y, Sun S, Li W, Song M, Ji Q, Wu Z, Liu Z, Fan Y, Liu F, Li J, Esteban CR, Wang S, Zhou Q, Belmonte JCI, Zhang W, Qu J, Tang F, Liu GH. A genome-wide CRISPR-based screen identifies *KAT7* as a driver of cellular senescence. Sci Transl Med. 2021; Jan 6;13(575):eabd2655. doi: 10.1126/scitranslmed.abd2655. PMID: 33408182.

(39) Ahire C, Nyul-Toth A, DelFavero J, Gulej R, Faakye JA, Tarantini S, Kiss T, Kuan-Celarier A, Balasubramanian P, Ungvari A, Tarantini A, Nagaraja R, Yan F, Tang Q, Mukli P, Csipo T, Yabluchanskiy A, Campisi J, Ungvari Z, Csiszar A. Accelerated cerebromicrovascular senescence contributes to cognitive decline in a mouse model of paclitaxel (Taxol)-induced chemobrain. Aging Cell. 2023 Jul;22(7):e13832. doi: 10.1111/acel.13832. Epub 2023; May 26. PMID: 37243381; PMCID: PMC10352561.

(40) Macías Á, Díaz-Larrosa JJ, Blanco Y, Fanjul V, González-Gómez C, Gonzalo P, Andrés-Manzano MJ, da Rocha AM, Ponce-Balbuena D, Allan A, Filgueiras-Rama D, Jalife J, Andrés V. Paclitaxel mitigates structural alterations and cardiac conduction system defects in a mouse model of Hutchinson-Gilford progeria syndrome. Cardiovasc Res. 2022; Jan 29;118(2):503-516. doi: 10.1093/cvr/cvab055. PMID: 33624748; PMCID: PMC8803078.

(41) Chen X, Yao H, Kashif M, Revêchon G, Eriksson M, Hu J, Wang T, Liu Y, Tüksammel E, Strömblad S, Ahearn IM, Philips MR, Wiel C, Ibrahim MX, Bergo MO. A small-molecule ICMT inhibitor delays senescence of Hutchinson-Gilford progeria syndrome cells. Elife. 2021; Feb 2;10:e63284. doi: 10.7554/eLife.63284. PMID: 33526168; PMCID: PMC7853716.

(42) Ibrahim MX, Sayin VI, Akula MK, Liu M, Fong LG, Young SG, Bergo MO. Targeting isoprenylcysteine methylation ameliorates disease in a mouse model of progeria. Science. 2013 Jun 14;340(6138):1330-3. doi: 10.1126/science.1238880. Epub 2013; May 16. PMID: 23686339; PMCID: PMC4295631.

(43) Cisneros B, García-Aguirre I. Nuclear protein export pathway in aging therapeutics. Aging (Albany NY). 2020 Mar 19;12(6):4682-4684. doi: 10.18632/aging.102948. Epub 2020; Mar 19. PMID: 32200356; PMCID: PMC7138584.

(44) García-Aguirre I, Alamillo-Iniesta A, Rodríguez-Pérez R, Vélez-Aguilera G, Amaro-Encarnación E, Jiménez-Gutiérrez E, Vásquez-Limeta A, Samuel Laredo-Cisneros M, Morales-Lázaro SL, Tiburcio-Félix R, Ortega A, Magaña JJ, Winder SJ, Cisneros B. Enhanced nuclear protein export in premature aging and rescue of the progeria phenotype by modulation of CRM1 activity. Aging Cell. 2019; Oct;18(5):e13002. doi: 10.1111/acel.13002. Epub 2019 Jul 15. PMID: 31305018; PMCID: PMC6718587.

(45) Batista NJ, Desai SG, Perez AM, Finkelstein A, Radigan R, Singh M, Landman A, Drittel B, Abramov D, Ahsan M, Cornwell S, Zhang D. The Molecular and Cellular Basis of Hutchinson-Gilford Progeria Syndrome and Potential Treatments. Genes (Basel). 2023; Feb 27;14(3):602. doi: 10.3390/genes14030602. PMID: 36980874; PMCID: PMC10048386.

