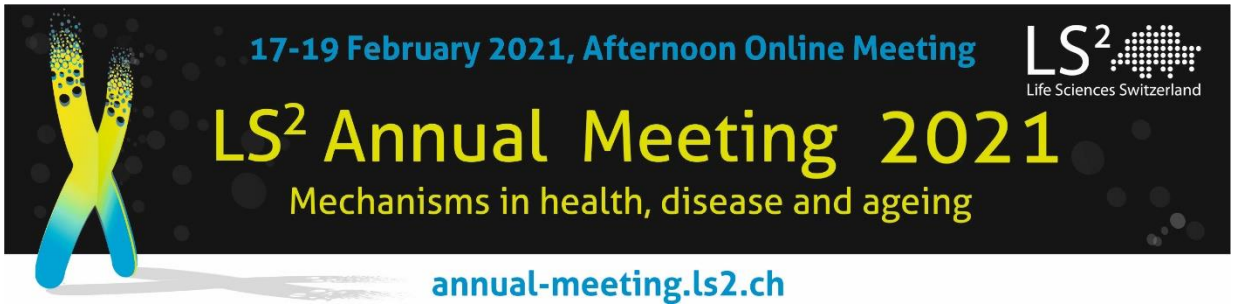

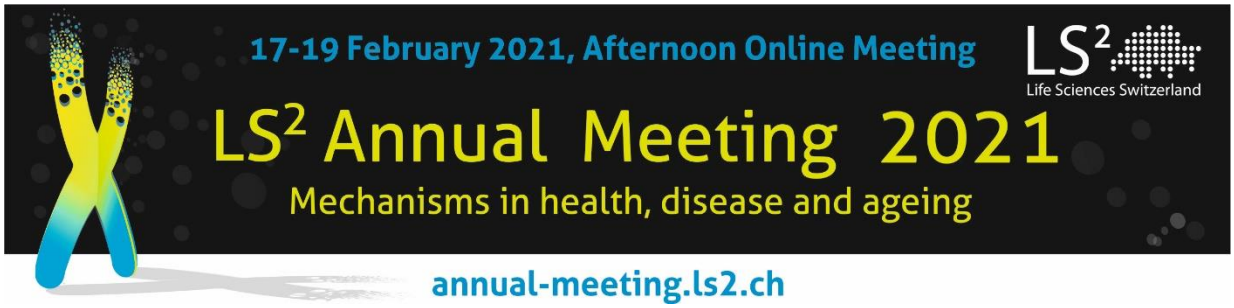

Abstracts of plenary lectures
LS² Annual e-Meeting

Wednesday 17 February 2021

13:10 – 13:50 (CET) Plenary Lecture I

- **Dario VALENZANO**
  Max Planck Institute for Biology of Ageing (DE)

African killifishes shed new light on life history evolution and reveal an important role of the gut microbiota in modulating vertebrate lifespan

Species in nature display a staggering diversity in individual lifespan. From mayfly that live a few hours after hatching, to thousands-year old plants that keep reproducing throughout their life. Lifespan in a given species is limited by external factors, such as predation, infections, starvation, dehydration, etc., as well as by internal factors, including molecular, cellular and tissue damage caused by natural biological processes, such as cell replication and accumulation of aberrant sub-cellular protein aggregates. In my presentation, I will discuss the case of African killifishes, a unique group of fishes that have repeatedly adapted their life cycle to survive in extreme environments, represented by savannah water pools that completely desiccate once a year during the dry season. Among African killifishes, the turquoise killifish (*Nothobranchius furzeri*) is the shortest-lived species, with a lifespan that ranges from four to eight months. I will describe the life cycle of the turquoise killifish and explain what it means for this fish to undergo "aging". In the final part of my talk I will present our recent findings on how the gut microbiota plays a causal role in modulating aging and lifespan and how understanding the interaction between adaptive immune system and the microbiota gives us novel insights into the biology of aging and offers new possibilities for future anti-aging therapeutic interventions.

13:50 – 14:20 (CET) Plenary Lecture II – Prix Schläfli

- **Alice BERHIN - WINNER PRIX SCHLÄFLI 2020**
  Louvain Institute of Biomolecular Science and Technology (Université Catholique de Louvain - BE)

Discovery of the Root Cap Cuticle: Structure and Functions.

During land colonization, plants developed extracellular diffusion barriers, such as cuticle to isolate themselves from the environment. The cuticle is a lipid layer, made of cutin, deposited at the surface of the plant shoot. It prevents the loss of water and nutrients and protect plants against stresses. Plant cuticles have been studied since the 19th century and only characterized in the shoot epidermal cells. A cuticle at the root was not imagined to be compatible with its uptake function. Hence, the specific localization of the cuticle at the epidermis of the aerial organ became a defined feature of the cuticle. However, the intriguing expression of genes involved in cutin biosynthesis at the tip of primary and lateral roots of Arabidopsis has led to the investigation of the cell wall ultrastructure at the root cap cells, the outer cell layer of the root tip.

