

International Journal of Pharmaceutical Sciences and Drug Research

2014; 6(4): 253-262



Review Article

ISSN: 0975-248X
CODEN (USA): IJPSPP

Hutchinson-Gilford Progeria Syndrome: A Prematurely Aging Disorder

Ahsas Goyal*, Neetu Agrawal, Bhupesh C. Semwal, Yogesh Murti

Institute of Pharmaceutical Research, GLA University, Mathura-281406, Uttar Pradesh, India

ABSTRACT

Hutchinson-Gilford Progeria Syndrome (HGPS) is an extremely rare genetic disorder characterized by premature aging, involving aberrant splicing of the *LMNA* gene, resulting in the production of a disease-causing mutant lamin A protein called progerin. Clinical manifestations are evident by the first or second year of life and include the physical characteristics usually associated with the elderly. Because neither parent carries or expresses the mutation, each case is believed to represent a sporadic, new mutation that happens most notably in a single sperm or egg immediately prior to conception. Clinical trials investigating farnesyltransferase inhibitors (FTIs), statins, and bisphosphonates as HGPS treatments are currently underway. FTIs prevent farnesylation and localization of progerin to the cell membrane but do not repair the function of the abnormal progerin protein within the cytoplasm that may result in abnormalities in cell function and DNA repair that, therefore, would not be treated with these drugs. Thus some other novel treatment strategies are required for the more effective treatment. This review summarizes the clinical characteristics of this disease, the underlying mutation in the lamin A (*LMNA*) gene that results in this phenotype and the recent advances in treatment strategies.

Keywords: Progeria, Lamin A, Hutchinson-Gilford progeria syndrome, farnesyl transferase inhibitor.

INTRODUCTION

The word Progeria comes from the Greek word "progeros" meaning prematurely old ("pro" means before and "geras" means old age). Progeria is also known as Hutchinson-Gilford Progeria Syndrome (HGPS) as it was first described by Dr. Jonathan Hutchinson in 1886^[1] and by Dr. Hastings Gilford in 1897.^[2] HGPS is a very rare, fatal genetic disorder occurring in childhood, characterised by a dramatic premature aging and accelerated cardiovascular disease.^[3] The other signs include growth failure, loss of body fat and hair, skin changes, stiffness of joints,

atherosclerosis,

cardiovascular disease, and stroke. Children with progeria die of atherosclerosis (heart disease) or stroke at an average age of 13 years (with a range of about 7-21 years).

There are currently fewer than 150 documented cases of HGPS worldwide. The children have a remarkably similar appearance, even though progeria affects children of all different ethnic backgrounds. The estimated incidence of progeria is 1 in 4-8 millions.^[4-5] It is a genetic condition that occurs as a new mutation and is not usually inherited, although there is a uniquely heritable form.^[6] In nearly all cases HGPS is caused due to denovo point mutation in codon 608 of exon 11 of *LMNA* gene.^[7-8] Even though no single mechanism has clearly emerged to explain the complex that farnesylated progerin is the molecular culprit.

*Corresponding author: Mr. Ahsas Goyal,
Institute of Pharmaceutical Research, GLA University,
Mathura-281406, Uttar Pradesh, India; Tel.: +91-
9012204640; E-mail: ahsasgoyal1990@gmail.com
Received: 03 September, 2014; Accepted: 08 September, 2014

Although children with progeria are born looking healthy, they begin to display many characteristics of accelerated aging by 18-24 months of age, or even earlier. Both boys and girls have an equal risk of having progeria. Remarkably, the intellect of children with progeria is unaffected, [9-10] and despite the physical changes in their young bodies, these extraordinary children are intelligent, courageous, and full of life. On average, death occurs at the age of 13, with at least 90% of subjects dying from progressive atherosclerosis of the coronary and cerebral arteries, with tissues such as bone and skin also prominently affected. Scientists are particularly interested in progeria because it may help in understanding the heart diseases and normal process of aging. Majority of affected patients show an autosomal dominant inheritance, although some cases of autosomal recessive inheritance are also reported. [10-15]

CLINICAL FINDINGS

The diagnosis of progeria is based on recognition of the following clinical features (summarized in Table 1) and is confirmed with molecular genetic testing. [16]

Effect on Growth

Growth in patients with Hutchinson-Gilford progeria syndrome is abnormal. Growth rate is decreased below the third percentile for normal height by 15 months of age: between 2 and 10 years, healthy children grow 5.84 cm per year, while HGPS children grow 3.58 cm per year. [6] These patients are usually short and thin with an average height of 100 cm and average weight of 12-15 kg or even less. [17] In general, HGPS children are characterized by short stature, below average weight. Weight is even more affected, with the weight curve running almost horizontally from 2 years of age. [18] Within the first year, growth is disturbed, with weight more affected than height. A ten-year-old HGPS patient will be of same height as an average three-year-old child. [17]

Effect on Dermatological Features

The first noticeable signs of HGPS are circumoral cyanosis (a blue tint to the skin surrounding the lips) and a visible vein across the nasal bridge. [6, 18] Typical dermatological features include dry, wrinkled skin, caused by the hardening of connective tissue and the loss of subcutaneous adipose tissue, as well as the uneven thickening of the skin due to the presence of scar tissue-like lesions. [17, 19] The skin is initially thick and swollen, with pitting oedema. Pitting oedema (slight swelling due to fluid build-up in the tissues) is seen in the lower abdomen, upper gluteal area, genitalia, and anterior thighs. [6, 18] Pitting oedema can arise anywhere from one and a half months to two years, taking on a thick, tight, stiff quality with time. [18] With time, it becomes more firm and sclerodermatous. The scleroderma disappears after 6 months to 2 years, after which the skin becomes thin, dry, and atrophic, with reduced turgor, and sometimes with fine scaling or hyperkeratosis.

Table 1: Various Clinical Findings in Hutchinson-Gilford Progeria Syndrome

	Clinical Findings
Growth	Short stature, below average weight
Dermatological	Circumoral cyanosis, visible vein across the nasal bridge, dry and wrinkled skin, pitting edema, hyperkeratosis, thinning of skin, loss of hair including eyebrows and eyelashes
Facial	Small jaw, proportionally large cranium, protruding eyes, narrow nose, prominent veins on the scalp, dental crowding, prominent outer ears, mild myopia
Speech & Hearing	High-pitched voice, mild conductive hearing loss
Musculoskeletal	Osteolysis, deterioration in joint mobility, joint and knee stiffness, osteopenia of the long bones, vertebral bodies are ovoid with a 'fish-mouth' appearance
Cardiovascular	Atherosclerosis, elevated blood pressure, shortness of breath, transient ischemic attacks, hypertrophy, loss of smooth muscles
Genital	Development of secondary sexual characteristics is rare

The skin over the phalanges usually becomes red and swollen, while the nails become dystrophic. Loss of subcutaneous fat leading to lipodystrophy can start at 6 months, becoming visible at 3-4 years of age. This fat loss occurs first in the limbs, followed by the thorax, neurocranium and face, with the buccal and pubic fat disappearing latest. Less intra-abdominal fat causes the characteristically prominent abdomen seen in nearly all children with HGPS. The disappearance of subcutaneous and intra-orbital fat and 'thinning' of the skin, cause the underlying blood vessels to be more clearly visible and the eyes to appear more prominent. [18]

Rarely, the hair is still present at the age of 12-15 year. [20] The eyebrows and eyelashes also disappear, although some of the lateral eyelashes may remain. [2] The hair usually becomes light in color, with rare exceptions. [20-21] Body hair (chest, axilla, pubis, limbs) is sparse or completely absent. Loss of hair, including eyebrows and eyelashes, makes patients almost bald by 2-3 years of age, and wide veins became clearly visible on the scalp. [6]

Effect on Facial Features

Phenotypes are most notable in the facial area, including a small jaw (micrognathia), proportionally large cranium, protruding eyes, narrow nose, and prominent veins on the scalp. [13] Other facial features are: narrow nasal bridge and ridge; thin skin that wrinkles easily around the mouth; irregular teeth with increased decay, dental crowding due to the limited size of both the maxilla and mandible, [22] other oral abnormalities such as hypodontia, ankyloglossia, ogival palate, double rows of teeth, delayed tooth eruption, vertical chewing where rotatory chewing should normally develop, [6] and difficult dental care due to a small oral aperture. [23] The other facial features of HGPS patients are small chin, prominent outer ears that lack lobules, flattened and subsequently collapsed point of the nose with a nasal ridge that becomes

convex and a viscerocranium that becomes relatively small compared with the neurocranium.

