Pitch Cor Calkhoven - Metabolic regulation of ageing and age-associated pathology through modulation of C/EBP functions

Note: this pitch has already been converted into an ENW-XL preproposal "Metabolic regulation of ageing and age-associated pathology through modulation of C/EBP functions"
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The challenge
Ageing in mammals is a multi-factorial process, wherein health- and lifespan are determined by systemic biological interactions. Insights into the nature and mechanisms of these processes and their interactions is crucial for fundamental understanding of ageing and will provide new concepts for mounting resilience against age-related diseases and frailty. Ageing is malleable and the challenge is to find factors that modulate ageing and can be used to developed strategies to extend health span and delay age-related conditions altogether.

The opportunity
In the past years, we discovered that two closely related transcription factors C/EBPα and C/EBPβ are linked to ageing and lifespan determination in mice (see references). The C/EBPs are widely expressed throughout the body and have pleiotropic functions in the sense that they affect multiple processes of ageing simultaneously. These include, energy metabolism, physical fitness and frailty, immunity and senescence. Altogether, our studies suggest that modulating C/EBP's metabolic functions can be used as an experimental tool as well as it may provide options for therapeutic interference with the ageing processes. However, we know very little about the accompanied changes of the proteome and metabolome, the involved molecular factors and mechanisms, or the role of mitochondrial function or senescence. In addition, its role in human ageing remains poorly understood.

The offer
The hypothesis is that studying C/EBP mediated gene-regulation and its (patho-)physiological consequences will reveal fundamental mechanisms of ageing and lifespan determination and opens up avenues for translational research. I was looking for partners that could help to characterize metabolic and senescence phenotypes, identify involved regulatory factors as well as to determine proteomic and metabolomic changes in mice and humans in a comprehensive yet detailed way that is not possible by our individual labs. The knowledge generated should provide new directions in further research into clinical/pharmacological application in order to improve the life quality of the elderly.

C/EBP-ageing relevant references:

Zidek, L. et al (2015) Deficiency in mTORC1-controlled C/EBPβ-mRNA translation improves metabolic health in mice. EMBO Reports 16, 1022-1036. DOI: 10.15252/embor.201439837

Müller, C., Zidek, L. et al (2018). Reduced expression of C/EBPβ-LIP extends health- and lifespan in mice. eLife 2018;7: e34985 DOI: 10.7554/eLife.34985

Zaini, M.A. et al (2018) A p300 and SIRT1 regulated acetylation switch of C/EBPα controls mitochondrial function. Cell Reports 22, 497-511. DOI: 10.1016/j.celrep.2017.12.061

Niehrs, C. and Calkhoven, C.F. (2020) The emerging role of C/EBPβ and epigenetic DNA methylation in ageing. Trends Genet, 6, 71-80 DOI: 10.1016/j.tig.2019.11.005