UniversitätsKlinikum Heidelberg

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External Seminar Speaker

Prof. Dr. Donald M. Bers, Ph.D.
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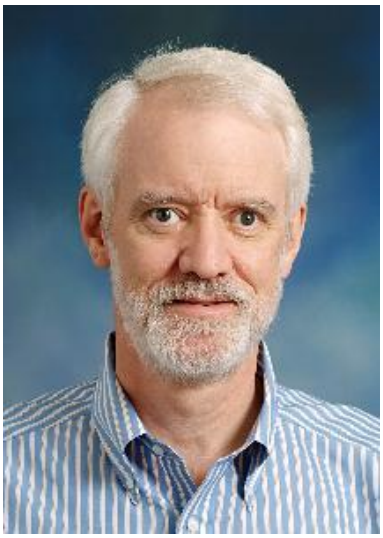

Place: **Analysezentrum 3, 2. OG, Room 02.332**
Date: **Thursday, 19.04.2018**
Time: **12.00 am**

Cardiac Calcium and Calmodulin signaling in Arrhythmias and Heart Failure

Ca is essential in cardiac electrophysiology, contraction, energetics and nuclear transcription. Calmodulin (CaM) and Ca/CaM-dependent protein kinase (CaMKII) are also important mediators of Ca signaling in myocytes. CaMKII can phosphorylate and modulate function of Na, Ca and K channels, ryanodine receptor (RyR) and IP3 receptor channels, the phospholamban-SERCA complex and myofilaments. Some of these pathways may contribute to decreased cardiac function and enhanced propensity for arrhythmias in hypertrophy and heart failure (HF). Since CaMKII expression and activation state is increased in HF, these pathways may be important in contributing to the development and consequences of HF and may represent important therapeutic targets. CaMKII effects on cardiac Na channels and RyRs may be particularly important in HF and arrhythmias, and these acquired CaMKII-dependent effects can recapitulate genetic mutations in these channels that are associated with long QT (LQT), Brugada syndromes and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). In particular CaMKII can phosphorylate NaV1.5 and cause both enhanced late I_{Na} (as observed in LQT3) and also loss of Na channel availability (as observed in NaV1.5 mutants linked to Brugada and short QT syndromes) which the outcome dependent on heart rate. RyR phosphorylation by CaMKII increases diastolic sarcoplasmic reticulum (SR) Ca leak (as occurs in CPVT-linked mutations in Ryr2, calsequestrin 2 and CaM). This altered RyR gating can lead to increase delayed afterdepolarizations (DADs) and serve as a source of triggered arrhythmias as well as cause reduced SR Ca content available for release in HF myocytes. Thus, CaMKII activation in HF and arrhythmogenic conditions can mediate acquired forms of cardiac arrhythmias and contractile dysfunction in pathologic conditions. We have used FRET-

based methods to identify fundamental changes in RyR conformation associated with pathological arrhythmogenic SR Ca leak, and this involves a loss in CaM affinity for the RyR. Dantrolene and increased CaM concentration can shift this conformational state back to normal and suppress diastolic SR Ca leak and arrhythmias. This raises the possibility of a novel RyR-related therapeutic strategy, namely new molecules that, like dantrolene, can shift the RyR conformational state from pathophysiological to physiological.

Host: **Prof. Dr. med. Johannes Backs**
Director of the Department Molecular Cardiology and Epigenetics
Department of Internal Medicine VIII
University of Heidelberg