UNIL | Université de Lausanne
Faculté de biologie et de médecine

Cardiovascular and Metabolism PhD Program

Mini-Symposium

"Model organisms for the study of aging and disease"

Organizer: Alejandro Ocampo, Department of Pharmacology and Toxicology, University of Lausanne

When: 26 April 2019 from 8:30 – 12:30
Where: CHUV Lausanne, main building BH08, Auditorium Tissot

PROGRAM

8:30 – 9:00	Welcome coffee
9:00 - 9:15	**Welcome** **Alejandro Ocampo, Department of Pharmacology and Toxicology, University of Lausanne**
9:15 - 10:00	**Jerome Mertens** (*Neural Aging Laboratory, University of Innsbruck, Austria & Salk Institute San Diego, USA)* **"Direct neuronal reprogramming to study human aging and neurodegeneration"**
10:00 - 10:45	**Collin Ewald** (*Laboratory of Molecular Mechanisms of Healthy Aging, ETH Zurich, Switzerland)* **"Transcriptomic signature of longevity in C. elegans implicates ECM remodeling"**
10:45 – 11:00	Coffee break
11.00 - 11:45	**Ferdinand von Meyenn** (*Laboratory of Nutrition and Metabolic Epigenetics, ETH Zurich, Switzerland)* **"Show me your epigenome and I tell you how old you are!"**
11.45 - 12.30	**Dario Valenzano** (*Laboratory of Evolutionary and Experimental Biology of Ageing, Max Planck Institute Cologne, Germany)* **"African killifishes shed light on lifespan evolution and on the role of the gut microbiota during ageing"**
12.30 – 14.00	Lunch
14:00 – 16:00	**Afternoon workshops for PhD students with symposium speakers**

The mini-symposium will be accredited by the Direction of veterinary affairs and their inspection (DAVI), section Lausanne, as a half day of continuing education.

The meeting is free of charge, but for organization purposes please register by filling the form here prior to April 1, 2019. The UNIL-FBM doctoral school attributes 1.0 ECTS to PhD students who present a signed participation form for the mini-symposium (0.25 ECTS morning session, 0.75 ECTS afternoon session). For additional information, please contact Dr. Ulrike Toepel (Ulrike.toepel@unil.ch)

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Talk abstracts

Jerome Mertens

Neural Aging Laboratory, University of Innsbruck, Austria & Salk Institute San Diego, USA

Direct neuronal reprogramming to study human aging and neurodegeneration

Old age is a major risk factor for many human diseases. Alzheimer's Disease (AD) represents a prime example, as it exclusively affects people at old age. Sporadic AD represents the overwhelming majority of all cases, and familial genetically defined early-onset cases are rare. Still, most research on AD has been performed on genetic causes and their directly related pathways, also because we were in lack of models that can reflect complex human genetics, physiology, and age in an appropriate human neuronal context. While patient-specific iPSC-based models represent an attractive solution, iPSC reprogramming results in cellular rejuvenation and thus yields phenotypically young neurons. By contrast, direct conversion of old patient fibroblasts into induced neurons (iNs) preserves endogenous signatures of aging. To control for the involvement of aging in human neuronal models for AD, we combined both technologies and generated age-equivalent fibroblast-derived iNs, as well as rejuvenated iPSC-derived neurons from a large cohort of AD patients and controls. In addition to their rejuvenated state, we found that iPSC neurons transcriptionally resemble prenatal developmental stages, while iNs reflect adult-like neuronal stages and show little correlation with the prenatal brain. Thus not surprisingly, only age-equivalent adult-like iNs, but not rejuvenated prenatal-like iPSC neurons, revealed strong AD patient-specific signatures. Our iN model further revealed high concordance with previous human post-mortem AD studies, and highlights pathological neuronal de-differentiated as a major phenotype that might underlie many previously observed changes in AD.

Collin Ewald

Laboratory of Molecular Mechanisms of Healthy Aging, ETH Zurich, Switzerland

Transcriptomic signature of longevity in C. elegans implicates ECM remodeling

Aging is the progressive decline of physiological integrity and function of an organism over time ultimately leading to the onset of age-dependent diseases. Longevity interventions, such as caloric restriction and reduced insulin/IGF-1 signaling, slow down the aging process. The nematode *Caenorhabditis elegans* is a key model system to study the role of aging and longevity. In the current literature, there is an abundance of studies describing gene expression changes associated with longevity. However, we currently lack an overall conceptual understanding of how the individual longevity interventions are related. Do longevity interventions share downstream targets or act via distinct mechanisms and are there genes, which consistently accompany longevity?

To answer these questions, we re-analyzed published longevity expression profiles (190 arrays, 130 sequencing runs) to directly compare longevity regulation across studies. We extracted and combined the gene expression changes caused by all known longevity interventions in *C. elegans* to identify the underlying gene expression signatures that might promote healthy aging. By re-analyzing the published datasets with a common pipeline, we are able to correct for variations arising from different laboratory conditions or used strains to extract the changes that are more longevity-specific. The majority of genes we found to be differentially expressed across longevity interventions in *C. elegans* are downregulated during physiological aging. Intriguingly, longevity interventions display a large overlap in their targeted pathways indicating a shared mode of action. To expand the view offered by annotated pathways, we performed a GO term enrichment and identified the extracellular matrix genes as a key target enriched in both aging and longevity. Our comparative approach revealed a more robust network of gene expression changes shared by longevity intervention. These findings can be directly used to generate hypothesis to reveal novel mechanisms that promote healthy aging.

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Ferdinand von Meyenn

Laboratory of Nutrition and Metabolic Epigenetics, ETH Zurich, Switzerland

Show me your epigenome and I tell you how old you are!

DNA methylation changes at a discrete set of sites in the human genome are predictive of chronological and biological age. However, it is not known whether these changes are causative or a consequence of an underlying ageing process. We have generated a comprehensive set of genome-scale base-resolution methylation maps from multiple mouse tissues spanning a wide range of ages which allowed us to develop a multi-tissue predictor of age in the mouse. Our model, which estimates age based on DNA methylation at 329 unique CpG sites, has a median absolute error of 3.33 weeks and has similar properties to the recently described human epigenetic clock. We find that while females and males show no significant differences in predicted DNA methylation age, ovariectomy results in significant age acceleration in females. Furthermore, we identify significant differences in age-acceleration dependent on the lipid content of the diet.

Dario Valenzano

Laboratory of Evolutionary and Experimental Biology of Ageing, Max Planck Institute Cologne, Germany

African killifishes shed light on lifespan evolution and on the role of the gut microbiota during ageing

African killifishes independently evolved annual life cycles at least three times, offering a unique natural experiment of diversification of life history strategies. Using a comprehensive whole-genome sampling of 46 species of African killifishes, we found that genome size correlates with annual life style and with climate. Annual species had genome-wide expansion of transposable elements, higher gene family turn-over rates and relaxed selection in genes in known ageing pathways. Whole-genome resequencing in wild *Nothobranchius* populations showed bottle-necks and a genome-wide signature of relaxation of selection in populations from dryer climates. We found that ecology drove the evolution of short lifespan, associated with the genome-wide accumulation of tens of thousands of slightly deleterious mutations.
The second part of my presentation will present our recent findings on how the gut microbiota plays a causal role in modulating ageing and lifespan and how understanding the interaction between adaptive immune system and the microbiota gives us novel insights into the biology of ageing.

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