UNIL | Université de Lausanne
Faculté de biologie et de médecine

Cardiovascular and Metabolism PhD Program

Mini-Symposium

"Stem cell regulation and metabolism"

Organizer: Marlen Knobloch, Department of Physiology, University of Lausanne

When: 21 November 2018 from 8:30 – 12:30
Where: CHUV Lausanne, main building BH08, Auditorium Mayor

PROGRAM

8:30 – 9:00	**Welcome coffee**
9:00 - 9:15	**Marlen Knobloch (Department of Physiology, University of Lausanne)** *Welcome*
9:15 - 10:00	**Clifford D. Folmes (Stem Cell and Regenerative Metabolism Laboratory, Mayo Clinic, Scottsdale, Arizona, U.S.A.)** *Metabolic Reprogramming and Stem Cell Fate*
10:00 - 10:45	**Alessandro Prigione (Max-Delbrück-Center for Molecular Medicine of the Helmholtz Society, Berlin, Germany)** *Stem cell metabolism and mitochondrial disease modelling*
10:45 – 11:00	**Coffee break**
11.00 - 11:45	**Marieke Essers (German Cancer Research Center (DKFZ), Heidelberg & HI-STEM - Heidelberg Institute for Stem Cell Technologies and Experimental Medicine gGmbH, Germany)** *Hematopoietic stem cells and their niche under inflammatory stress*
11.45 - 12.30	**Olaia Naveiras (Laboratory of Regenerative Hematopoiesis, ISREC & Institute of Bioengineering; Ecole Polytechnique Fédérale de Lausanne)** *Bone Marrow Adiposity: an emerging tissue with metabolic and regulatory functions*
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 November 10, 2018. A maximum of 120 participants can be accommodated.

The UNIL-FBM doctoral school attributes 1.0 ECTS for PhD students who present a signed participation form for the mini-symposium (0.25 ECTS morning session, 0.75 ECTS afternoon session). Workshop registration closes on October 30, 2018.

For additional information, please contact Dr. Ulrike Toepel (Ulrike.toepel@unil.ch)

Co-organized by UNIL | Université de Lausanne Faculté de biologie et de médecine CHUV

Talk abstracts

Clifford D. Folmes
Stem Cell and Regenerative Metabolism Laboratory, Mayo Clinic, Scottsdale, Arizona, U.S.A.

Metabolic Reprogramming and Stem Cell Fate

Energy metabolism is traditionally considered a reactive homeostatic system that prioritizes specific pathways to match stage-specific cellular energy demands. There is, however, growing appreciation of metabolic pathways in the active control of vital cell functions. Case in point, the stem cell lifecycle – from maintenance and acquisition of stemness to lineage commitment and specification – is increasingly recognized as a metabolism-dependent process. Specifically, we have demonstrated that nuclear reprogramming of somatic cells for the generation of induced pluripotent stem cells (iPSCs) requires remodeling of the metaboproteome and mitochondrial infrastructure in support of a metabolic switch from oxidative metabolism to glycolysis. This metabolic transition is an early contributor to the orchestrated reacquisition of stemness and represents a critical determinant of the efficiency of pluripotent induction. We have also applied nuclear reprogramming and somatic cell nuclear transfer to generate stem cells from patients with both heteroplasmic and homoplasmic mutations in their mitochondrial DNA. These complementary reprogramming strategies have enabled us to generate isogenic iPSC clones with and without the disease-causing mutation and subsequent metabolic impairment, offering a new resource for disease modeling, compound screening and regenerative applications. Convergence of metabolic reprogramming with regulation of stem cell fate thus opens a new avenue to understand developmental biology and the impact of aging and disease on stem cell function. Ultimately, this knowledge will lead to metabolism-based regenerative medicine strategies to enhance stem cell-based repair, improve innate tissue regenerative capacity and delay aging-associated degeneration.

Alessandro Prigione
Max-Delbrück-Center for Molecular Medicine of the Helmholtz Society, Berlin, Germany

Stem cell metabolism and mitochondrial disease modelling

In the first part of the lecture, I will discuss the role of mitochondrial metabolism for pluripotency and the establishment of neural fate.
Modulation of energy metabolism is emerging as a key aspect associated with cell fate transition. Given their dynamic and multifaceted role in energy metabolism, redox and calcium balance, as well as cell death, mitochondria appear at the interface between environmental cues and epigenetic control of cellular identity. The programming of a correct metabolic program is particularly relevant for neuronal cells given their high bioenergetic requirements. We show that mitochondrial

metabolism is relevant not only for fully differentiated neurons but also for proliferative neural precursors. The data suggest targeting neurogenesis as a strategy for improving neurological diseases with mitochondrial impairment.

