Seminar:
“Abnormalities in Sodium Current and Calcium Homeostasis as Drivers of Arrhythmogenesis in Hypertrophic Cardiomyopathy”

Abstract:
Hypertrophic cardiomyopathy (HCM) is a common inherited monogenic disease with a prevalence of 1/500 in the general population, representing an important cause of arrhythmic sudden cardiac death (SCD), heart failure, and atrial fibrillation in the young. HCM is a global condition, diagnosed in more than 50 countries and in all continents, HCM affects people of both sexes and various ethnic and racial origins, with similar clinical course and phenotypic expression.

The most unpredictable and devastating consequence of HCM is represented by arrhythmic SCD, most commonly caused by sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). Indeed, HCM represents one of the main causes of arrhythmic SCD in the young, with a marked preference for children and adults <30 years. SCD is most prevalent in patients with pediatric onset of HCM, but may occur at any age. However, risk is substantially lower after 60 years, suggesting that the potential for ventricular tachyarrhythmias is mitigated by ageing. SCD had been linked originally to sports and vigorous activity in HCM patients. However, it is increasingly clear that the majority of events occur at rest or during routine daily occupations, suggesting that triggers are far from consistent. In general, the pathophysiology of SCD in HCM remains unresolved. While the pathologic and physiologic substrates abound and have been described in detail, specific factors precipitating ventricular tachyarrhythmias are still unknown. SCD is a rare phenomenon in HCM cohorts (<1%/year) and attempts to identify patients at risk, while generating clinically useful algorithms for primary prevention, remain very inaccurate on an individual basis. One of the reasons for our limited understanding of these phenomena is that limited translational research exists in the field, while most efforts have focused on clinical markers of risk derived from pathology, instrumental patient evaluation and imaging.

Specifically, few studies have focused targeting the cellular mechanisms of arrhythmogenesis in HCM, despite potential implications for therapeutic innovation and SCD prevention. As an array of novel experimental opportunities have emerged to investigate these mechanisms, including novel “disease-in-the-dish” cellular models with patient-specific induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs), important gaps in knowledge remain. In this seminar, I will try to provide a contemporary reappraisal of the cellular basis of SCD-predisposing arrhythmias in patients with HCM and discuss the implications for risk stratification and management.