(46) Subburayan K, Thayyullathil F, Pallichankandy S, Rahman A, Galadari S. Par-4-dependent p53 up-regulation plays a critical role in thymoquinone-induced cellular senescence in human malignant glioma cells. Cancer Lett. 2018; Jul 10;426:80-97. doi: 10.1016/j.canlet.2018.04.009. Epub 2018 Apr 12. PMID: 29656006.

(47) Kang SM, Yoon MH, Ahn J, Kim JE, Kim SY, Kang SY, Joo J, Park S, Cho JH, Woo TG, Oh AY, Chung KJ, An SY, Hwang TS, Lee SY, Kim JS, Ha NC, Song GY, Park BJ. Progerinin, an optimized progerin-lamin A binding inhibitor, ameliorates premature senescence phenotypes of Hutchinson-Gilford progeria syndrome. Commun Biol. 2021; Jan 4;4(1):5. doi: 10.1038/s42003-020-01540-w. Erratum in: Commun Biol. 2021 Mar 2;4(1):297. PMID: 33398110; PMCID: PMC7782499.

(48) Kang SM, Seo S, Song EJ, Kweon O, Jo AH, Park S, Woo TG, Kim BH, Oh GT, Park BJ. Progerinin, an Inhibitor of Progerin, Alleviates Cardiac Abnormalities in a Model Mouse of Hutchinson-Gilford Progeria Syndrome. Cells. 2023; Apr 24;12(9):1232. doi: 10.3390/cells12091232. PMID: 37174632; PMCID: PMC10177486

(49) Interventional Phase I Study of Progerinin in Healthy Volunteers, ClinicalTrials.gov ID NCT04512963. PRG Science & Technology Co., Ltd.

(50) Ferreira-Marques M, Carvalho A, Franco AC, Leal A, Botelho M, Carmo-Silva S, Águas R, Cortes L, Lucas V, Real AC, López-Otín C, Nissan X, de Almeida LP, Cavadas C, Aveleira CA. Ghrelin delays premature aging in Hutchinson-Gilford progeria syndrome. Aging Cell. 2023; Dec;22(12):e13983. doi: 10.1111/acel.13983. Epub 2023 Oct 19. PMID: 37858983; PMCID: PMC10726901.

(51) Amitani M, Amitani H, Cheng KC, Kairupan TS, Sameshima N, Shimoshikiryo I, Mizuma K, Rokot NT, Nerome Y, Owaki T, Asakawa A, Inui A. The Role of Ghrelin and Ghrelin Signaling in Aging. Int J Mol Sci. 2017; Jul 12;18(7):1511. doi: 10.3390/ijms18071511. PMID: 28704966; PMCID: PMC5536001.

(52) Cardoso AL, Fernandes A, Aguilar-Pimentel JA, de Angelis MH, Guedes JR, Brito MA, Ortolano S, Pani G, Athanasopoulou S, Gonos ES, Schosserer M, Grillari J, Peterson P, Tuna BG, Dogan S, Meyer A, van Os R, Trendelenburg AU. Towards frailty biomarkers: Candidates from genes and pathways regulated in aging and age-related diseases. Ageing Res Rev. 2018; Nov;47:214-277. doi: 10.1016/j.arr.2018.07.004. Epub 2018 Jul 30. PMID: 30071357.

(53) O'Reilly C, Lin L, Wang H, Fluckey J, Sun Y. Ablation of Ghrelin Receptor Mitigates the Metabolic Decline of Aging Skeletal Muscle. Genes (Basel). 2022; Jul 30;13(8):1368. doi: 10.3390/genes13081368. PMID: 36011279; PMCID: PMC9407208.

(54) Wu CS, Wei Q, Wang H, Kim DM, Balderas M, Wu G, Lawler J, Safe S, Guo S, Devaraj S, Chen Z, Sun Y. Protective Effects of Ghrelin on Fasting-Induced Muscle Atrophy in Aging Mice. J Gerontol A Biol Sci Med Sci. 2020; Mar 9;75(4):621-630. doi: 10.1093/gerona/gly256. PMID: 30407483; PMCID: PMC7328200.