Effect on Eyes

With one exception, [24] cataracts have not been found in patients with HGPS. But strabismus and mild myopia is common. Unusual eye findings are irregular nystagmoid movements, [5] ptosis and Marcus-Gunn phenomenon, [25] retinal arteriolar narrowing and tortuosity, [26] and photophobia. [27]

Effect on Speech, language and Hearing

Auditory comprehension and expressive language skills were reported to be average in HGPS patients, [6] in contrast to a mild conductive hearing loss reported in a majority of European patients. [18] Almost all patients have a high-pitched voice. In spite of the unusual voice, children generally speak well, are usually alert, active and cheerful, and have a normal psychosocial development. [18] Conductive hearing loss [28] and moderate bilateral sensory neural loss [29] has been occasionally seen, but mild conductive hearing loss was found in most European patients.

Effect on Musculoskeletal Function

Osteolysis is always present, in the distal phalanges, clavicles, mandible, neurocranium, and viscerocranium. It causes a reduction in size of the chin during the first 2 years of life and characteristic narrow shoulders with a gradual narrowing of the upper part of the thorax. As the mandibular osteolysis is greater than that of the viscerocranium, retrognathia also occurs. There is deterioration in joint mobility and in late phases the ankles, wrists, shoulders, and hips are also involved. The clavicle has a small and tapered distal end, the angle between the head and neck of the femur and its shaft are substantially increased (an extreme *coxa valga*), and the vertebral bodies are ovoid with a 'fish-mouth' appearance. [18] Joint mobility is normal at birth but decreases from the 2nd to 3rd year, initially in the knees followed by the elbows and fingers. In one recent study every patient showed an abnormal range of motion in at least three peripheral joints and developed a wide based, shuffling gait, resulting from joint and knee stiffness and joint deformities. [6] Radiologically, with time osteopenia of the long bones develops. The long bones are slender and sometimes somewhat bowed. [30-32]

Effect on Cardiovascular System

Cardiovascular complications generally cause death in Hutchinson-Gilford progeria syndrome. Autopsy reports have described varying degrees of generalized atherosclerosis, mainly involving the larger arteries. Coronary occlusions with myocardial infarctions were found more frequently than cerebral vascular lesions. [10] Medial smooth-muscle cells are lost, with secondary maladaptive vascular remodeling, intimal thickening, disrupted elastin fibres, and deposition of extracellular matrix; sclerotic plaques in the aorta and coronary arteries are associated with stenosis. [33-34] There is stiffening of blood vessels with elevated systolic and diastolic blood-pressure levels and an increased arterial

augmentation rate. Peripheral vascular disease, with reduced ankle-brachial indexes and vessel occlusion has been seen in few cases. [6] Thickening of the coronary arteries has been found, with or without calcification. Affected children gradually develop shortness of breath with exertion and easy fatigability starting at 6-8 years of age, when pulse rates and blood pressure increase. A hypertrophy of myocardial cells often accompanied by interstitial fibrosis occurs. [35-38] Marked medial hypertrophy of the pulmonary muscular arteries with fibrous intimal thickening as a result of fatal pulmonary hypertension has been also reported. [38] These changes tend to occur after age of seven [39] but transient ischemic attacks can occur at an age of four. [16]

Effect on Genital System

There is no pre-pubertal or pubertal growth spurt. Marked hypoplasia of the nipples has frequently been described, [40] although true athelia has not been found. [18] Genitalia are normal or may include somewhat small penis, with testes usually descended. Complete absence of spermatogenesis, [35, 41] maturation arrest of spermatogenesis, [42] normal spermatogenesis, [43] and nocturnal emissions [2, 44] have been reported. Development of secondary sexual characteristics is rare, although some of the oldest children have reached a Tanner developmental stage II (first appearance of pubic hair, breast buds, and slight enlargement of penis and testicles). Female external and internal genitalia have been reported to be normal, except for hypoplastic labia in an adult, [45] a single large ovarian cyst adenoma, [46] and multiple follicular ovarian cysts of various sizes. [47] Development of secondary sexual characteristics is very unusual; breast development is virtually absent, as is axillary and pubic hair growth. While a 32-year-old woman with non-classical progeria had her menarche at 12 years and gave birth to a healthy child at 23 years; however no male patient is known to have fathered a child. [6, 20, 45]

Other early distinguishing physical features include sleeping with eyes open, thin lips, nearly normal neurocranial growth paralleling brain growth, and a narrow nasal bridge with a sharp nasal tip. [16, 18]

POSSIBLE MECHANISM INVOLVED IN OCCURANCE OF PROGERIA

Past few year studies have suggested that in humans, some genetic defect causes progeroid syndrome that interferes with formation of mature Lamin A (*LMNA*). The genetic basis of HGPS was uncovered in 2003, when it was found that most cases of the disease are associated with a single nucleotide substitution that leads to aberrant splicing of *LMNA*, the gene that encodes the A-type nuclear lamins. [7-8, 48]

Normal processing of Lamin A

Lamins are type V intermediate filamentous proteins and have a short N-terminal "head" domain, an α -helical "central rod" domain, and a globular tail domain. [49] They are major determinants of nuclear size

and shape and are involved in essential functions such as chromatin organization, DNA replication and transcription, RNA processing. [50-51] There are two types of lamins: Type A and Type B. A-type lamins include two major products, lamin A and lamin C, and two minor products, lamin A Δ 10, and lamin C2, which results from an alternative mRNA splicing within exon 10. [52]

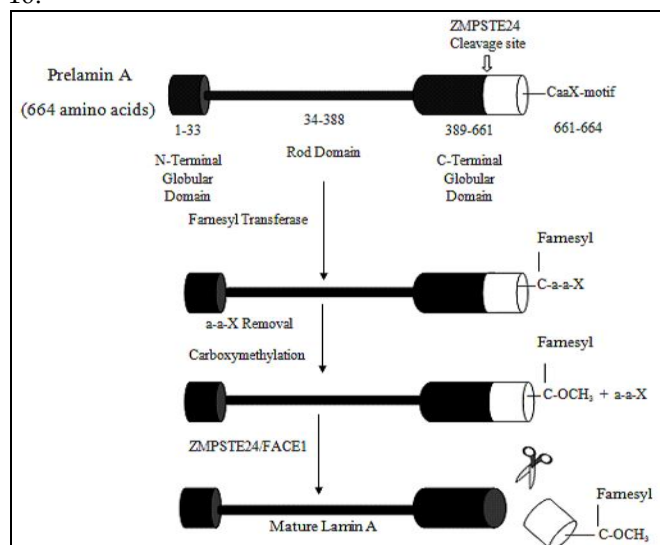


Fig. 1: Normal Lamin A Processing: Farnesylation of prelamins A; removal of a-a-X sequence and carboxymethylation, finally release of mature Lamin A by enzyme ZMPSTE24

