Title: Hutchinson-Gilford Progeria Syndromes *GeneReview* Preclinical Studies

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Preclinical Studies in HGPS Cells and Murine Models

The inability to release progerin from the nuclear membrane results in structural stress on the nucleus. Immunofluorescence of HGPS fibroblasts with antibodies directed against lamin A reveals a visible abnormality, an irregular shape of the nuclear envelope, in 40%-50% of cells [Eriksson et al 2003]. It is hypothesized that this permanently farnesylated mutant form of prelamin A (progerin) acts in a dominant-negative fashion and leads to the progressive defects in nuclear architecture that are seen in HGPS [Goldman et al 2004]. Progerin also mislocalizes into insoluble cytoplasmic aggregates and membranes during mitosis, causing abnormal chromosome segregation, binucleation, and a lag in progression out of late mitosis [Cao et al 2007].

Functionally, patient cells exhibit loss of plasticity and increased stiffness [Dahl et al 2010], which may be in part why tissues exposed to mechanical stress (vasculature, bone, joints) are clinically affected. Nuclear function is globally abnormal in patient cells, with widespread alterations of chromatin structure, such as the loss of heterochromatin domains, changes in epigenetic markers maintenance of genomic integrity [Pegoraro et al 2009], DNA repair defects [Musich & Zou 2009, Benson et al 2010], replication fork stalling [Liu et al 2006], and telomere dysfunction [Benson et al 2010, Cao et al 2011].

Broad abnormalities in cellular stress-response pathways involved in HGPS include hyperactivation of p53 signaling [Varela et al 2005, Liu et al 2006, Kudlow et al 2008], decreased numbers of adult stem cells [Espada et al 2008, Scaffidi & Misteli 2008, Rosengardten et al 2011], dysregulation of the somatotrophic axis and several miRNA-controlled circuits [Marino et al 2010, Ugalde et al 2011], and profound changes in glucose and lipid metabolism [Marino et al 2008].

Induced pluripotent stem cells (iPSC) and their potential. Patient-derived iPSC currently provide a unique tool to study HGPS cells and pathways normally unavailable for study, such as mesenchymal stem cells and differentiation pathways of tissues affected by the disease such as vascular smooth muscle cells (VSMCs), adipose tissue and bone [Zhang et al 2011]. In addition, they have been used to develop strategies that can successfully correct the HGPS mutation [Liu et al 2011].

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