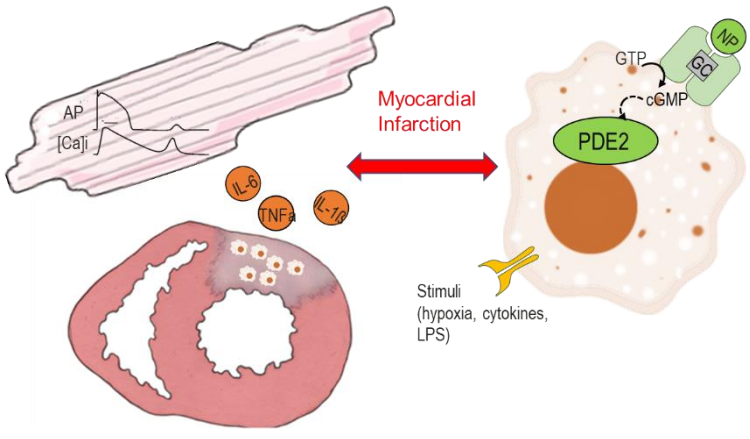
Project: Ali El-Armouche, Susanne Kämmerer **Institute of Pharmacology and Toxicology**

Impact of Natriuretic peptides on Inflammatory Immune Cell Responses Early After Myocardial Infarction

Myocardial infarction (MI) remains a leading cause of death in patients with cardio-metabolic diseases. The acute ischemia/reperfusion (IR) injury during MI results in the decline of myocardial contractility, which further lead to complex humoral and inflammatory responses.
The cardiac inflammation is mediated by recruited monocytes to the infarcted zone that differentiate into macrophages. After exposure to IR injury environment, macrophages assume a pro-inflammatory M1 polarization and secrete multiple cytokines (IL-1β, IL-6, TNF-α) and matrix metalloproteins (MMPs). Macrophages and macrophage-related cytokines were shown to promote the development of arrhythmia via elevating the sympathetic tone, ion channel remodeling and scar formation.
The neurohormonal activation comprises three major components: (i) The sympathetic nervous system and (ii) the renin-angiotensin-aldosterone pathway initially compensate the reduced cardiac function but have ultimately maladaptive consequences promoting cardiac remodeling with hypertrophy, fibrosis and arrhythmia. (iii) In addition, the counteracting system of natriuretic peptides (NP) is activated during MI mediating important pleiotropic natriuretic, vasodilatatory as well as anti-hypertrophic and anti-fibrotic effects. Notably, ANP, BNP and CNP were also shown to exhibit anti-inflammatory and immune-modulatory actions. Thus, NP inhibit cytokine secretion from monocytes and macrophages. The underlying cellular mechanisms of NP-mediated effects in monocytes and macrophages are not known.
NP exert their functions via cGMP-generating guanylyl cyclase NP receptors (NPR). Recently, we have shown that the phosphodiesterase 2 (PDE2) contributes to mediate intracellular NP signals due to its unique property to be stimulated by cGMP. In isolated murine cardiomyocytes, CNP-induced PDE2 activity reduced arrhythmogenic Ca^{2+} releases, decreased the number of spontaneous action potentials and modulated ion channel activity upon β-adrenergic stimulation (Cachorro *et al*., 2022 Circ Res.). Therefore, we hypothesize that the intracellular NP-PDE2-signaling might not only reduce cardiac arrhythmia but also attenuate cardiac inflammation and cytokine release after MI. Interestingly, in alveolar macrophages, ANP-mediated PDE2 activation significantly decreased expression of pro-inflammatory enzymes serving as a negative regulator.
In the project, we will investigate the role of NP-PDE2 signaling pathways in macrophages analyzing the influence on macrophage polarization and cytokine release. We will study the effects of NP-induced PDE2 stimulation on macrophage invasion, cardiac inflammation, infarct size and occurrence of arrhythmia after myocardial IR. Finally, we will proof wether the NP-PDE2 axis might serve as potential therapeutical target to improve the outcome after MI. To this aim, we will use human macrophage cell lines, primary murine and human macrophages as well as myeloid cell-specific PDE2 knockout mice. We will combine *in vivo* and *in vitro* techniques such as FACS analysis, transwell migration and phagocytosis assays, ELISA and western blot techniques, Calcium-Imaging, ECG telemetry and echocardiography.



The PhD candidate will join the International research training group (IRTG) 2251 “Immunological and Metabolic Strategies in Metabolic Disease” (https://tu-dresden.de/med/mf/irtg2251) and will be eligible for a joint PhD degree from both TU Dresden and Kings College London and a research experience in London. The preferred start is 01.04.2023.