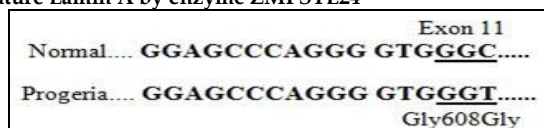


Fig. 2: *de novo* point mutation in Exon 11 of LMNA gene

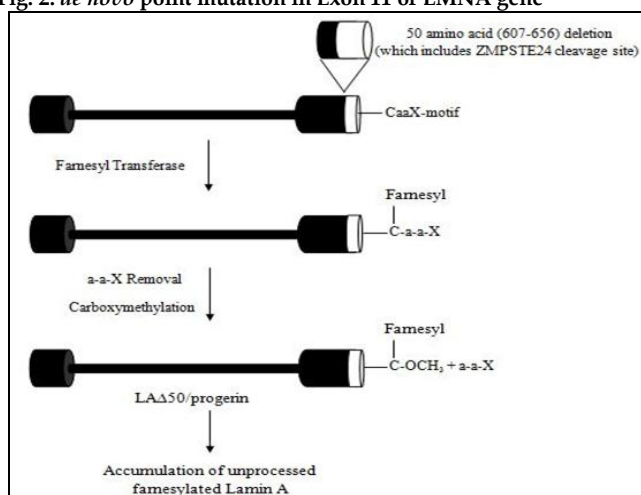


Fig. 3: Defect in Lamin A processing in Progeria: Farnesylation of prelamins A; removal of a-a-X sequence and carboxymethylation, permanent anchoring of unprocessed Lamin A in the nuclear membrane due to lack of ZMPSTE24 cleavage site

The lamin gene is made up of 12 exons. Exons 1-10 encode the N-terminal 566 amino acids of lamins A and C; however, exons 11 and 12 are unique to lamin A mRNA and code for an additional 98-amino acid C-terminal region which contains functionally important post-translational modification sites. Thus, lamin C differs at the C-terminal from lamin A, since it lacks the final part of exon 10, as well as exons 11 and 12. [52]

Lamins A and C are major constituents of the nuclear lamina, form either homodimers or heterodimers to create the filamentous structure of the nuclear lamina that support the inner nuclear membrane and also extend throughout the nucleus. [53-55] In contrast to lamin C, lamin A is produced by post-translational processing of the prelamins A precursor. Lamin A is expressed in only differentiated tissue fulfilling essential functions in organ and tissue homeostasis, while Lamin B is expressed throughout the development forming the fundamental constituents of the nuclear envelope, essential for cell viability and normal embryonic development. Thus defects in Lamin B are generally more lethal. [56]

Normally lamin A maturation involves a series of post-translational modifications of newly translated prelamins A protein to form mature lamin A by two transfer reactions and two proteolytic cleavages. [57] In normal cells, pre-lamin A (664 amino acids) contains a cysteine-aliphatic-aliphatic-any amino acid (CaaX) motif at the carboxy-terminal, where the cysteine residue becomes farnesylated by the enzyme farnesyl transferase. [58-59] The 4-amino acid tail serves as a recognition site for posttranslational modifications where a 15-carbon farnesyl group is added. The presence of a farnesyl group at the carboxy-terminal end, along with the CaaX motif allows the prelamins A to be embedded in nuclear membrane and these are thus essential for correct localization of the mature protein. [60] This farnesylated protein then undergoes a two step endo-proteolytic cleavage by a zinc metalloproteinase enzyme ZMPSTE24/FACE1. [61] First the C-terminal aaX sequence is cleaved and the remaining farnesyl cysteine is then methylated. The addition of farnesyl and methyl group increases the hydrophobicity [62] and thus helps in association of Prelamins A with nuclear membrane. In the second step, 15 amino acids at the C-terminal end including the farnesylated cysteine are cleaved by ZMPSTE24 releasing mature Lamin A (Fig. 1). [58] The removal of the terminating 15 amino acids allows detachment of lamin A from the nuclear membrane. [63]

Defect in normal processing of Lamin A in Progeria

The HGPS arise from deficiencies in these post-translational modifications of prelamins A. In the majority of HGPS patients, there is a *de novo* nucleotide substitution i.e. GGC to GGT in exon 11 of LMNA gene on chromosome 1 at position 1824 of the coding sequence (Fig. 2). [7-8] However this mutation does not cause change in amino acid sequence in protein (G608G), it generates a cryptic splice donor site in exon 11 which results in removal of 150 base pairs and thus in-frame deletion of last 50 amino acids (607-656) from C-terminal of exon 11, but does not affect the CaaX motif.

Because exon 12 does not undergo any change, the first 3 steps of prelamins processing occur normally (farnesylation of the CaaX site, removal of the aaX, and

addition of the methyl group at C-terminal). But unfortunately, it lacks an endoproteolytic cleavage site required for normal processing of the lamin A precursor because the necessary sites for Zmpste24 cleavage are among the 50 amino acids not translated. [7-8, 64] This new molecule, with a 50-amino acid deletion from the exon 11 and preservation of the 3' farnesyl group, is called "L Δ 50/progerin". [65-66] As a result L Δ 50/progerin remains permanently farnesylated [67-68] and thus permanently anchored in the nuclear membrane (Fig. 3).

HGPS PHENOTYPES

The abnormal progerin protein acts in a dominant-negative manner to prevent the normal assembly of nuclear lamins into the nuclear lamina. Its accumulation causes disruption of nuclear integrity and leads to formation of abnormally shaped nuclei, a prominent characteristic seen in HGPS. [69-70] It leads to all of the downstream nuclear defects that are characteristic of HGPS. Nuclei appear larger, distorted, blebbed, and have a thicker nuclear lamina. [69] Moreover there is heterochromatin disorganization, mislocalization of nuclear envelope proteins, disrupted gene transcription, [68, 71-73] and increase in DNA damage with a loss of DNA repair efficiency. [74-75] It is evident that not the absence of Lamin A, but the accumulation of progerin is responsible for the toxic effects in affected cells. [70, 76-77]

Transcriptional misregulation has also been reported in HGPS fibroblasts. [73, 78] In HGPS cells, the mechanical properties of nuclear lamina gets reduce. The nuclei become stiffer, have reduced deformability, [79] and do not respond to mechanical force in the same manner as normal cells. [80] When Lamin A/C-deficient mouse embryo fibroblasts are subjected to mechanical strain show increased nuclear deformation, defective mechanotransduction, and impaired viability [81] which may be responsible for cardiac-muscle and skeletal muscle pathologies in HGPS patients, as resulting from mechanical damage during muscle contraction.

Cells derived from patients with HGPS and HGPS mouse models display some signs of activated DNA-damage response, including enhanced phosphorylation of histone H2AX and markedly increased transcription of p53 target genes. [74, 82] Cell division is also modified during nuclear envelope dissolution and reassembly. The lamina becomes depolymerized during the disassembly of the nuclear membrane in mitosis, and improper assembly at the end of mitosis leads to cell death. [83] During mitosis progerin plus normal lamin A mis-localize into insoluble cytoplasmic aggregates and membranes, delaying their return to the inner nuclear membrane and lamina of the reformed nucleus. This causes spatial and functional disruption of interphase G₁ chromatin and may lead to formation of bi-nucleate cells. [67-68] These structural, spatial and DNA damage/repair changes lead to increased genome instability and cytotoxicity due to accumulation of

progerin in aging HGPS cells. [50, 69, 84] HGPS also results in a decreased epidermal population of adult stem cells and impaired wound healing in mice. [85]

In nearly all cases HGPS is caused due to denovo point mutation in codon 608 of exon 11 of LMNA gene. [7-8] However other heterozygous and homozygous mutations have also been found in HGPS patients, such as R471C, R527C, G608S, c.2036C>T, T528M, M540T, R644C, T623S, A57P, R133L, L140R, K542N 14, 86-90, and some of which show a less severe form of the disease. [86-90]

Several laboratory studies have indicated that progeria patients excrete an excessive amount of glycosaminoglycan hyaluronic acid. [91-93] Fibroblasts from patients with progeria show a 3-fold increase in total glycosaminoglycan and, in particular, hyaluronic acid, compared with age-matched control groups which results from an abnormality in degradation and is not caused by increased synthesis. This increase in hyaluronic acid level may be responsible for decreased density of vasculature, sclerodermatous changes, and calcification of blood vessels.

TREATMENT

Prior to the HGPS gene discovery, progeria patients were given nutritional treatment and growth hormone therapy, which was unsuccessful and resulted in only transient improvements. [9] But now many mouse models have been generated that allows better understanding of Lamin A and more insights into HGPS treatment strategies.

