CIRCULATION: It's never too late to treat progeria

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Scientists from the CNIC and the CIBERCV have generated the first experimental animal model that develops Hutchinson-Gilford Progeria Syndrome and allows its controlled reversal

Scientists at the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) and the Spanish Cardiovascular Research Network (CIBERCV), led by Dr. Vicente Andrés, have generated the **HGPSrev** experimental mouse model. This is the first animal model to develop Hutchinson-Gilford Progeria Syndrome (HGPS) and also allow its suppression through the controlled regulation of the expression of progerin, the aberrant protein that causes the disease. Using the new model, the researchers have demonstrated that it is never too late to treat HGPS.

The study, published today in *Circulation*, also establishes that the cardiovascular alterations and early death associated with HGPS can be prevented with treatments specifically targeting cells of the cardiovascular syste

HGPS is an ultra-rare genetic disease that affects fewer than 400 children worldwide and for which there is no known cure. The disease is caused by a mutation in the *LMNA* gene and is characterized by accelerated aging and death in the second decade of life, principally due to cardiovascular complications derived from atherosclerosis.

In the absence of mutations, ***LMNA* encodes type A lamin proteins** (Lamins A and C). The mutation found in HGPS patients results in the synthesis of progerin, a mutant protein that provokes multiple molecular and cellular alterations in the tissues where it accumulates, causing their life to pass at an highly accelerated rate, where minutes are hours and hours are lost days.

Now, thanks to the *HGPSrev* mouse generated by the CNIC Molecular and Genetic Cardiovascular Pathophysiology group, the research team has managed to suppress progerin expression and reestablish lamin A expression in mice of different ages, both throughout all body tissues and in specific cell types.

The characterization of the animal model was carried out with the participation of researchers at Queen Mary University of London.

Joint first authors **Drs Amanda Sánchez López and Carla Espinós Estévez** explained that while some palliative therapies are effective in animal models and are the subject of clinical trials, their therapeutic benefit is very limited. “A true cure would require the elimination of the culprit mutation,” commented Dr Sánchez López. However, this is not yet possible, and progeria is only diagnosed once the first symptoms have already appeared. “We therefore sought to reverse symptoms once they are already present and to determine how long treatment could be delayed and still have a beneficial impact,” explained Dr Espinós Estévez.

The extent to which the damage caused by progerin can be reversed is currently not known, and patients often do not start to receive treatment until symptoms are quite advanced. The investigators therefore addressed a key question: Can the progression of HGPS be stopped or slowed if treatment commences when the disease is advanced, or does therapeutic benefit depend on starting treatment early, when symptoms are mild?

Another important question is how treatment should be targeted. Progerin is expressed in many tissues, but it was not known if treatment needs to be directed at all affected cells or if it would be effective if targeted at a specific cell type.

To answer these questions, Dr Andrés’s team used CRISPR-Cas9 technology to generate *HGPSrev* mice.

The results published today in *Circulation* show that *HGPSrev* mice develop the major features of the human disease, including growth retardation, lipodystrophy, cardiovascular alterations, and early death.

The investigators also showed that elimination of progerin and restoration of lamin A expression increased life expectancy by 84.5% in *HGPSrev* mice with very mild symptoms and, moreover, extended lifespan by 6.7% even in mice with very advanced symptoms.

These results establish not only that starting treatment when symptoms are mild has a huge positive impact, but also that treatment can be beneficial no matter how late it is started

“We managed to prevent vascular alterations and normalize survival in progeric mice by eliminating progerin expression and restoring lamin A expression specifically in vascular smooth cells and cardiomyocytes, even though other cell types remained diseased,” explained Dr Andrés.

The investigators conclude that these results “could contribute to the design of future clinical treatments, given that they suggest that strategies exclusively targeting the cardiovascular system could have a very significantly beneficial effect on patients’ life quality and expectancy.”

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