The root cap cells of young primary roots and lateral roots of Arabidopsis, as well as of other species, are covered by an layer highly similar to the Arabidopsis leaf cuticle. The structure, the composition and the biosynthesis pathway of the root cap cuticle was investigated. The root cap cuticle of young primary and emerging lateral roots plays important roles in root physiology and development such as diffusion barrier protecting the root meristem from toxic compounds and the reduction of organ adhesion causing a delay in lateral root emergence.

Until now, plant cuticles of different aerial organs have been exclusively associated with epidermal tissues of the shoot, our discovery of a cuticle at the root cap now challenges this dogma and adds a new element to our understanding of root anatomy, development, and physiology.

14:20 – 14:50 (CET) Plenary Lecture III – Friedich Miescher Award

- **Andrea ABLASSER**
  EPFL – CH

Sensing DNA as a danger signal through the cGAS-STING pathway

The life of any organism depends on the ability of its cells to recognize and respond to pathogenic microbes. To accomplish this vital task cells rely on intricate signaling pathways that couple sensing of pathogen-associated danger signals to the execution of antimicrobial immune responses. The cGAS-(cGAMP)-STING signaling pathway constitutes a highly conserved innate immune sensing strategy that originated in bacteria to protect from phage infection. In mammals, the pathway detects intracellular DNA to then initiate an antiviral and inflammatory state. It is becoming increasingly apparent that the cGAS-STING pathway plays a critical role in regulating a number of (patho-)physiological processes that fall outside its original function in host defense. As such, activation of this pathway is implicated in

several inflammatory disease states where homeostasis is compromised and out-of-context self DNA accumulates, including autoimmunity, cancer, and neurodegeneration.

In this talk I will present advances in our understanding of the activation and regulation of the cGAS-STING pathway.

- **Prisca LIBERALI**
  Friedich Miescher Institute – CH

Symmetry breaking and self-organization in intestinal organoids

Multicellular organisms are composed of cells and tissues with identical genomes but different properties and functions. They all develop from one cell to form multicellular structures of astounding complexity. During development, in a series of spatio-temporal coordinated steps, cells differentiate into different cell types and establish tissue-scale architectures and functions. Throughout life, continuous tissue renewal and regeneration is required for tissue homeostasis, which also requires fine-tuned spatio-temporal coordination of cells. I will discuss how cellular interactions generate the specific contexts and spatio-temporal coordination underlying development and regeneration and how we specifically investigate what are the molecular and physical mechanisms that allow a cell, in a tissue, to sense its complex environment, to take individual coordinated decisions. Moreover, I will discuss the molecular mechanisms of intestinal organoid self-organization and the role of cell-to-cell variability in populations of differentiating cells during symmetry breaking.

16:50 – 17:20 (CET) Invited speaker at the Young Scientists' Symposium

- **Lars DITTRICH**

Science Communication - but reasonably

The relevance of science communication is underscored by many people's reaction during the current SARS-CoV-2 pandemic, which is why we have invited the professional science communicator Dr. Lars Dittrich to provide junior researchers with the right methods and tool to communicate their science.

How to best explain to one's family and friends, what we are doing in the lab all day? How to react to hostilities against to animal testing? Or how to respond to twitter tirades from corona deniers? Packed with tales and practical recommendations, this keynote lecture will be everything but boring.

Thursday 18 February 2021

17:25 – 18:05 (CET) Plenary Lecture IV

- **Tony WYSS-CORAY**
  Stanford University

Circulatory factors as regulators of aging and brain function

Brain aging leads to cognitive decline and is the main risk factor for sporadic forms of neurodegenerative diseases including Alzheimer's disease. While brain cell- and tissue-intrinsic factors are likely key determinants of the aging process recent studies document a remarkable susceptibility of the brain to circulatory factors. Thus, blood borne factors from young mice or humans are sufficient to slow aspects of brain aging and improve cognitive function in old mice and, vice versa, factors from old mice are detrimental for young mice and impair cognition. In trying to understand the molecular basis of these observations we found evidence that the cerebrovasculature is an important target and that brain endothelial cells show prominent age-related transcriptional changes in response to plasma. We discovered that plasma proteins are taken up broadly into the brain and that this process various between individual endothelial cells and with aging. We are exploring the relevance of these findings for neurodegeneration and potential applications towards therapies.

