Genetic and Metabolic Control of Aging and Healthspan

Johan Auwerx, EPFL, LISP

Abstract/subject proposal:

Aging, defined as the time-dependent general molecular and physiological decline, ultimately leading to death, is a pervasive property of biological systems. By 2050, older people (>60 yrs) are predicted to outnumber young people (<24 yrs) worldwide, posing significant medical and societal challenges, as increased lifespan does not necessarily translate into an increase in healthspan, the duration spent in good health. Prolonging lifespan without improving healthspan causes a rise in age-associated non-communicable diseases (NCDs) and the loss of independence in elderly. Fundamental understanding of the aging process and healthspan—which is distinct from lifespan and more medically actionable—is still lacking. Most healthspan studies in vertebrates have been restricted to animals on a single genetic background, and previous studies in rodent genetic reference populations (GRPs) only measured a limited number of clinical or molecular traits, limiting their ability to model the factors that govern healthspan in humans. Our ERC-funded (AdG-787702) longitudinally-designed healthspan study in a large mouse GRP consisting of ~4000 mice from 82 strains, termed the "Healthspan Diversity Project" (HDP), addresses these pitfalls by incorporating continuous life-long activity monitoring using digital ventilated cages (DVC®), coupled to extensive longitudinal cardiometabolic and neurobehavioral phenotyping in adult (4-8 mo) and aged (16-20 mo) mice, roughly corresponding to 30-40 and 50-70 yrs in humans. In addition, a biobank of more than 100'000 samples from young (2 mo), adult (8 mo) and old (18 and 20 mo) mice enables extensive deep molecular phenotyping. The current application builds on this huge resource by adding a genetic dimension, as well as deep molecular multi-omics phenotypes in 3 cardiometabolic tissues, i.e., liver, kidney, skeletal muscle, at each timepoint. Our plan is structured on achieving the following three specific aims: (1) Defining healthspan metrics and trajectories in mice—derived from life-long monitoring and extensive phenotyping data of the HDP GRP—and in humans—acquired from large cohort studies, such as the UK Biobank; (2) Integrating these healthspan trajectories with multi-tissue, multi-omic data to establish links between genetic variants, multi-tissue deep molecular traits and healthspan; and (3) Mechanistically validating the most important candidate genes/pathways, using LOF studies in human iPSC cells/organoids and mice; and clinically translating promising hits through genetic epidemiology studies in human cohorts. The insight gained from this work will mechanistically refine the molecular features of the aging process and identify the gene networks—from mouse to human—that maintain healthspan. It will as such provide the next step in finding ways of interfering with the aging process and translate them into human therapy.