Farnesyltransferase inhibitors

Mouse lines absent in the lamin A Zmpste24 cleavage sites or Zmpste24 deficient mice demonstrate HGPS-like symptoms, [94-95] illustrating the importance of Zmpste24 cleavage and the deleterious effects of accumulated farnesylated prelamin A. Thus, a potential therapeutic approach involves farnesyl inhibition using farnesyl transferase inhibitors (FTIs) as a potential method for treatment of HGPS. Indeed, issues arise with nonfarnesylated prelamin A potentially causing toxicity in the cell, just as farnesylated prelamin A does. [96] Thus it may be possible that FTIs could improve HGPS disease phenotypes but the resultant accumulation of nonfarnesylated prelamin A produce other disease phenotypes. [97-98]

FTI treatment is also correlated with the relocalization of the lamin A protein away from the nuclear periphery and partially rescues the nuclear morphology phenotype. [97-101] Furthermore, FTIs improved the survival of mice missing the enzyme, *Zmpste*, which is responsible for the cleavage events that produce mature lamin A. [96] Toth and co-workers [98] hypothesized that the partially processed prelamin A of Zmpste24 deficient cells accumulates at the nuclear lamina, interfering with normal lamina formation, and causing nuclear blebbing. Their hypothesis is supported by the nuclear shape normalization observed in these cells after been treated with FTI. [97-98]

Indeed, nuclear blebbing might not be the accurate indicator of disease phenotype at the whole-body level in humans, because other *LMNA* mutations cause human disease without any effect on nuclear shape. [102] Only a small amount of mature LA is necessary for proper nuclear-envelope assembly. [103] In support of this idea, clinical trials using FTIs demonstrate little toxicity, even when levels of unfarnesylated prelamin A are raised significantly. [104] However, the absence of LA leads to serious cellular consequences and disease. [105]

Treatment with protein FTI reverses aberrant nuclear shapes and improves the abnormal phenotypes in mice with an HGPS mutation in *LMNA*. [106] These fascinating laboratory studies have led to clinical trials of protein prenylation inhibitors in children with HGPS. However, progeroid mice treated with FTI as well as mice that express a progerin variant that cannot be farnesylated still have a fairly severe disease phenotype and die prematurely. [107]

Interfering with lamin A processing in the mouse, either by deleting *Zmpste24* or by expressing progerin, results in an HGPS-like phenotype. [106, 108-109] Treating these mice with FTIs markedly ameliorates many of the HGPS-like phenotypes such as lack of adipose tissue, growth retardation and skeletal pathology. [97, 106, 110] It has been also established by Mehta and co-workers [111] that exposure to farnesyl transferase inhibitors restores the mis-localized chromosome territories to a nuclear position similar to chromosomes in proliferating control cells. Some additional studies reveal that in mouse models of HGPS, FTIs improved bone quality, growth, and survival. [97, 107, 110] Such findings have led to the first HGPS treatment clinical trials with the FTI to investigate the efficacy of FTIs as treatments for HGPS. [112]

FTI treatments may result in an alternative route of prelamin A prenylation known as geranylgeranylation, which is an alternative form of prenylation which may reduce the efficacy of FTIs. Treatment of HGPS mice with statins and bisphosphonates inhibits both farnesylation and geranylgeranylation and improves nuclear shape. The utilization of statins and bisphosphonates resulted in reduced lipodystrophy, reduced hair loss, improved bone defects, and enhanced longevity. [82] Pravastatin (a statin) and zoledronic acid (a bisphosphonate) are being studied in a second set of clinical trials as treatments for patients with HGPS. A third set of trials has also been initiated in 2009 which examines FTI, Pravastatin, and Zoledronic acid in combination. [112] The dose-dependent administration of the FTI Tipifarnib (R115777, Zarnestra) to the HGPS mouse model can significantly prevent both the onset of the cardiovascular phenotype as well as the late progression of existing cardiovascular disease. [113]

The results of the first-ever clinical drug trial for children with progeria reveal that Lonafarnib, a FTI

originally developed to treat cancer, has proven effective for progeria. Every child showing improvement in one or more of four ways: gaining additional weight, better hearing, improved bone structure and/or, most importantly, increased flexibility of blood vessels. [114] It should be noted that FTIs prevent farnesylation and localization of progerin to the cell membrane but do not ameliorate the function of the abnormal progerin protein within the cytoplasm, which may result in abnormalities in cell function and DNA repair that, therefore, would not be treated with these drugs. [75, 115]

New treatment strategies

Recent studies have indicated that the nuclear blebbing phenotype in HGPS fibroblasts can be ameliorated with morpholino antisense reagents [70] or by expressing short hairpin RNA constructs (RNA interference). Literature suggests that selective inhibition through small molecules (or other RNA interference techniques) of the alternative splicing caused by the classical mutation is one of the most promising therapies for HGPS. [116-118] The addition of a synthesized dsRNA with the *LMNA* sequence would prompt the cell to eliminate all mutated lamin proteins at the post-transcriptional level, thereby reducing progerin expression. [119] Several recent studies have shown that antisense oligonucleotides (ASOs) have the potential to modulate splice site utilization. [120-123] Moreover, treating *Zmpste24*^{-/-} cells with a prelamin A-specific antisense oligonucleotide reduced prelamin A levels and significantly reduced the frequency of misshapen nuclei. [110] It has been shown that cellular disease phenotype is reversible in cells from HGPS patients. The repeated transfection of a morpholino oligonucleotide directed against the exon 11 splice donor site has been shown to inhibit alternate splicing. Upon splicing correction, HGPS fibroblasts assume normal nuclear morphology, the lamina-associated protein's distribution and cellular levels are rescued, defects in heterochromatin-specific histone modifications are normalized, the dynamic properties of lamin A are restored, and proper expression of several misregulated genes is re-established. [70]

Osorio and co-workers [124] also observed the effectiveness of morpholino antisense nucleotide which led to a marked amelioration of their progeroid phenotype and substantially extended their life span in the mutant mice. In a study by Fong and co-workers [125] demonstrated that the one of the 2'-MOE ribose oligonucleotide has moderately decreased the progerin level in comparison to others that have increased the progerin level, which suggests that ASOs with similar properties could be therapeutically useful. Hernandez and co-workers [126] observe decreased Wnt signaling and extracellular matrix gene expression in a murine model of the disease, suggesting potential therapeutic strategies. Wnt signaling regulates extracellular matrix composition and is critical for cartilage development as

well as osteoblast and chondrocyte differentiation during vertebrate skeletogenesis. Then they treated cultured fibroblasts of mice model of the disease and further two human subjects with HGPS with a GSK-3 β inhibitor, which is known to activate the Wnt effector protein β -catenin, improved survival, and restored proliferation. This preliminary observation suggests a potential new therapeutic option for HGPS.

Recent experimental studies demonstrate that rapamycin decreases the amount of the disease-causing protein progerin by 50%, improves the abnormal nuclear shape, extends the lifespan of progeria cells [127] and leads to autophagic degradation of toxic farnesylated Prelamin A and progerin. [128-129]

Hutchinson-Gilford progeria syndrome is a rare, segmental premature aging syndrome of accelerated atherosclerosis, cardiovascular diseases and early death from myocardial infarction or stroke. Progeria has fascinated clinicians for a century because the disease has been seen as a window into the process of aging for all of us. A better understanding of the pathogenesis of this human progeroid syndrome is likely to improve our understandings about several areas of cell biology, mainly in the areas of nuclear structure, dynamics and DNA repair, as well as how defects in these fundamental biological processes lead to cellular and organismal disease phenotypes. Current clinical trials show that this disease may be controlled symptomatically using farnesyl transferase inhibitors. We believe that it will be important to continue to develop other therapeutic strategies, such as approaches to reduce the alternative splicing event that lies at the root of the disease, or to eliminate prelamin A transcripts with antisense approaches.

