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Hutchinson-Gilford progeria syndrome

Shelley L. Davies, Jordi Bozzo
Prous Science, P.O. Box 540, Barcelona 08080, Spain

CONTENTS

Abstract

The rare genetic autosomal dominant condition Hutchinson-Gilford progeria syndrome (HGPS) is characterized by a dramatic, rapid appearance of aging beginning in childhood. HGPS progression generates vascular disease, which generally leads to death during the teenage years. There is currently no treatment for this genetic disorder, although since the identification of the underlying genetic mutation, new targets and potential strategies have emerged. The large majority of HGPS cases carry a single nucleotide substitution within exon 11 of the LMNA gene and abnormal splicing results in production of a truncated prelamin A protein (progerin). Subsequent farnesylation of mutated prelamin A targets the protein to the nuclear envelope, resulting in nuclear deformations and blebbing. Recent studies have shown that blocking farnesylation of progerin via the use of farnesyltransferase inhibitors can reduce nuclear blebbing and thus HGPS pathogenicity. Lentiviral administration of short hairpin RNA constructs to target and reduce progerin has also demonstrated efficacy in HGPS fibroblasts. Therefore, pharmacological targeting to correct cellular phenotypes associated with HGPS could be utilized in the future for therapeutic intervention.

Introduction

Hutchinson-Gilford progeria syndrome (HGPS) is a very rare genetic autosomal dominant condition characterized by the dramatic, rapid appearance of aging beginning in childhood. Children with HGPS have characteristic craniofacial abnormalities and exhibit retarded growth, osteoporosis, osteolytic bone lesions, alopecia, wrinkled/aged skin due to loss of subcutaneous adipose tissue and vascular disease, which generally leads to death during the teenage years. This condition results from mutations in the *LMNA* gene that produces a protein called prelamin A, which provides structural and mechanical stability for the nuclear envelope.

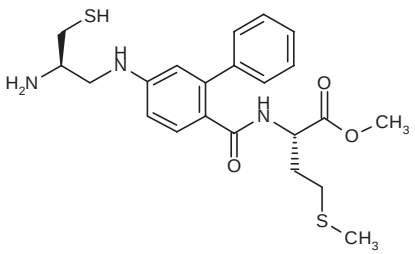
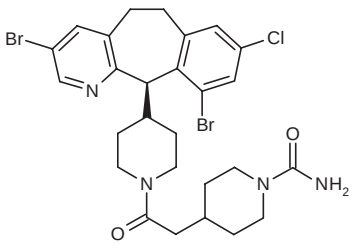
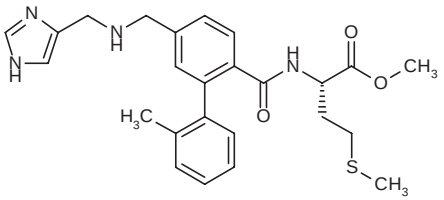
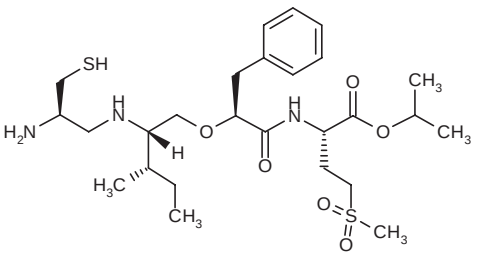
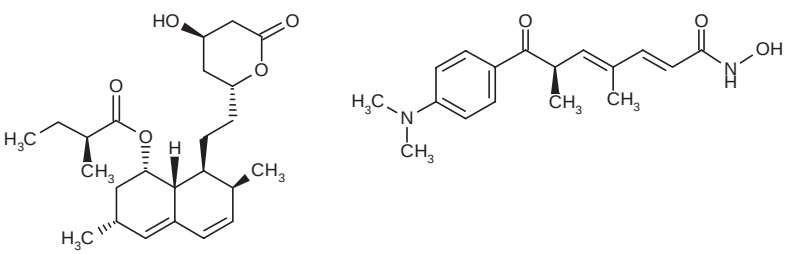
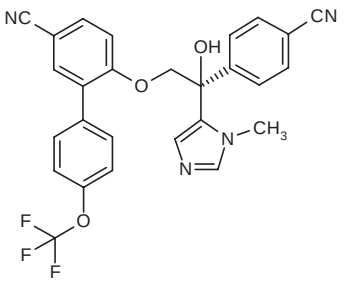
Therapy for individuals with HGPS is currently symptomatic and supportive. To date, no specific pharmacological agents have been identified for this genetic disorder, which is estimated to affect approximately 1 child in 4 million (1). However, recent studies have identified new targets and potential therapeutic strategies. Table I presents the therapeutic candidates for HGPS, which are discussed in more detail below.