In the second part of the lecture, I will present our efforts in using iPSCs for discovering novel treatment strategies for rare mitochondrial diseases.
A major hurdle for the study of mitochondrial diseases is the paucity of mechanistic model systems. Mitochondrial DNA (mtDNA) mutations cannot be easily modeled due to challenges of engineering mtDNA. Mutations in nuclear encoded genes are also not always recapitulated in animals. We focus primarily on Leigh syndrome, which is the most frequent and severe neurological condition affecting 1/40,000 newborns. We show that neural cells differentiated from Leigh syndrome iPSCs can be used as a model system to study the disease and carry out phenotypic compound screenings. Our data pave the way to the identification of disease-modifying therapies for currently incurable mitochondrial disorders.

Marieke Essers
German Cancer Research Center (DKFZ), Heidelberg & HI-STEM - Heidelberg
Institute for Stem Cell Technologies and Experimental Medicine gGmbH, Germany

Hematopoietic stem cells and their niche under inflammatory stress

Infections are associated with extensive consumption of differentiated hematopoietic cells, representing a high risk for health. However, the mechanism coordinating the rapid and efficient regeneration of these differentiated cells during such stress conditions remains unclear. Recently, we have reported that the phenotypic hematopoietic stem cell (HSC) compartment contains stem-like megakaryocyte-committed progenitors (SL-MkPs), a cell population that shares many features with multipotent HSCs and serves as a lineage-restricted emergency pool for inflammatory insults. This study revealed an elegant emergency machinery that counteracts life-threatening platelet depletions during acute inflammation. Furthermore, these data indicated heterogeneity within the phenotypic HSC pool regarding lineage commitment. By quantitatively integrating flow cytometric, transcriptomic and functional lineage fate data at the single-cell level we confirmed this heterogeneity and the presence of Mk primed progenitor cells in the phenotypic human HSC pool. Furthermore, our data suggest that HSC lineage commitment occurs in a gradual manner best described by a continuous Waddington landscape with initially flat but progressively deepening valleys. Our data determine a detailed model of developmental trajectories within this landscape, as well as their underlying gene expression modules and biological processes. In addition to identifying how HSCs respond under inflammatory conditions, we also investigate the response of the BM niche to inflammatory stress and how different components of the BM niche support the response of quiescent HSCs to inflammatory stress *in vivo*.

Olaia Naveiras
Laboratory of Regenerative Hematopoiesis, ISREC & Institute of Bioengineering
Ecole Polytechnique Fédérale de Lausanne

Bone Marrow Adiposity: an emerging tissue with metabolic and regulatory functions

The epidemic of diabetes and obesity has motivated very significant advances in the understanding of adipocyte regulation, the cellular complexity of the adipose tissue, and the plasticity of subcutaneous and retroperitoneal white and brown adipose depots.
Less attention has been paid to bone marrow adiposity (BMA), which in humans constitutes on average 1.3 kg of adipose tissue and 8% of the total fat mass, ranging from 1-30% depending on age and pathophysiological condition. Indeed, BMA increases with age, glucocorticoid treatment, obesity, cold exposure and upon moderate caloric restriction. Bone marrow adipocytes contribute to circulating adiponectin and are thought to play a role in skeletal muscle adaptation upon caloric restriction. Thus, BMA is now thought of as an endocrine organ on its own right.
Being the main production site for blood cells in mammals, the bone marrow harbors an intricate crosstalk between bone-forming cells, specialized sinusoidal vasculature, hematopoietic cells and bone marrow adipocytes. Although an increase in bone marrow adipocytes has been long associated with osteoporosis and constitutes the hallmark of hematopoietic failure syndromes, the causal relationship and molecular mechanisms for such negative association have been elusive.
In 2009 we determined a net negative effect of bone marrow adipocytes in hematopoiesis both in homeostasis (mostly reflecting the effect of constitutive BMA) and upon stress hematopoiesis following irradiation-mediated aplasia (mostly reflecting the effect of regulated BMA). Others have since validated the potent effect of PPARg inhibitors in accelerating hematopoietic recovery. Recent data indicating that preadipocytes support hematopoiesis while fully mature adipocytes inhibit rapid HSC proliferation will be discussed.