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: 473-477.
2. Gilford H. On a condition of mixed premature and immature development. *Med Chir Trans.* 1897; 80: 17-46.
3. Brown WT. Progeria: a human-disease model of accelerated aging. *Am J Clin Nutr.* 1992; 55(6): 1222S-1224S.
4. Brown WT, Zebrower M, Kieras FJ. Progeria, a model disease for the study of accelerated aging. *Basic Life Sci.* 1985; 35: 375-396.
5. DeBusk FL. The Hutchinson-Gilford progeria syndrome. Report of 4 cases and review of the literature. *J Pediatr.* 1972; 80(4): 697-724.
6. Merideth MA, Gordon LB, Clauss S, Sachdev V, Smith AC, Perry MB, Brewer CC, Zalewski C, Kim HJ, Solomon B, Brooks BP, Gerber LH, Turner ML, Domingo DL, Hart TC, Graf J, Reynolds JC, Gropman A, Yanovski JA, Gerhard-Herman M, Collins FS, Nabel EG, Cannon RO 3rd, Gahl WA, Introne WJ. Phenotype and course of Hutchinson-Gilford progeria syndrome. *N Engl J Med.* 2008; 358(6): 592-604.
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; 423(6937): 293-298.
8. De Sandre-Giovannoli A, Bernard R, Cau P, Navarro C, Amiel J, Boccaccio I, Lyonnet S, Stewart CL, Munnich A, Le Merrer M, Levy N. Lamin A truncation in Hutchinson-Gilford progeria. *Science* 2003; 300(5628): 2055.
9. Abdenur JE, Brown WT, Friedman S, Smith M, Lifshitz F. Response to nutritional and growth hormone treatment in progeria. *Metabolism* 1997; 46(8): 851-856.
10. Mounkes LC, Kozlov S, Hernandez L, Sullivan T, Stewart CL. A progeroid syndrome in mice is caused by defects in A-type lamins. *Nature* 2003; 423(6937): 298-301.
11. Maciel AT. Evidence for autosomal recessive inheritance of progeria (Hutchinson Gilford). *Am J Med Genet.* 1988; 31(3): 483-487.
12. Khalifa MM. Hutchinson-Gilford progeria syndrome: report of a Libyan family and evidence of autosomal recessive inheritance. *Clin Genet.* 1989; 35(2): 125-132.
13. Pollex RL, Hegele RA. Hutchinson-Gilford Progeria. *Clin Genet.* 2004; 66(5): 375-381.
14. Plasilova M, Chattopadhyay C, Pal P, Schaub NA, Buechner SA, Mueller H, Miny P, Ghosh A, heinimann K. Homozygous missense mutation in the lamin A/C gene causes autosomal recessive Hutchinson-Gilford progeria syndrome. *J Med Genet.* 2004; 41(8): 609-614.
15. Wuyts W, Biervliet M, Reyniers E, D'Apice MR, Novelli G, Storm K. Somatic and gonadal mosaicism in Hutchinson-Gilford progeria. *Am J Med Genet A.* 2005; 135(1): 66-68.
16. Gordon LB, Brown WT, Collnis FS: Hutchinson-Gilford Progeria Syndrome (January 2011) in: GeneReviews at GeneTests: Medical Genetics Information Resource database online. Copyright, University of Washington, Seattle, 1997-2010. Available at www.genetests.org.
17. Sarkar PK, Shinton RA. Hutchinson-Guilford progeria syndrome. *Postgraduate Medicine Journal* 2001; 77(907): 312-317.
18. Hennekam RC. Hutchinson-Gilford progeria syndrome: review of the phenotype. *Am J Med Genet A.* 2006; 140(23): 2603-24.
19. Uitto J. Searching for clues to premature aging. *Trends in Molecular Medicine* 2002; 8(4): 155-157.
20. Ishii T. Progeria: autopsy report of one case, with a review of pathologic findings reported in the literature. *J Am Geriatr Soc.* 1976; 24(5): 193-202.
21. Labeille B, Dupuy P, Frey-Follezou I, Larregue M, Maquart FX, Borel JP, Gallet M, Risbourg B, Denoeux JP. Progeria de Hutchinson-Gilford neonatale avec atteinte cutanee sclerodermiforme. *Ann Dermatol Venereol.* 1987; 114(2): 233-242.
22. Gorlin RO, Sedano HO. Progeria Hutchinson-Gilford syndrome. *Mod Med.* 1968; 46: 62.
23. Batstone MD, Macleod AW. Oral and maxillofacial surgical considerations for a case of Hutchinson-Gilford progeria. *Int J Paediatr Dent.* 2002; 12(6): 429-432.
24. Dyck JD, David TE, Burke B, Webb GD, Henderson MA, Fowler RS. Management of coronary artery disease in Hutchinson-Gilford syndrome. *J Pediatr.* 1987; 111(3): 407-410.
25. Gupte S. Progeria with Marcus-Gunn phenomenon. *Indian Pediatr.* 1983; 20(9): 694-695.
26. Atkins L. Progeria: Report of a case with post-mortem findings. *N Engl J Med.* 1954; 250(25): 1065-1069.
27. Doub H. Progeria. *Med Radiogr Photogr.* 1953; 29(2-3): 60-62.
28. Baker PB, Baba N, Boesel CP. Cardiovascular abnormalities in Progeria. *Arch Pathol Lab Med.* 1981; 105(7): 384-386.
29. Nelson M. Progeria: Audiologic aspects. *Arch Pediatr.* 1962; 79: 87-90.
30. Schwarz E. Roentgen findings in Progeria. *Radiology.* 1962; 79: 411-414.
31. Kozlowski K. Radiographic study of senile dwarfism (progeria). *Ann Radiol.* 1965; 8: 92-96.