(55) O'Reilly C, Lin L, Wang H, Fluckey J, Sun Y. Ablation of Ghrelin Receptor Mitigates the Metabolic Decline of Aging Skeletal Muscle. Genes (Basel). 2022; Jul 30;13(8):1368. doi: 10.3390/genes13081368. PMID: 36011279; PMCID: PMC9407208.

(56) Tian J, Du E, Jia K, Wang T, Guo L, Zigman JM, Du H. Elevated Ghrelin Promotes Hippocampal Ghrelin Receptor Defects in Humanized Amyloid-β Knockin Mice During Aging. J Alzheimers Dis. 2023;96(4):1579-1592. doi: 10.3233/JAD-231002. PMID: 38007666; PMCID: PMC10841720.

(57) Morley JE. Pathophysiology of the anorexia of aging. Curr Opin Clin Nutr Metab Care. 2013; Jan;16(1):27-32. doi: 10.1097/MCO.0b013e328359efd7. PMID: 23041615.

(58) Ueno H, Shiiya T, Nakazato M. Translational research of ghrelin. Ann N Y Acad Sci. 2010; Jul;1200:120-7. doi: 10.1111/j.1749-6632.2010.05509.x. PMID: 20633140.

(59) Sun Y, Garcia JM, Smith RG. Ghrelin and growth hormone secretagogue receptor expression in mice during aging. Endocrinology. 2007; Mar;148(3):1323-9. doi: 10.1210/en.2006-0782. Epub 2006 Dec 7. PMID: 17158206.

(60) Stoyanova II. Ghrelin: a link between ageing, metabolism and neurodegenerative disorders. Neurobiol Dis. 2014; Dec;72 Pt A:72-83. doi: 10.1016/j.nbd.2014.08.026. Epub 2014 Aug 27. PMID: 25173805.

(61) Ma X, Lin L, Qin G, Lu X, Fiorotto M, Dixit VD, Sun Y. Ablations of ghrelin and ghrelin receptor exhibit differential metabolic phenotypes and thermogenic capacity during aging. PLoS One. 2011; Jan 26, 6(1)16391. doi: 10.1371/journal.pone.0016391. PMID: 21298106; PMCID: PMC3027652.

(62) Frankel D, Delecourt V, Novoa-Del-Toro EM, Robin JD, Airault C, Bartoli C, Carabalona A, Perrin S, Mazaleyrat K, De Sandre-Giovannoli A, Magdinier F, Baudot A, Lévy N, Kaspi E, Roll P. miR-376a-3p and miR-376b-3p overexpression in Hutchinson-Gilford progeria fibroblasts inhibits cell proliferation and induces premature senescence. iScience. 2022; Jan 10;25(2):103757. doi: 10.1016/j.isci.2022.103757. PMID: 35118365; PMCID: PMC8800101.

(63) van der Kwast RVCT, Parma L, van der Bent ML, van Ingen E, Baganha F, Peters HAB, Goossens EAC, Simons KH, Palmen M, de Vries MR, Quax PHA, Nossent AY. Adenosine-to-Inosine Editing of Vasoactive MicroRNAs Alters Their Targetome and Function in Ischemia. Mol Ther Nucleic Acids. 2020 Sep 4;21:932-953. doi: 10.1016/j.omtn.2020.07.020. Epub 2020; Jul 21. PMID: 32814251; PMCID: PMC7452086.

(64) Tekin SS, Erdal ME, Asoğlu M, Ay Öİ, Ay ME, Yılmaz ŞG. Biomarker potential of hsa-miR-145-5p in peripheral whole blood of manic bipolar I patients. Braz J Psychiatry. 2022; Jun 24;40(44):378-387. doi: 10.47626/1516-4446-2021-2260. PMID: 35749663; PMCID: PMC9375662.

(65) Singh A, Willems E, Singh A, Ong IM, Verma AK. Ultraviolet radiation-induced differential microRNA expression in the skin of hairless SKH1 mice, a widely used mouse model for dermatology research. Oncotarget. 2016; Dec 20;7(51):84924-84937. doi: 10.18632/oncotarget.12913. PMID: 27793049; PMCID: PMC5356709.

(66) Toury L, Frankel D, Airault C, Magdinier F, Roll P, Kaspi E. miR-140-5p and miR-140-3p: Key Actors in Aging-Related Diseases? Int J Mol Sci. 2022; Sep 28;23(19):11439. doi: 10.3390/ijms231911439. PMID: 36232738; PMCID: PMC9570089.