Targets and therapeutic advances

Approximately 80% of HGPS cases carry a single nucleotide substitution at position 1824, C > T (G608G), within exon 11 of LMNA (GGC > GGT), and abnormal splicing results in the output of a truncated protein product with 50 amino acids deleted near its carboxy terminus. This mutant prelamin A is commonly known as progerin (2). Farnesylation, one of the enzymatic post-translational modifications involved in the generation of mature lamin A, is important for the targeting of prelamin A to the nuclear envelope (3). Although truncation of progerin prevents the production of mature lamin A, it is thought that progerin does not side-step farnesylation and is thus transferred to the nuclear envelope, where it adversely affects the integrity of the nuclear lamina, resulting in nuclear deformations, blebbing and loss of peripheral heterochromatin (4).

Several studies have hypothesized that blocking farnesylation of progerin via the use of farnesyltransferase inhibitors, developed to treat cancer, may prevent its targeting to the nuclear envelope and reduce nuclear blebbing. Application of the farnesyltransferase inhibitor FTI-277 has been shown to decrease the proportion of abnormal nuclei from 31% to 8% (5). Further investigation of other farnesyltransferase inhibitors, including the clinical candidate lonafarnib (Sch-66336, Sarasar™), FTI-2153 and L-744832, indicated that these agents restore normal nuclear architecture in progerin-transfected HeLa, HEK-293 and NIH/3T3 cells and successfully reduce nuclear blebbing in human early- and late-stage HGPS fibroblasts (6). The farnesyltransferase inhibitor lovastatin in combination with the histone deacetylase

Table I: Chemical structures of therapeutic candidates for HGPS.

Drug	Structure	Ref.
FTI-277		5
Lonafarnib		6
FTI-2153		6
L-744832		6
Lovastatin + Trichostatin A		7
ABT-100		8

inhibitor trichostatin A also rescued heterochromatin organization and transcript distribution, effects that were associated with a dramatic reduction in progerin levels in a small sample of fibroblasts obtained from HGPS patients (7).

In vivo assessment of the therapeutic potential of farnesyltransferase inhibition was carried out in an animal model of mandibuloacral dysplasia, a progeroid disorder similar to HGPS, which is caused by deficiency of the zinc mellanoproteinase ZMPSTE24, which cleaves the prelamin A precursor and its farnesyl lipid anchor to generate lamin A. ABT-100 (hydrochloride) improved body weight, grip strength, bone integrity and survival (8).

Overall, it appears that preventing farnesylation of progerin may be an effective strategy to reduce HGPS pathogenicity (3, 9, 10).

A recent study utilized gene therapy to correct cellular phenotypes associated with HGPS. Short hairpin RNA constructs, developed to target the mutated progerin mRNA, were applied to HGPS fibroblasts via lentiviral transmission. This RNA interference technology reduced progerin expression by 26%, with an associated normalization of nuclear morphology, improvement in proliferative potential and a reduction in senescent cells (11).

Some studies also suggest that the symptoms of HGPS may be due to the production of a biologically inactive form of growth hormone, accompanied by an elevated basal metabolic rate. A small study that applied nonaggressive nutritional therapy with growth hormone treatment indicated that this combination improved growth velocity, increased growth factor levels and decreased the basal metabolic rate, although these effects were not maintained and did not prevent the progression of vascular disease (12).

The National Institutes of Health Clinical Center is conducting a clinical investigation into HGPS. This study will examine which body systems are affected in progeria and how each system is affected over time in order to develop new treatments (13).

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Online links

Subscribers to Drugs of the Future can access an online animation to illustrate the underlying genetic cause of HGPS.