32. Monu JUV, Benka-Coker LBO, Fatunde Y. Hutchinson-Gilford Progeria syndrome in siblings. *Skel Radiol.* 1990; 19(8): 585-590.
33. Stehbens WE, Wakefield SJ, Gilbert-Barness E, Olson RE, Ackerman J. Histological and ultrastructural features of atherosclerosis in progeria. *Cardiovasc Pathol.* 1999; 8(1): 29-39.
34. Stehbens WE, Delahunt B, Shozawa T, Gilbert-Barness E. Smooth muscle cell depletion and collagen types in progeric arteries. *Cardiovasc Pathol.* 2001; 10(3): 133-136.
35. Orrico J, Strada F. Anatomico-clinical study of a case of senile dwarfism (progeria). *Arch Med Infant.* 1927; 30: 385-398.
36. King CR, Lemmer J, Campbell JR, Atkins AR. Osteosarcoma in a patient with Hutchinson-Gilford Progeria. *J Med Genet.* 1978; 15(6): 481-484.
37. Baker PB, Baba N, Boesel CP. Cardiovascular abnormalities in Progeria. *Arch Pathol Lab Med.* 1981; 105(7): 384-386.
38. Shiraishi I, Hayashi S, Hirai E, Onouchi Z, Hamaoka K. Fatal pulmonary hypertension associated with an atypical case of Hutchinson-Gilford progeria. *Pediatr Cardiol.* 2001; 22(6): 530-533.
39. Olive M, Harten I, Mitchell R, Beers JK, Djabali K, Cao K, Erdos MR, Blair C, Funke B, Smoot L, Gerhard-Herman M, Machan JT, Kutys R, Virmani R, Collins FS, Wight TN, Nabel EG, Gordon LB. Cardiovascular pathology in Hutchinson-Gilford progeria: correlation with the vascular pathology of aging. *Arterioscler Thromb Vasc Biol.* 2010; 30(11): 2301-2309.
40. Ackerman J, Gilbert-Barness E. Hutchinson-Gilford progeria syndrome: a pathologic study. *Pediatr Pathol Mol Med.* 2002; 21(1): 1-13.
41. Talbot NB, Butler AM, Pratt EL, MacLachlan EA, Tannheimer J. Progeria. Clinical, metabolic and pathologic studies on a patient. *Amer J Dis Child.* 1945; 69: 267-279.
42. Reichel W, Garcia-Bunuel R. Pathologic findings in Progeria: Myocardial fibrosis and lipofuscin pigment. *Am J Clin Pathol.* 1970; 53(2): 243-253.
43. Manschot WA. A Case of *Progeronanism*. (*Progeria of Gilford*). *Ned Tijdschr Geneesk.* 1940; 84: 3774-3782.
44. Plunkett ER, Sawtelle WE, Hamblen EC. Report of a patient with typical progeria, including data from urinary hormone studies. *J Clin Endocrinol.* 1954; 14(7): 735-741.
45. Corcoy R, Aris A, de Leiva, A. Fertility in a case of progeria. *Am J Med Sci.* 1989; 297(6): 383-384.
46. Rosenbloom AL, Kappy MS, DeBusk FL, Francis GL, Philpot TJ, Maclaren NK. Progeria: Insulin resistance and hyperglycemia. *J Pediatr.* 1983; 102(3): 400-401.
47. Gabr M, Hashem N, Hashem M, Fahmi A, Safouh M. Progeria, a pathologic study. *J Pediatr.* 1960; 57: 70-77.
48. Cao H, Hegele RA. LMNA is mutated in Hutchinson-Gilford progeria (MIM 176670) but not in Wiedemann-Rautenstrauch progeroid syndrome (MIM 264090). *J Hum Genet.* 2003; 48(5): 271-274.
49. Goldman RD, Gruenbaum Y, Moir RD, Shumaker DK, Spann TP. Nuclear lamins: building blocks of nuclear architecture. *Genes Dev.* 2002; 16(5): 533-547.
50. Dechat T, Pfliegerhaer K, Sengupta K, Shimi T, Shumaker DK, Solimando L, Goldman RD. Nuclear lamins: Major factors in the structural organization and function of the nucleus and chromatin. *Genes Dev.* 2008; 22(7): 832-853.
51. Prokocimer M, Davidovich M, Nissim-Rafinia M, Wiesel-Motiuk N, Bar DZ, Barkan R, Meshorer E, Gruenbaum Y. Nuclear lamins: key regulators of nuclear structure and activities. *J Cell Mol Med.* 2009; 13(6): 1059-85.
52. Lin F, Worman HJ. Structural organization of the human gene encoding nuclear lamin A and nuclear lamin C. *J Biol Chem.* 1993; 268(22): 16321-16326.
53. Ye Q, Worman HJ. Protein-protein interactions between human nuclear lamins expressed in yeast. *Exp Cell Res.* 1995; 219(1): 292-298.
54. Stuurman N, Heins S, Aebi U. Nuclear lamins: their structure, assembly, and interactions. *J Struct Biol.* 1998; 122(1-2): 42-66.
55. Hutchinson CJ. Lamins: building blocks or regulators of gene expression. *Nat. Rev. Mol. Cell Biol.* 2002; 3(11): 848-858.
56. Vergnes L, Peterfy M, Bergo MO, Young SG, Reue K. Lamin B1 is required for mouse development and nuclear integrity. *Proc Natl Acad Sci USA.* 2004; 101(28): 10428-33.
57. Davies BS, Fong LG, Yang SH, Coffinier C, Young SG. The posttranslational processing of prelamin A and disease. *Annu Rev Genomics Hum Genet.* 2009; 10: 153-74.
58. Weber K, Plessmann U, Traub P. Maturation of nuclear lamin A involves a specific carboxy-terminal trimming, which removes the polyisoprenylation site from the precursor; implications for the structure of the nuclear lamina. *FEBS Lett.* 1989b; 257: 411-414.
59. Beck LA, Hosick TJ, Sinensky M. Isoprenylation is required for the processing of the lamin A precursor. *J Cell Biol.* 1990; 110(5): 1489-1499.
60. Hennekes H, Nigg EA. The role of isoprenylation in membrane attachment of nuclear lamins. A single point mutation prevents proteolytic cleavage of the lamin A precursor and confers membrane binding properties. *J Cell Sci.* 1994; 107(Pt 4): 1019-1029.
61. Sinensky M, Fantle K, Trujillo M, McLain T, Kupfer A, Dalton M. The processing pathway of prelamin A. *J Cell Sci.* 1994; 107(Pt 1): 61-67.
62. Silvius JR, Heureux F. Fluorimetric evaluation of the affinities of isoprenylated peptides for lipid bilayers. *Biochemistry* 1994; 33(10): 3014-22.
63. Boban M, Braun J, Foisner R. Lamins: 'structure goes cycling'. *Biochem Soc Trans.* 2010; 38(Pt 1): 301-6.
64. Glynn MW, Glover TW. Incomplete processing of mutant lamin A in Hutchinson-Gilford progeria leads to nuclear abnormalities, which are reversed by farnesyltransferase inhibition. *Hum Mol Genet.* 2005; 14(20): 2959-2969.
65. Young SG, Fong LG, Michaelis S. Prelamin A, Zmpste24, misshapen cell nuclei, and progeria: new evidence suggesting that protein farnesylation could be important for disease pathogenesis. *J Lipid Res.* 2005; 46(12): 2531-2558.
66. Shackleton S, Smallwood DT, Clayton P, Wilson LC, Agarwal AK, Garg A, trembath RC. Compound heterozygous ZMPSTE24 mutations reduce prelamin A processing and result in a severe progeroid phenotype. *J Med Genet.* 2005; 42(6): e36.
67. Cao K, Capell BC, Erdos MR, Djabali K, Collins FS. A lamin A protein isoform overexpressed in Hutchinson-Gilford progeria syndrome interferes with mitosis in progeria and normal cells. *Proc Natl Acad Sci USA* 2007; 104(12): 4949-4954.
68. Dechat T, Shimi T, Adam SA, Rusinol AE, Andres DA, Spielmann HP, Sinensky MS, Goldman RD. Alterations in mitosis and cell cycle progression caused by a mutant lamin A known to accelerate human aging. *Proc Natl Acad Sci USA* 2007; 104(12): 4955-4960.
69. Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, Gordon LB, Gruenbaum Y, Khuon S, Mendez M, Varga R, Collins FS. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci USA* 2004; 101(24): 8963-8968.
70. Scaffidi P, Misteli T. Reversal of the cellular phenotype in the premature aging disease Hutchinson-Gilford progeria syndrome. *Nat Med.* 2005; 11(4): 440-445.
71. Capell BC, Collins FS. Human laminopathies: nuclei gone genetically awry. *Nat Rev Genet.* 2006; 7(12): 940-952.
72. Cao K, Capell BC, Erdos MR, Djabali K, Collins FS. A lamin A protein isoform overexpressed in Hutchinson-Gilford progeria syndrome interferes with mitosis in progeria and normal cells. *Proc Natl Acad Sci USA.* 2007; 104(12): 4949-4954.
73. Csoka AB, English SB, Simkevich CP, Ginzinger DG, Butte AJ, Schatten GP, Rothman FG, Sedivy JM. Genome-scale expression profiling of Hutchinson-Gilford progeria syndrome reveals widespread transcriptional misregulation

