Internship Proposal

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Project Title:
Rejuvenation effect of FOXM1 gene therapy in progeria

Level:

Master Student

Project Summary:

Hutchinson-Gilford progeria syndrome (HGPS), also known as progeria, is a fatal genetic condition of accelerated aging. Affected children have severe clinical manifestations such as growth impairment, lipodystrophy, dermal and bone abnormalities, alopecia, and cardiovascular alterations which are the leading cause of death.

Previously, our group showed that the transcription factor FOXM1 (Forkhead box M1) is gradually repressed in accelerated and natural aging models, and that induction of a FOXM1 transgene (FOXM1tg) is able to extend the lifespan by 25% in both models. Importantly, an extra copy of FOXM1 was shown to act prophylactically in major progeroid features of the LAKI mice, such as loss of weight and body fat, skeleton abnormalities (e.g. kyphosis) and aortic dysfunction (main cause of death). Moreover, an increased body size was observed upon FOXM1tg induction. This raised the question whether FOXM1 improves the somatotropic axis (growth hormone (Gh)/ insulin-like growth factor 1 (Igf-1) axis), the key endocrine mechanism that regulates organismal growth. We hypothesize that FOXM1-driven transcriptional reprogramming restores the synthesis of IGF-1 in the liver of LAKI mice, which in turn acts to correct insulin resistance and cardiovascular disease (CVD), the main cause of death in HGPS.

Work to be developed by the student:

In this project, to ascertain the effect of FOXM1-driven transcriptional reprogramming in tissue rejuvenation, we will firstly determine if transcriptional and epigenetic signatures of progeroid tissues are reprogrammed towards rejuvenated states. Secondly, since FOXM1tg induction appears to increase body size in progeria mice, we will investigate for the mechanistic link between FOXM1 and GH/IGF-1 somatotropic axis in regulating organismal growth. Finally, we will validate the effect of FOXM1-driven reprogramming and

somatotropic axis reset in the correction of cardiovascular disease, the main cause of death in HGPS.

References:

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