UNIL | Université de Lausanne
Faculté de biologie et de médecine

Cardiovascular and Metabolism PhD Program

Mini-Symposium

"Extracellular Matrix Alterations in Cardiovascular Diseases"

Organizer: Nathalie Rosenblatt-Velin, Clinical Physiopathology, Angiology Service, CHUV Lausanne and University of Lausanne (UNIL)

When: 25 April 2024 from 9:00 – 13:00
Where: Grand Auditoire, DNF Building, Rue Bugnon 9, Lausanne

8:30 – 9:00	**COFFEE & CROISSANTS**
9:00 - 9:15	**WELCOME** NATHALIE ROSENBLATT-VELIN, CHUV-UNIL & CO-DIRECTOR OF THE CVM PHD PROGRAM
9:15 - 10:00	**CELLULAR AND MOLECULAR MECHANISMS OF CARDIAC FIBROSIS** NIKOLAOS G FRANGOGIANNIS, ALBERT EINSTEIN COLLEGE OF MEDICINE, NEW YORK, U.S.A.
10:00 - 10:45	**CARDIAC REMODELING AND FIBROSIS IN HEART FAILURE: FROM MOLECULAR MECHANISMS TO THERAPEUTICS** ROSALINDA MADONNA, DEPARTMENT OF SURGICAL, MEDICAL, MOLECULAR AND CRITICAL AREA PATHOLOGY, UNIVERSITY OF PISA, ITALY.
10:45 – 11:15	**COFFEE BREAK**
11.15 - 12:00	**DIRECT 3D-BIOPRINTNG OF HIPSC-DERIVED CARDIOMYOCYTES TO GENERATE FUNCTONAL CARDIAC TISSUES.** FELIX ENGEL, EXPERIMENTAL RENAL AND CARDIOVASCULAR RESEARCH, UNIVERSITY OF ERLANGEN-NUREMBERG, GERMANY.
12:00- 12.45	**BIOFABRICATION OF 3D VASCULARIZED ORGAN-SPECIFIC MODELS FOR THE STUDY OF HUMAN PHYSIOLOGY AND DISEASE** SIMONE BERSINI, FACULTY OF BIOMEDICAL SCIENCES OF UNIVERSITÀ DELLA SVIZZERA ITALIANA (USI), SWITZERLAND.
14:00 – 16:00	**AFTERNOON WORKSHOPS FOR DOCTORAL CANDIDATES WITH SYMPOSIUM SPEAKERS**

The event will be submitted to 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 HERE** prior to April 10, 2024. 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 questions, 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

Cellular and molecular mechanisms of cardiac fibrosis

Nikolaos G Frangogiannis, MD. Albert Einstein College of Medicine, Bronx NY. USA

Fibrosis, the expansion of the interstitium through deposition of extracellular matrix proteins, is a common pathophysiologic companion of most myocardial diseases and can be reparative or maladaptive. Cardiac fibroblasts are the main cellular effectors of fibrosis and are responsible for the production of structural matrix proteins. Fibroblast populations are characterized by heterogeneity and remarkable phenotypic plasticity, exhibiting marked alterations in phenotype and function, in response to soluble bioactive mediators, metabolic overload, or mechanical stimuli. Several other cell types, including macrophages, endothelial cells, pericytes, macrophages, lymphocytes, platelets and cardiomyocytes may contribute to fibrotic remodeling of the heart by secreting fibroblast-activating growth factors and matricellular proteins, or by regulating matrix metabolism. Cytokines and growth factors play a central role in activation of fibrogenic signaling. This presentation will discuss the cellular basis and molecular mechanisms of fibroblast expansion and activation following cardiac injury in both reparative and maladaptive fibrotic responses. Evidence supporting the functional diversity and heterogeneity of cardiac fibroblasts will be presented. Recent and ongoing studies investigating the role of pericytes in reparative and maladaptive cardiac fibrosis will be discussed. The central role of the TGF-beta cascades will be highlighted. Understanding the pathogenesis of cardiac fibrosis is important to design therapies for patients with heart failure.

Cardiac Remodeling and Fibrosis in Heart Failure: From Molecular Mechanisms to Therapeutics

Rosalinda Madonna, Department of Surgical, Medical, Molecular and Critical Area Pathology, University of Pisa, Italy.

Abstract to follow

Direct 3D-Bioprinting of hiPSC-Derived Cardiomyocytes to Generate Functional Cardiac Tissues

Felix Engel, Experimental Renal and Cardiovascular Research, University of Erlangen-Nuremberg, Germany.

3D-bioprinting is a promising technology to produce human tissues as drug screening tool or for organ repair. However, direct printing of living cells has proven difficult. Here, a method is presented to directly 3D-bioprint human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes embedded in a collagen-hyaluronic acid ink, generating centimeter-sized functional ring- and ventricle-shaped cardiac tissues in an accurate and reproducible manner. The printed tissues contain hiPSC-derived cardiomyocytes with well-organized sarcomeres and exhibit spontaneous and regular contractions, which persist for several months and are able to contract against passive resistance. Importantly, beating frequencies of the printed cardiac tissues can be modulated by pharmacological stimulation. This approach opens up new possibilities for generating complex functional cardiac tissues as models for advanced drug screening or as tissue grafts for organ repair or replacement. However, there is a long way to go to achieve a reasonable pump function. Current issues and possible approaches for improvement are presented.

Biofabrication of 3D vascularized organ-specific models for the study of human physiology and disease

Simone Bersini, Faculty of Biomedical Sciences of Università Della Svizzera Italiana (Usi), Switzerland.

Biofabrication is an emerging research field aimed at recapitulating in vitro the architecture and functionality of basic tissue units of the human body. A key aspect of biofabrication is the combination of 3D tissue models with microfabrication technologies and tools (e.g. 3D printing, soft lithography, microfluidics) that allow to create spatially confined microenvironments (e.g. an interface between vasculature and a tissue-niche), apply electro-mechanical stimulations promoting tissue maturation (e.g. compression, shear) and live track the dynamic interactions among different cell types.
The design of biofabricated models of human tissues allows to complement currently available pre-clinical assays and partially overcome their limitations, including the limited complexity of 2D cultures and the low-throughput of animal experiments.
Starting from the lab expertise in biofabrication of human microvascular networks, here we will discuss specific examples of 3D models for the study of:
1) Basic mechanisms of cancer cell dissemination through blood vessels. Organ-specific models of bone and skeletal muscle microenvironment were developed to study the interaction between endothelial cells (ECs) and circulating tumor and immune cells, with the goal to analyze the process of extravasation and colonization of the tissue. We observed that

cell extravasation was affected by the properties of the endothelium and by secreted factors of the surrounding microenvironment.
2) Key biological processes and potential targets involved in vascular aging in physiology and disease. We designed a multi-analytical strategy combining organs-on-a-chip, gene expression and secretome analyses to identify an aging signature of ECs and mural cells. To validate our approach, we developed a 3D human microenvironment of the skin vasculature containing dermal ECs and fibroblasts, and a model of human blood-brain-barrier embedding brain-specific ECs, pericytes and astrocytes. We found that it was possible to partially rejuvenate old and compromised vasculatures by modulating the local microenvironment and we identified candidate biomarkers of vascular aging that were validated in human tissue biopsies.
Overall, we will discuss biofabricated microscale models that allowed to mimic specific features of cancer dissemination and aging, highlighting the key role played by the vasculature. These models are compatible with proteomics, flow cytometry and gene expression analyses, hence allowing to monitor the dynamic evolution of the system when challenged with cellular, biochemical and biophysical stimuli.