- leading to mesodermal/mesenchymal defects and accelerated atherosclerosis. *Aging Cell*. 2004; 3(4): 235-243.
74. Liu B, Wang J, Chan KM, Tjia WM, Deng W, Guan X, Huang JD, Li KM, Chau PY, Chen PY, Chen DJ, Pei D, Pendas AM, Cadinanos J, Lopez-Otin C, Tse HF, Hutchison C, Chen J, Cao Y, Cheah KS, Tryggvason K, Zhou Z. Genomic instability in laminopathy-based premature aging. *Nat Med*. 2005; 11(7): 780-785.
 75. Liu Y, Rusinol A, Sinensky M, Wang Y, Zou Y. DNA damage responses in progeroid syndromes arise from defective maturation of prelamin A. *J Cell Sci*. 2006; 119(Pt 22): 4644-4649.
 76. Fong LG, Ng JK, Meta M, Cote N, Yang SH, Stewart CL, Sullivan T, Burghardt A, Majumdar S, Reue K, Bergo MO, Young SG. Heterozygosity for Lmna deficiency eliminates the progeria-like phenotypes in Zmpste24-deficient mice. *Proc Natl Acad Sci USA*. 2004; 101(52): 18111-18116.
 77. Fong LG, Ng JK, Lammerding J, Vickers TA, Meta M, Cote N, Gavino B, Qiao X, Chang SY, Young SR, Yang SH, Stewart CL, Lee RT, Bennett CF, Bergo MO, Young SG. Prelamin A and lamin A appear to be dispensable in the nuclear lamina. *J Clin Invest*. 2006; 116(3): 743-752.
 78. Ly DH, Lockhart DJ, Lerner RA, Schultz PG. Mitotic misregulation and human aging. *Science* 2000; 287(5462): 2486-2492.
 79. Dahl KN, Scaffidi P, Islam MF, Yodh AG, Wilson KL, Misteli T. Distinct structural and mechanical properties of the nuclear lamina in Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci USA* 2006; 103(27): 10271-6.
 80. Verstraeten VL, Ji JY, Cummings KS, Lee RT, Lammerding J. Increased mechanosensitivity and nuclear stiffness in Hutchinson-Gilford progeria cells: effects of farnesyltransferase inhibitors. *Aging Cell* 2008; 7(3): 383-393.
 81. Lammerding J, Schulze PC, Takahashi T, Kozlov S, Sullivan T, Kamm RD, Stewart CL, Lee RT. Lamin A/C deficiency causes defective nuclear mechanics and mechanotransduction. *J Clin Invest*. 2004; 113(3): 370-378.
 82. Varela I, Pereira S, Ugalde AP, Navarro CL, Suarez MF, Cau P, Cadinanos J, Osorio FG, Foray N, Cobo J, de Carlos F, Levy N, Freije JM, Lopez-Otin C. Combined treatment with statins and aminobisphosphonates extends longevity in a mouse model of human premature aging. *Nat Med*. 2008; 14(7): 767-72.
 83. Steen RL, Collas P. Mistargeting of B-type lamins at the end of mitosis: implications on cell survival and regulation of lamins A/C expression. *J Cell Biol*. 2001; 153(3): 621-626.
 84. Musich PR, Zou Y. Genomic Instability and DNA Damage Responses in Progeria Arising from Defective Maturation of Prelamin A. *Aging (Albany NY)* 2009; 1(1): 28-37.
 85. Rosengarten Y, McKenna T, Grochová D, Eriksson M. Stem cell depletion in Hutchinson-Gilford progeria syndrome. *Aging Cell* 2011; 10(6): 1011-20.
 86. Csoka AB, Cao H, Sammak PJ, Constantinescu D, Schatten GP, Hegele RA. Novel lamin A/C gene (LMNA) mutations in atypical progeroid syndromes. *J Med Genet*. 2004; 41(4): 304-308.
 87. Fukuchi K, Katsuya T, Sugimoto K, Kuremura M, Kim HD, Li L, Ogihara T. LMNA mutation in a 45 year old Japanese subject with Hutchinson-Gilford progeria syndrome. *J Med Genet*. 2004; 41(5): e67.
 88. Cao H, Hegele RA. LMNA is mutated in Hutchinson-Gilford progeria (MIM 176670) but not in Wiedemann-Rautenstrauch progeroid syndrome (MIM 264090). *J Hum Genet*. 2003; 48(5): 271-274.
 89. Verstraeten VL, Broers JL, van Steensel MA, Zinn-Justin S, Ramaekers FC, Steijlen PM, Kamps M, Kuipers HJ, Merckx D, Smeets HJ, Hennekam RC, Marcelis CL, van den Wijngaard A. Compound heterozygosity for mutations in LMNA causes a progeria syndrome without prelamin A accumulation. *Hum Mol Genet*. 2006; 15(16): 2509-2522.
 90. Chen L, Lee L, Kudlow BA, Dos Santos HG, Sletvold O, Shafeghati Y, Botha EG, Garg A, Hanson NB, Martin GM, Mian IS, Kennedy BK, Oshima J. LMNA mutations in atypical Werner's syndrome. *Lancet* 2003; 362(9382): 440-445.
 91. Kieras FJ, Brown WT, Houck GE, Zebrower M. Elevation of urinary hyaluronic acid in Werner syndrome and progeria. *Biochem Med Metab Biol*. 1985; 36(3): 276-82.
 92. Zebrower M., Kieras FJ, Brown WT. Urinary hyaluronic acid elevation in Hutchinson-Gilford progeria syndrome. *Mech Ageing Dev*. 1986; 35(1): 39-46.
 93. Tonunaga M, Wakamatsu E, Soto K. Hyaluronuria in a case of progeria (Hutchinson - Gilford syndrome). *J Am Geriatr Soc*. 1978; 26(7): 296-302.
 94. Varela I, Cadinanos J, Pendas AM, Gutierrez-Fernandez A, Folgueras AR, Sanchez LM, Zhou Z, Rodriguez FJ, Stewart CL, Vega JA, Tryggvason K, Freije JM, Lopez-Otin C. Accelerated ageing in mice deficient in Zmpste24 protease is linked to p53 signalling activation. *Nature* 2005; 437(7058): 564-568.
 95. Stewart CL, Kozlov S, Fong LG, Young SG. Mouse models of the laminopathies. *Exp Cell Res*. 2007; 313(10): 2144-56.
 96. Young SG, Meta M, Yang SH, Fong LG. Prelamin A Farnesylation and Progeroid Syndromes. *J Biol Chem*. 2006; 281(52): 39741-39745.
 97. Yang SH, Bergo MO, Toth JI, Qiao X, Hu Y, Sandoval S, Meta M, Bendale P, Gelb MH, Young SG, Fong LG. Blocking protein farnesyltransferase improves nuclear blebbing in mouse fibroblasts with a targeted Hutchinson-Gilford progeria syndrome mutation. *Proc Natl Acad Sci USA* 2005; 102(29): 10291-10296.
 98. Toth JI, Yang SH, Qiao X, Beigneux AP, Gelb MH, Moulson CL, Miner JH, Young SG, Fong LG. Blocking protein farnesyltransferase improves nuclear shape in fibroblasts from humans with progeroid syndromes. *Proc Natl Acad Sci USA* 2005; 102(36): 12873-12878.
 99. Mallampalli MP, Huyer G, Bendale P, Gelb MH, Michaelis S. Inhibiting farnesylation reverses the nuclear morphology defect in a HeLa cell model for Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci USA* 2005; 102(40): 14416-14421.
 100. Glynn MW, Glover TW. Incomplete processing of mutant lamin A in Hutchinson-Gilford progeria leads to nuclear abnormalities, which are reversed by farnesyltransferase inhibition. *Hum Mol Genet*. 2005; 14(20): 2959-2969.
 101. Capell BC, Erdos MR, Madigan JP, Fiordalisi JJ, Varga R, Conneely KN, Gordon LB, Der CJ, Cox AD, Collins FS. Inhibiting farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci USA* 2005; 102(36): 12879-12884.
 102. Broers JL, Hutchison CJ, Ramaekers FC. Laminopathies. *J Pathol*. 2004; 204(4): 478-488.
 103. Lourim D, Krohne G. Membrane-associated lamins in *Xenopus* egg extracts: identification of two vesicle populations. *J Cell Biol*. 1993; 123(3): 501-512.
 104. Taveras AG, Kirschmeier P, Baum CM. Sch-66336 (sarasar) and other benzocycloheptapyridyl farnesyl protein transferase inhibitors: discovery, biology and clinical observations. *Curr Top Med Chem*. 2003; 3(10): 1103-1114.
 105. Sullivan T, Escalante-Alcade D, Bhatt H, Anver M, Bhat N, Nagashima K, Stewart CL, Burke B. Loss of A-type lamin expression compromises nuclear envelope integrity leading to muscular dystrophy. *J Cell Biol*. 1999; 147(5): 913-920.
 106. Yang SH, Meta M, Qiao X, Frost D, Bauch J, Coffinier C, Majumdar S, Bergo MO, Young SG, Fong LG. A farnesyltransferase inhibitor improves disease phenotypes in mice with a Hutchinson-Gilford progeria syndrome mutation. *J Clin Invest*. 2006; 116(8): 2115-2121.
 107. Yang SH, Andres DA, Spielmann HP, Young SG., Fong LG. Progerin elicits disease phenotypes of progeria in mice whether or not it is farnesylated. *J Clin Invest*. 2008; 118(10): 3291-3300.
 108. Pendas AM, Zhou Z, Cadinanos J, Freije JM, Wang J, Hultenby K, Astudillo A, Wernerson A, Rodriguez F, Tryggvason K, Lopez-Otin C. Defective prelamin A