(67) Koblan LW, Erdos MR, Wilson C, Cabral WA, Levy JM, Xiong ZM, Tavarez UL, Davison LM, Gete YG, Mao X, Newby GA, Doherty SP, Narisu N, Sheng Q, Krilow C, Lin CY, Gordon LB, Cao K, Collins FS, Brown JD, Liu DR. In vivo base editing rescues Hutchinson-Gilford progeria syndrome in mice. Nature. 2021 Jan;589(7843):608-614. doi: 10.1038/s41586-020-03086-7. Epub 2021; Jan 6. PMID: 33408413; PMCID: PMC7872200.

(68) Santiago-Fernández O, Osorio FG, Quesada V, Rodríguez F, Basso S, Maeso D, Rolas L, Barkaway A, Nourshargh S, Folgueras AR, Freije JMP, López-Otín C. Development of a CRISPR/Cas9-based therapy for Hutchinson-Gilford progeria syndrome. Nat Med. 2019; Mar;25(3):423-426. doi: 10.1038/s41591-018-0338-6. Epub 2019 Feb 18. PMID: 30778239; PMCID: PMC6546610.

(69) Lin P, Jiang J, Wu M. CRISPR base editor treats premature-aging syndrome. Signal Transduct Target Ther. 2021; Apr 16;6(1):158. doi: 10.1038/s41392-021-00576-6. PMID: 33863871; PMCID: PMC8050807.

(70) Pickar-Oliver A, Gersbach CA. The next generation of CRISPR-Cas technologies and applications. Nat Rev Mol Cell Biol. 2019; Aug;20(8):490-507. doi: 10.1038/s41580-019-0131-5. PMID: 31147612; PMCID: PMC7079207.

(71) De Sandre-Giovannoli A, Bernard R, Cau P, Navarro C, Amiel J, Boccaccio I, Lyonnet S, Stewart CL, Munnich A, Le Merrer M, Lévy N. Lamin a truncation in Hutchinson-Gilford progeria. Science. 2003; Jun 27;300(5628):2055. doi: 10.1126/science.1084125. Epub 2003 Apr 17. PMID: 12702809.

(72) Attar AG, Paturej J, Banigan EJ, Erbaş A. Chromatin phase separation and nuclear shape fluctuations are correlated in a polymer model of the nucleus. Nucleus. 2024 Dec;15(1):2351957. doi: 10.1080/19491034.2024.2351957. Epub 2024 May 16. PMID: 38753956.

(73) Wang M, Zhang J, Qiu J, Ma X, Xu C, Wu Q, Xing S, Chen X, Liu B. Doxycycline decelerates aging in progeria mice. Aging Cell. 2024 Apr 30:e14188. doi: 10.1111/acel.14188. Epub ahead of print. PMID: 38686927.

(74) Zhou M, Gamage ST, Tran KA, Bartee D, Wei X, Yin B, Berger S, Meier JL, Marmorstein R. Molecular Basis for RNA Cytidine Acetylation by NAT10. bioRxiv [Preprint]. 2024 Mar 27:2024.03.27.587050. doi: 10.1101/2024.03.27.587050. PMID: 38585770; PMCID: PMC10996708.

(75) Sun Y, Xu L, Li Y, Jia S, Wang G, Cen X, Xu Y, Cao Z, Wang J, Shen N, Hu L, Zhang J, Mao J, Xia H, Liu Z, Fu X. Mitophagy defect mediates the aging-associated hallmarks in Hutchinson-Gilford progeria syndrome. Aging Cell. 2024 Mar 14:e14143. doi: 10.1111/acel.14143. Epub ahead of print. PMID: 38482753.

(76) Son SM, Park SJ, Breusegem SY, Larrieu D, Rubinsztein DC. p300 nucleocytoplasmic shuttling underlies mTORC1 hyperactivation in Hutchinson-Gilford progeria syndrome. Nat Cell Biol. 2024 Feb;26(2):235-249. doi: 10.1038/s41556-023-01338-y. Epub 2024 Jan 24. PMID: 38267537; PMCID: PMC10866696.