

# BDR SEMINAR (Kobe & online hybrid)

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**Tuesday, November 29, 2022**

15:00-15:50

1F Auditorium, DB Building C, Kobe / Broadcast online via Zoom

Zoom meeting URL will be announced on the event day by e-mail.

※Non-BDR members: Please register from the following link.

<https://krs1.riken.jp/m/bdrseminarregistration>

## Determining the molecular mechanism(s) of cellular aging in the premature aging syndrome Hutchinson-Gilford Progeria

### Summary

Hutchinson-Gilford Progeria (HGPS) is a segmental premature aging syndrome caused by aberrant splicing of *LMNA* that results in a truncated and permanently farnesylated form of lamin A, called progerin. HGPS patients exhibit alopecia, impaired growth, lipodystrophy, skin alterations, bone defects and die in their mid-teens as a result of cardiovascular complications. Our goal is to elucidate the molecular mechanism that accelerates aging in progeria and understand its relevance to normal aging.

On a cellular level, progerin expression causes heterochromatin loss, telomeric DNA damage, impaired proliferation and premature senescence, which are prevented by ectopic expression of telomerase, or by modulating the DNA damage response specifically at telomeres. However, the precise mechanism, structural features of the mutant protein and causality of these phenotypes require further investigation.

To address these questions, we generated an inducible expression system to introduce different lamin A mutants into human primary and telomerase-immortalized skin fibroblasts. This system, in conjunction with single-cell immunofluorescence microscopy, enabled us to delineate the temporal chain of events that occurs upon progerin expression across the cell cycle, and ultimately culminates in premature senescence. Moreover, this experimental set up allowed us to determine the precise structural features of progerin required to elicit a disease phenotype. As perturbations of the nuclear lamina are known to occur during chronological aging, these results provide evidence for a mechanistic link between the nuclear envelope, chromatin structure and telomeres that is disrupted in progeria and possibly normal human aging.



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