- processing and muscular and adipocyte alterations in Zmpste24 metalloproteinase-deficient mice. *Nature Genet.* 2002; 31(1): 94-99.
109. Bergo MO, Gavino B, Ross J, Schmidt WK, Hong C, Kendall LV, mohr A, meta M, Genant H, Jiang Y, Wisner ER, Van Bruggen N, Carano RA, Michaelis S, Griffey SM, Young SG. Zmpste24 deficiency in mice causes spontaneous bone fractures, muscle weakness, and a prelamin A processing defect. *Proc. Natl Acad Sci USA* 2002; 99(20): 13049-13054.
 110. Fong LG, Frost D, Meta M, Qiao X, Yang SH, Coffinier C, Young SG. A protein farnesyltransferase inhibitor ameliorates disease in a mouse model of progeria. *Science* 2006; 311(5767): 1621-1623.
 111. Mehta IS, Eskiw CH, Arican HD, Kill IA, Bridger JM. Farnesyltransferase inhibitor treatment restores chromosome territory positions and active chromosome dynamics in Hutchinson-Gilford progeria syndrome cells. *Genome Biol.* 2011; 12(8): R74.
 112. Progeria Research Foundation. cited 2011 February 26; Progeria Clinical Trials. Available from: http://www.progeriaresearch.org/clinical_trial.html.
 113. Capell BC, Olive M, Erdos MR, Cao K, Faddah DA, Tavarez UL, Conneely KN, Qu X, San H, Ganesh SK, Chen X, Avallone H, Kolodzie FD, Virmani R, Nabel EG, Collins FS. A farnesyltransferase inhibitor prevents both the onset and late progression of cardiovascular disease in a progeria mouse model. *Proc Natl Acad Sci USA* 2008; 105(41): 15902-15907.
 114. Gordon LB, Kleinman ME, Miller DT, Neuberger D, Giobbie-Hurder A, Gerhard-Herman M, Smoot LB, Gordon CM, Cleveland R, Snyder BD, Fligor B, Bishop WR, Statkevich P, Regen A, Sonis A, Riley S, Ploski C, Correia A, Quinn N, Ullrich NJ, Nazarian A, Liang MG, huh SY, Schwartzman A, Kieran MW. Clinical Trial of a Farnesyltransferase Inhibitor in Children with Hutchinson-Gilford Progeria Syndrome. *Proc Natl Acad Sci USA* 2012; 109(41): 16666-16671.
 115. Shumaker DK, Dechat T, Kohlmaier A, Adam SA, Bozovsky MR, Erdos MR, Eriksson M, Goldman AE, Khuon S, Collins FS, Jenuwein T, Goldman RD. Mutant nuclear lamin A leads to progressive alterations of epigenetic control in premature aging. *Proc Natl Acad Sci USA* 2006; 103(23): 8703-8708.
 116. Garcia-Blanco MA. Making antisense of splicing. *Curr Opin Mol Ther.* 2005; 7(5): 476-482.
 117. Huang S, Chen L, Libina N, Janes J, Martin GM, Campisi J, Oshima J. Correction of cellular phenotypes of Hutchinson-Gilford Progeria cells by RNA interference. *Hum Genet.* 2005; 118(3-4): 444-450.
 118. Soret J, Bakkoui N, Maire S, Durand S, Zekri L, Gabut M, Fic W, Divita G, Rivalle C, Dauzonne D, Nguyen CH, Jeanteur P, Jamal T. Selective modification of alternative splicing by indole derivatives that target serine-arginine-rich protein splicing factors. *Proc Natl Acad Sci USA* 2005; 102(24): 8764-8769.
 119. Matzke AJ, Matzke MA. Planting the seeds of a new paradigm. *PLOS Biology* 2004; 2(5): E133.
 120. Sazani P, Gemignani F, Kang S H, Maier MA, Manoharan M, Persmark M, Bortner D, Kole R. Systemically delivered antisense oligomers upregulate gene expression in mouse tissues. *Nat Biotechnol.* 2002; 20(12): 1228-1233.
 121. Hua Y, Vickers TA, Baker BF, Bennett CF, Krainer AR. Enhancement of SMN2 exon 7 inclusion by antisense oligonucleotides targeting the exon. *PLoS Biol.* 2007; 5(4): e73.
 122. Vickers TA, Zhang H, Graham MJ, Lemonidis KM, Zhao C, Dean NM. Modification of MyD88 mRNA splicing and inhibition of IL-1 β signaling in cell culture and in mice with a 2'-O-methoxyethyl-modified oligonucleotide. *J Immunol.* 2006; 176(6): 3652-3661.
 123. Hua Y, Vickers TA, Okunola HL, Bennett CF, Krainer AR. Antisense masking of an hnRNP A1/A2 intronic splicing silencer corrects SMN2 splicing in transgenic mice. *Am J Hum Genet.* 2008; 82(4): 834-848.
 124. Osorio FG, Navarro CL, Cadiñanos J, Lopez-Mejia IC, Quiros PM, Bartoli C, Rivera J, Tazi J, Guzman G, Varela, I, Depetris D, de Carlos F, Cobo J, Andres V, De Sandre-Giovannoli A, Freije JM, Levy N, Lopez-Otin, C. Splicing-directed therapy in a new mouse model of human accelerated aging. *Sci Transl Med.* 2011; 3(106): 106ra107.
 125. Fong LG, Vickers TA, Farber EA, Choi C, Yun UJ, Hu Y, Yang SH, Coffinier C, lee R, Yin L, Davies BS, Andres DA, Spielmann HP, Bennett CF, Young SG. Activating the synthesis of progerin, the mutant prelamin A in Hutchinson-Gilford progeria syndrome, with antisense oligonucleotides. *Hum Mol Genet.* 2009; 18(13): 2462-2471.
 126. Hernandez L, Roux KJ, Wong ESM, Mounkes LC, Mutalif R, Navasankari R, Rai B, Cool S, Jeong JW, Wang H, Lee HS, Kozlov S, Grunert M, Keeble T, Jones CM, Meta MD, Young SG, Daar IO, Burke B, perantoni AO, Stewart CL. Functional coupling between the extracellular matrix and nuclear lamina by Wnt signaling in progeria. *Dev Cell.* 2010; 19(3): 413-425.
 127. Cao K, Graziotto JJ, Blair CD, Mazzulli JR, Erdos MR, Krainc K, Collins FS. Rapamycin Reverses Cellular Phenotypes and Enhances Mutant Protein Clearance in Hutchinson-Gilford Progeria Cells. *Sci Transl Med.* 2011; 3(89): 89ra58.
 128. Cenni V, Capani C, Columbaro M, Ortolani M, D'Apice MR, Novelli G, Fini M, Marmioli S, Scarano E, Maraldi NM, Squarzone S, Prencipe S, Lattanzi G. Autophagic degradation of farnesylated prelamin A as a therapeutic approach to lamin-linked progeria. *Eur J Histochem.* 2011; 55(4): e36.
 129. Graziotto JJ, Cao K, Collins FS, Krainc D. Rapamycin activates autophagy in Hutchinson-Gilford progeria syndrome: Implications for normal aging and age-dependent neurodegenerative disorders. *Autophagy* 2012; 8(1): 147-151.

Source of Support: Nil, Conflict of Interest: None declared.
--