Letter

DOI: 10.5582/irdr.2015.01003

# Can Hutchinson-Gilford progeria syndrome be cured in the future?

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**Summary** **Progeria is a rare genetic disease that manifests with progressive symptoms eventually leading to death. The only current treatment protocol of such patients is symptom based. However, recent trials are testing potential and promising drugs to treat the underlying genetic mutation and increase life expectancy of such patients.**

***Keywords:*** Progeria, Cure, farnesyltransferase inhibitors

Progeria or Hutchinson-Gilford progeria syndrome (HGPS) is a very rare and fatal premature genetic disease belonging to the group of progeroid syndromes. Having an incidence of 1 per 8 million live births, the disease manifests with symptoms of accelerated aging among children, eventually leading to death at an early age. HGPS is caused by mutation of the *LMNA* gene that produces farnesylated abnormal Lamin A protein, Progerin. Physiologically, *LMNA* gene encodes for a pre-structural protein prelamin A that provisionally attaches to the nuclear rim on farnesylation with a functional group. Once attached, the farnesyl group is eliminated from prelamin A forming the protein Lamin A which in turn forms the nuclear lamina. However in HGPS, a point mutation of *LMNA* gene causes the fanesyl functional group to become permanently attached to prelamin A preventing further modification to Lamin A. Accumulation of "Progerin" on the nuclear rim disintegrates structural support of nuclear lamina and disorganizes nuclear processes like DNA and RNA synthesis (*1*). No specific treatment is available so far with management aiming only to control complications (especially cardiovascular problems).

Current preclinical studies have revealed quite promising results for farnesyltransferase inhibitors (FTIs) and other potential drugs for treatment of this disease. Initially developed as a target drug for an oncogenic *RAS* gene, FTIs have shown to block the enzyme responsible for the farnesylation step on prelamin A in HGPS children. Although not curing the pathological cause, inhibition of this step averts buildup of Progerin on the nuclear rim preventing further progress of the disease among children (*2*). Frequency of clinical strokes, headaches, and other complications were greatly reduced improving the lifespan of children in a trial (*2*). In another trial, Wang *et al*. demonstrated reversing nucleus abnormalities in HGPS transgenic mice using FTIs or statins (Pravastatin and Zoledronate) by blocking farnesylation. Also, positive outcomes showing reversal of the disease for *in-vivo* cultured cells derived from humans were noted in the study (*3*). Ibrahim *et al*. recent preclinical study has further helped us find another solution for HGPS. By inhibiting isoprenylcysteine methylation (responsible for accumulation of Progerin), normal cellular processes were reported in transgenic mice and human cells (*4*). However, inhibition only prevented further progression of HGPS.

Although there is still no approved drug for treatment of HGPS by the Food and Drug Administration, these trials are offering a glimpse of something big for HGPS treatment in the future. There is a long way to finding a cure but there is no doubt that such outcomes have a massive potential of helping us find one.

Released online in J-STAGE as advance publication April 7, 2015.

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*(Received February 15, 2015; Revised March 8, 2015; Accepted March 30, 2015)*