UNIL | Université de Lausanne
Faculté de biologie et de médecine

Cardiovascular and Metabolism PhD Program

Mini-Symposium

"Genetics of Cardiac Diseases"

Organizer: Dr. M. Z. A. Bhuiyan

When: 06 October 2017 from 8:30 – 12:30h

Where: Auditorium Auguste Tissot, CHUV main building, floor 8

PROGRAM

8:30 – 9:00	Welcome coffee
9:00-9:15	**Welcome:** M. Z. A. Bhuiyan, Directeur du laboratoire de diagnostic moléculaire, Service de Médicine Génétique, CHUV
9:15 -10:00	**Peter J. Mohler** (Department of Physiology and Cell Biology, University of Ohio College of Medicine, Columbus, Ohio, USA): **Defining new mechanisms underlying cardiovascular disease**
10:00-10:45	**Elijah Behr** (St George's University of London, London, U.K.): **The Genetics of Sudden Death**
10:45 – 11:00	Coffee Break
11.00-11:45	**Bianca Brundel** (Department of Physiology, Free University of Amsterdam, Netherlands): **Role of gene mutations in derailment of cardiomyocyte proteostasis: role in Atrial Fibrillation?**
11.45-12.30	**Hugues Abriel** (Institute of Biochemistry and Molecular Medicine, University of Bern, Switzerland): **Roles of the cationic calcium-activated channel TRPM4 in cardiac genetic disorders**
12.30 – 14.00	Lunch
14:00 – 16:00	**Afternoon workshops for PhD students with symposium speakers**

This mini-symposium will be accredited by the Association of Cantonal Veterinarians (SCAV), 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 September 15, 2017. The maximal number of participants is limited to 120.
The UNIL 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).
For additional information, please contact Dr. Ulrike Toepel or Dr. Marta Bellone at lnds@unil.ch.

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

Talk abstracts

Peter J. Mohler (Department of Physiology and Cell Biology, University of Ohio College of Medicine, Columbus, Ohio, USA)
Defining new mechanisms underlying cardiovascular disease

Our research is focused on the mechanisms underlying the targeting and regulation of membrane-associated (ion channels, transporters, receptors) and signaling proteins in cardiac and other excitable cells. In particular, we are interested in the role of membrane-associated ankyrin and spectrin family of polypeptides in the targeting and function of ion channels and transporters as well as kinases and phosphatases. A primary focus of the lab is the role of the ankyrin-G-based pathway for targeting voltage gated sodium channels to the intercalated disc of cardiomyocytes. We have discovered a direct requirement of ankyrin-G for Na channel targeting and have linked human Na channel arrhythmia mutations with loss of ankyrin-G binding, and Na channel targeting resulting in defects in Na channel function and myocyte excitability. A second line of work in the lab establishes that loss-of-function mutation in ankyrin-B is the basis for a human cardiac arrhythmia syndrome associated with sinus node dysfunction, repolarization defects, and polymorphic tachyarrhythmia in response to stress and/or exercise ("ankyrin-B syndrome"). Additionally, our work revealed that reduction of ankyrin-B in mice results in reduced levels and abnormal localization of Na/Ca exchanger, Na/K ATPase, and InsP3 receptor at T-tubule/SR sites in cardiomyocytes and leads to altered Ca2+ signaling and extrasystoles that provide a rationale for the arrhythmia. These studies establish a physiological requirement for ankyrins and spectrins in localization of a variety of ion channels in excitable membranes in the heart and demonstrate a new class of functional 'channelopathies' due to abnormal cellular localization of functionally-related ion channels and transporters. More recently, we have developed a third line of research in the lab focused on the molecular mechanisms underlying kinase and phosphatase targeting in excitable cardiomyocytes. Specifically, work from our lab has shown the importance of CaMKII and PP2A targeting for myocyte and cardiac function.

Elijah Behr (St George's University of London, London, U.K.)
The Genetics of Sudden Death

The lecture will review prior approaches to investigating the genetic risk for sudden death in general and then will focus on unexplained sudden death (SADS), monogenic disorders and drug-induced arrhythmia. The importance of rare and common genetic variation will be further explored in this context. Views on future trends in research will also be discussed.

Bianca Brundel (Department of Physiology, Free University of Amsterdam, Netherlands)
Role of gene mutations in derailment of cardiomyocyte proteostasis: role in Atrial Fibrillation?

The most common clinical tachyarrhythmia atrial fibrillation (AF) is present in 1-2% of the population. Although common risk factors, including hypertension, diabetes and obesity, frequently underlie AF onset, it has been recognized that in 10-20% of the AF population, AF

can be familial. In some instances, the number of pedigrees with AF at young age are large and its pattern of inheritance is highly suggestive for a monogenic -autosomal dominant- mode of inheritance. According to the HRS/EHRA expert consensus statement on genetic testing for channelopathies and cardiomyopathies, there is no indication for diagnostic genetic screening in AF patients/families, even though some genes have been identified underlying familial AF, such as mutated genes encoding potassium channels and their subunits. Interestingly, AF families have been identified bearing a mutation in the genes encoding intermediate filament proteins desmin (DES), lamin AC (LMNA), or Titin which have a strong association with the development of cardiomyopathy. In several of these families, AF represented the initial manifestation of disease, sometimes even preceding cardiomyopathy by several years. Over 50% of patients with LMNA of Titin mutations have AF, while it is the most prevalent arrhythmia in DES mutation carriers (>30% of reported arrhythmias).

Accumulating evidence indicate that mutations in intermediate filament proteins challenge protein homeostasis (proteostasis), by inducing degradation of sarcomeres by proteasomal degradation and autophagy, which are both associated with AF onset and progression. Intermediate filament proteins integrate sarcolemma, Z-disk and nuclear membrane and thereby regulate sarcomere architecture and function. Intermediate protein expression, transport and, ultimately, breakdown is monitored and supported by various classes of proteins, collectively called 'protein quality control' (PQC). A balanced intermediate filament proteostasis thus depends on proper PQC and is crucial for cardiac function. In case of a mutation in the intermediate filament proteins, a gradual accumulation of misfolded or damaged proteins with concomitant failure of PQC may result in proteotoxic stress and cardiac disease onset, including AF. Detailed knowledge on the role how intermediate filament proteins mutations derail proteostasis is important to develop novel therapeutic strategies to prevent AF and cardiomyopathy development.

Hugues Abriel (Institute of Biochemistry and Molecular Medicine, University of Bern, Switzerland)

Roles of the cationic calcium-activated channel TRPM4 in cardiac genetic disorders

The calcium-activated cationic channel TRPM4 (transient receptor potential melastatin 4) is predominantly expressed in cells of the cardiovascular, nervous and immune system, pancreas and kidney. TRPM4 is involved in many calcium-dependent cellular processes, such as control of excitable cell activity, insulin secretion or mast cells degranulation. More than 20 genetic variants in the human gene of TRPM4 were recently linked to conduction disorders leading to cardiac arrhythmias in patients. In this presentation, I will present the most recent genetic findings suggesting a key role of TRPM4 in cardiac conduction and diseases. Molecular and functional data addressing the question of the mutation-induced alterations of TRPM4 will be presented.