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

New program updated since one speaker had to cancel his participation to the symposium

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	**M. Z. A. Bhuiyan** (Directeur du laboratoire de diagnostic moléculaire, Service de Médicine Génétique, CHUV): ***Malignant Arrhythmias linked to Fatty Acid Oxidation Pathway***
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

M. Z. A. Bhuiyan (Directeur du laboratoire de diagnostic moléculaire, Service de Médicine Génétique, CHUV)

Malignant Arrhythmias linked to Fatty Acid Oxidation Pathway

Primary cardiac arrhythmias are rare, hereditary disorders caused predominantly by defects in the cardiac ion channel encoding-genes or their ancillary proteins encoding-genes.
Heart secures 70-80% of its energy, ATP, through fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) in the mitochondria. Deficiency of the FAO enzymes could lead to debilitating cardiac arrhythmias and sudden cardiac deaths, usually with accompanying extra-cardiac phenotypes e.g. steatosis and hepatomegaly. Interestingly, dysregulation in FAO-OXPHOS enzymes are also reported in common cardiac diseases e.g. in ischemia and heart failure patients.
We have reported a new type of malignant cardiac arrhythmia (CPVT3, OMIM # 614021) due to mutations in TECRL, a putative cardiac gene in the FAO-OXPHOS pathway. Our patients did not have any extra-cardiac manifestations (OMIM # 614021). We postulate that a significant number of cardiac arrhythmias in children and young adults, especially in the Middle Eastern countries are due to defects involving the genes in FAO-OXPHOS pathway, which is the present focus of our research.

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.