Friday 19 February 2021

13:00 – 14:50 (CET) PIs of Tomorrow competition

- **Eduardo MARTIN MORAUD**
  Department of Clinical Neurosciences, University Hospital Lausanne

Closing the loop in neuromodulation therapies: towards personalized treatments after neurological disorders

Research statement: Neuromodulation therapies using electrical stimulation have shown impressive results to help alleviate deficits in a variety of neurological disorders. For instance, deep brain stimulation has become a common approach for the symptomatic treatment of Parkinson's disease. Similar solutions exist, and are being optimized, for epilepsy and chronic pain. Despite these advances, current therapies are only tuned manually, solely during in-clinic visits. They then remain unchanged for months -- This lack of adaptability fails to address essential time-related fluctuations affecting the

medical condition of patients, whether fast variations throughout the day, or slow progressions over weeks.

My past and present work focuses on bringing adaptability, automatic control and machine intelligence into neuromodulation protocols, to truly personalize therapies to the ongoing state of each patient.

During my PhD, I pioneered the first closed-loop system to control spinal-cord stimulation after spinal cord injury. This allowed to selectively restore leg movements and improve gait rehabilitation in paralyzed rodents. I helped extend this approach to non-human primates and combined it with brain decoding to devise the first Brain-Spinal Interface. Similar protocols have since then been employed in the framework of a clinical trial at CHUV with highly promising results. I then translated these concepts to deficits of gait and balance in Parkinson's patients, for which current therapies exhibit very modest improvements. By leveraging the latest implantable technologies, which enable to record patients' brain activity chronically and in real-time, I am decoding neural signatures that underlie well-defined impairments, and devising stimulation protocols to prevent them.

My long-term goal is to reinforce this research direction as a well-grounded clinical practice. Neurotechnologies that synergistically leverage recordings and stimulation from various neural structures, simultaneously and in closed-loop, will allow to predict and prevent impairments using feedback of ongoing clinical needs, and have the potential to greatly improve patient's lives.

- **Elisa ARALDI**
  ETH Zürich

Bridging physiology and big data analysis to rediscover cholesterol biosynthesis

Research statement: Genetic inborn errors of cholesterol biosynthesis highlight an intriguing paradigm of biology. Lack of cholesterol itself cannot explain the variety of phenotypic manifestations across these syndromes, and it is speculated that lack or accumulation of cholesterol biosynthetic intermediates (CBIs) are instead the main culprits. Since the knowledge on CBIs is currently scarce, I am proposing to systematically study cholesterol biosynthetic intermediates and their yet undiscovered roles in development, physiology, and disease progression.

During my training I gained a strong expertise in cholesterol biosynthesis, physiology and big data analysis. In my PhD, I demonstrated that lanosterol, the first synthesized sterol, is an important player in innate immune responses in vitro and in vivo (Araldi et al, Cell Reports, 2017). During my postdoctoral training, I used in vivo models and genetic analysis from biobanks to study the role of PAM, a peptidylglycine-amidating monooxygenase, in diabetes onset and progression, and in endocrine disorders (manuscripts in submission).

For my independent research, I will carry out the first systematic study of signaling properties of CBIs and their signaling networks. I propose an approach that combines a novel experimental strategy to discover CBI interacting proteins with an innovative analysis exploiting genomic and phenotypic data from large biobanks. The goal is to infer and validate the relationships between CBIs and their signaling mediators, and to determine the role of individual sterols in relevant pathologies. Ultimately, the

knowledge gained will be translated in genetic in vivo models of CBIs gain or loss, and in relevant murine disease models where CBIs and their mediators can be targeted with drugs.

Identifying the receptors, signaling pathways and functional mechanisms of CBIs might provide novel therapeutic targets both for the devastating and lethal congenital disease driven by inborn errors of cholesterol synthesis, and for other physiological processes mediated through CBI-mediated signaling pathways.

- **Traian POPA**
  EPFL

Non-invasive modulation of deep brain structures in health and disease

Research statement: My overall aim is to develop and implement new non-invasive neuromodulation techniques that can efficiently re-establish the connectivity equilibrium in neuronal networks impaired by neurological disorders.

I have used the movement disorders as a prime field for exploring the subcortico-cortico interactions, and the clinical effects of neuromodulation on these dynamics. I found that the cerebellum is controlling the way in which sensory information is fed into the motor control system, thus remotely tuning the heterosynaptic but not homosynaptic plasticity in other parts of the brain. Starting from this discovery, I deployed cerebellar stimulation in movement disorders and found that abnormal subcortico-cortical interactions can be partially corrected with significant clinical benefit. For example, in essential tremor, one week of inhibitory stimulation could reduce the tremor up to 2 weeks, while in Parkinson's disease, the abnormal cortical plastic response could be corrected after two weeks ofinhibitory stimulation, which was further associated with reduced severity of dyskinetic episodes. In healthy older adults, artificial cerebellar inhibition could boost the impaired cortical plasticity. When applied in combination with a motor sequence learning task, the stimulation of the right but not the left cerebellum was able to bidirectionally influence the learning curve by modulating the same corticosubcortical networks that are used in language production.

