Cardiovascular diseases have a high socio-economic burden, among which heart failure plays a major role. However, while the pathophysiology of left ventricular heart failure (LVF) is quite well established and effective therapies for LVF are available, right ventricular heart failure (RVF) remains a mystery. We and others have shown that RV hypoxia is a universal finding in various forms of RVF and precedes the development of overt failure. Therefore, we hypothesize that combating RV hypoxia could prevent the development of RVF. Thus our goal is to verify if a new drug myo-inositol trispyrophosphate (ITPP), a hemoglobin effector that increases oxygen delivery in hypoxic tissues, can prevent the development of RVF in two rat models of RVF: pulmonary artery banding (PAB) and post-myocardial infarction (post-MI) model and study its mechanisms at the whole body, organ, cellular and subcellular level. Specifically, the project will address the following research questions. Do hypoxia and impaired energetics drive the development of RVF? Does hypoxia impair red blood cell metabolism and contribute to RVF pathology? Can alleviation of hypoxia by ITPP improve RV function and survival? Is RV fibrosis the eventual mediator of hypoxia in RV pathology? Are there sex-related differences in response to RV overload and hypoxia? Are there sex-related differences in ITPP effectiveness? Is ITPP able to reverse molecular signature associated with RV hypoxia and RVF? Can we confirm that these mechanisms also operate in humans, getting us closer to use of anti-hypoxia therapies in prevention of RVF in the clinical setting?

We will use to rat models of RVF, post-MI and PAB. After surgical induction of either MI or PAB the rats will receive ITPP or placebo. The rats will be monitored for 8 weeks. We will use echocardiography and catheterization to monitor cardiac function, we will measure RV oxygen content, we will test red blood cells for their oxygen carrying ability. We will use special thin cardiac slices to precisely measure cardiac metabolism and function and we will conduct a series of histological and immunohistochemistry experiments to characterize RVF and effect of ITPP. Eventually we will use a cutting-edge technology, single nuclei RNA sequencing to precisely characterize specific cardiac cells in the RV of treated and untreated rats to comprehensively understand the pathophysiology of RVF and effects of ITPP.

Eventually we will use anonymized human failing and healthy hearts from our Biobank to verify the project concept in the human material, i.e. that RV hypoxia drives RVF.

This translational project will provide both novel data on the pathophysiology of RVF and new data on the role of combating hypoxia in the prevention and treatment of RVF. Since ITPP has been already successfully tested in humans in phase 1 clinical trial, if our study proves it is effective in preventing RVF, it could directly go to clinical trials in patients with pulmonary hypertension and RVF.