iCase Project / AY 2023 -2024

Characterisation of new cellular pathways reversing cellular ageing

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Department/Institute: Pharmacology

Industrial Partner: Altos Labs Cambridge

Research area: Cellular mechanisms of ageing

Project outline:

We recently carried out the first of its kind, multiparametric "anti-ageing" CRISPR screen that identified 43 genes whose deletion reversed multiple cellular ageing phenotypes.

The hits are significantly enriched for genes in pathways regulating cell homeostasis including proteasome-mediated degradation and protein translation. While deregulation of these pathways has been reported in ageing and in various age-related diseases, how the novel players we identified here restore cellular integrity and homeostasis is completely unknown. This PhD project will therefore investigate the molecular mechanism behind this rescue, initially focusing on the top five hits. This work will explore the mechanisms by which gene depletion or chemical inhibition reverses cellular ageing, using fibroblasts from several healthy aged individuals as well as rejuvenated fibroblasts, evaluating the impact of knocking-out the hits on several ageing readouts. The project will therefore involve the use of CRISPR/Cas9 gene editing, super resolution fluorescence microscopy and biochemical assays to assess markers of nuclear envelope and DNA integrity, chromatin organization and proteostasis.

In addition, through a partnership with Altos Labs in Cambridge, this work will also interrogate the ageing epigenetic clock upon depletion of the hits, through analysis of DNA methylation profiles.

Through this work, we will therefore gain molecular insights into the function of these new anti-ageing genes in the modulation of cellular integrity and homeostasis.

BBSRC DTP main strategic theme: Bioscience for an integrated understanding of health