I am currently developing in collaboration with colleagues from EPFL and Imperial College London a new technique of direct non-invasive modulation of deep structures, using the temporal interferences of oscillating electrical fields. I plan to further refine this approach and deploy it in cognitive and motor disorders, with a particular focus on cognitive decline associated with Parkinson's disease. I intend to use the previous knowledge of subcortico-cortical interactions to define the targets for the multi-channel temporal interference, to entrain neuronal oscillations towards a normal range.

- **Karina SILINA**
  UZH

Tertiary Lymphoid Structures - Immune Outposts on the Cancer Frontier

Research statement: Studying the literature at the time when little was known about tertiary lymphoid structures (TLS) in cancer led me to hypothesize about the beneficial role of tumour infiltrating B cells

in the context of lymphoid neogenesis – a process that generates TLS. I pursued this idea in my second postdoc. I developed novel TLS analysis approaches and established the concept of TLS maturation and its relevance in improved lung cancer prognosis, highlighted in the recent TLS review (Sautès-Fridman C., et al., 2019, Nat Rev Cancer). In collaboration with clinicians in the Netherlands Cancer Institute, we demonstrated that TLS development in tumours is a significant trait of response to immune checkpoint inhibition. However, my recent unpublished data show that TLS are negative prognosticators in kidney cancer revealing the complexity of tumour-associated TLS biology that is poorly understood.

In my future research, I aim to decipher the mechanisms of TLS development and functions in various tumours and clinical settings. In collaboration with a computational pathology lab, we developed a unique deep learning algorithm HookNet for automated TLS quantification in histology images. This approach will allow me to go beyond the state of the art by analysing TLS in a pan-cancer setting using the vast data of The Cancer Genome Atlas. Here I will determine tumour-intrinsic factors affecting TLS development and its prognostic validation. Next, I will employ spatial transcriptomics, a novel unbiased mRNA quantification approach in tissue sections to unravel the differences of TLS in cancers with opposing prognostic associations (lung and kidney). This will reveal potential protecting or tumourpromoting capacities of TLS. I will use independent patient cohorts and animal models to validate these findings.

The obtained results will contribute to our basic knowledge of tumour immunology as well as reveal potential biomarkers and therapy options for cancer patients.

14:50 – 15:20 (CET) Plenary Lecture V: Lelio Orci Award

- **Jean GRUENBERG**
  University of Geneva - CH

Mechanisms of multivesicular endosome biogenesis

Cell surface proteins, including receptors and their ligands, lipids as well as solutes, are endocytosed from the plasma membrane via several pathways that merge in a common early endosome. From there, some components are recycled back to the plasma membrane, or retrieved and returned to the Golgi. Other components, including downregulated receptors, are sorted into the forming intralumenal vesicles (ILVs) of nascent multivesicular endosomes (MVEs). Once formed, MVEs detach — or mature — from early endosomes, and transport ILVs towards late endosomes and lysosomes, where ILVs are degraded together with their protein cargo. Alternatively, MVEs can also undergo fusion with the plasma membrane and secrete their ILVs into the extracellular medium as exosomes. Some of the mechanisms that drive the biogenesis of ILVs, as well as cargo sorting into ILVs or exosomes will be discussed.

17:50 – 18:30 (CET) Plenary Lecture VI

➢ **Katrien DE BOCK**
ETH Zürich

Metabolic interactions between the endothelium and the muscle

Angiogenesis, the formation of new blood vessels from existing ones, is initiated by the secretion of growth factors – the vascular endothelial growth factor VEGF is the best described one - from a hypoxic environment. To grow under low oxygen conditions, ECs have unique metabolic characteristics. Indeed, even though they are located next to the blood stream - and therefore have access to the highest oxygen levels - ECs are highly glycolytic. However, when they need to sprout into avascular areas and form new vessels, they upregulate glycolysis even further to fuel migration and proliferation. Suppression of glycolysis via inhibition of the glycolytic regulator PFKFB3 (phosphofructokinase-2/fructose-2,6-bisphosphatase isoform 3) in endothelial cells prevents blood vessel growth in the retina of the mouse pup and also in various models of pathological angiogenesis. While we now know that ECs are metabolically preconditioned to rapidly form new vessels, it remains an outstanding question whether this also holds true in muscle and whether endothelial metabolism can become a target for the treatment of peripheral artery disease. The Laboratory of Exercise and Health aims to investigate whether muscle endothelial cells need to reprogram their metabolism to promote optimal muscle angiogenesis. Moreover, we try to understand how muscle and the endothelium communicate to ensure optimal nutrient and oxygen delivery into the muscle.