ERA-NET on Cardiovascular Diseases (ERA-CVD), Joint Transnational Call 2019 (JTC2019)

"Transnational Cardiovascular Research Projects Driven by Early Career Scientists"

In January 2019, ERA-CVD published its 4th Joint Transnational Call (JTC 2019) for "Cardiovascular Research Projects driven by **Early Career Scientists** - ECS", sharing its theme with the 3rd Joint Transnational Call of 2018. With these two calls, the ERA-CVD funding organizations wish to promote multi-disciplinary work for Early Career Researchers across different countries, in order to build effective collaborations and interchange on common research projects. The opportunity to independently develop and perform highly innovative research projects enables capacity building and empowering of Early Career Researchers. Therefore, JTC2019 will support **early career scientists** in cardiovascular research, by funding 11 projects with a budget of over 8.5 Mio euro. Altogehter, 37 research groups from 11 countries collaborate in 11 consortia.

ERA-CVD NEWS

ERA-CVD announced the 5th Joint Transnational Call for Proposals 2020 on January 2020. JTC will aim at Prevention of Vascular Cognitive Impairment through Early Detection of Cardiovascular Diseases. Read more at: https://www.era-cvd.eu/405.php

France | Canada | Slovakia | Austria | The Netherlands | Germany | Israel | Italy | Poland | Spain | Belgium

Contact: DLR Project Management Agency (DLR-PT), Health Research, Heinrich-Konen-Straße 1, 53227 Bonn Germany
Phone : +49 228 3821-1144
Mail: Wolfgang.Ballensiefen@dlr.de
www.era-cvd.eu/

ERA-CVD
JANUARY 2020

NEWSLETTER5

France | Canada | Slovakia | Austria | The Netherlands | Germany | Israel | Italy | Poland
Spain | Belgium

Strategic Research Agenda (SRA) for CVD - Results of the Prioritisation Consultation:

Following the release of the ERA-CVD Strategic Research Agenda (SRA), everyone involved or affected with CVD was invited to fill out an online questionnaire. The objective was to prioritise the 15 research domains highlighted in SRA-CVD. The request was communicated via different channels such as ERA-CVD partners, the European Heart Network (EHN), the European Society of Cardiology (ESC), and the 2019 ESC Congress. The main outcomes of this consultation are now available in the following document: https://www.era-cvd.eu/396.php

EPCA 2018

Excellent Paper in Cardiovascular Research Award

After 2018, also in 2019 and EPCA has been awarded by ERA-CVD under the theme of "Transnational Cardiovascular Research Projects Driven by Early Career Scientists" EPCA award was granted. This award recognizes an outstanding scientific article by young researchers in the field of CVD.

This year's winner is Dr. Wouter C. Meijers, a cardiology resident from University Medical Center Groningen, The Netherlands. His article "Heart Failure Stimulates Tumor Growth by Circulating Factors", did get the majority majority of the ERA-CVD steering committee members votes, and awarded him with a prize. The prize and certificate were granted by the ERA-CVD coordinator Wolfgang Bellensiefen at the ESC congress in Paris in September 2019.

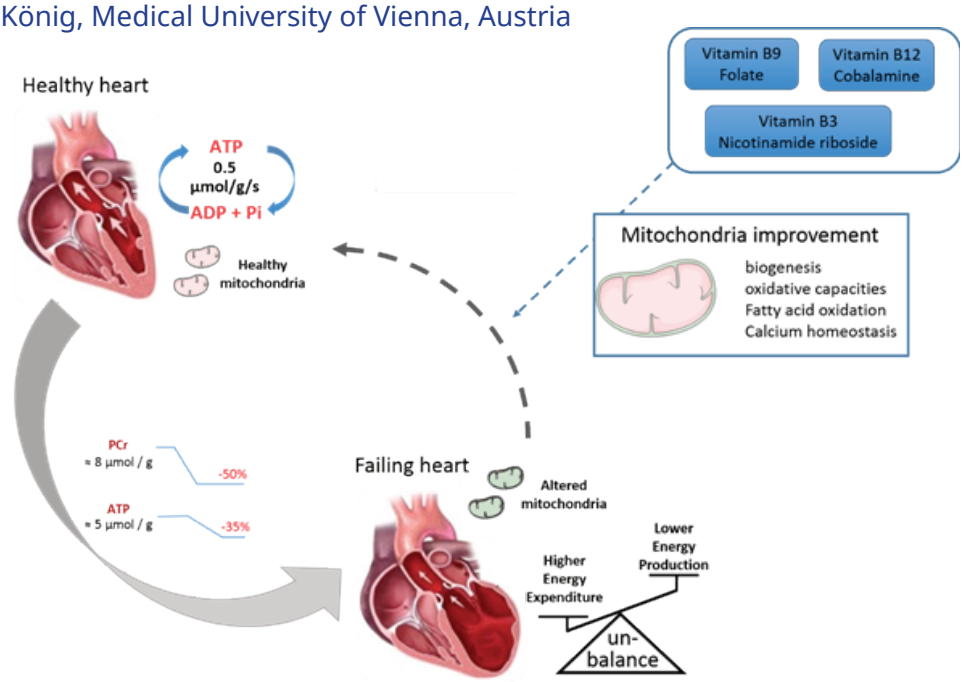
Read more at: https://doi.org/10.1161/CIRCULATIONAHA.117.030816
PMID: 29459363

Jérôme Piquereau

HF-MetaB

Project Title: Metabolic therapy of heart failure: which role for B vitamins

Coordinator:
Jérôme Piquereau, INSERM, Paris Sud University, France
Contact
Jerome.piquereau@u-psud.fr
Partners:
Matthieu Ruiz, Université de Montréal , Canada
Alexandra Zaharadnikova, Slovak Academy of Sciences, Slovakia
Xaver König, Medical University of Vienna, Austria



Heart failure (HF) is a major cause of death worldwide. Profound modulations of energy metabolism are involved in the development of HF, such as a drop in the cardiac levels of energy carrier compounds (ATP, Phosphocreatine (PCr)) and nicotinamide adenine dinucleotide (NAD+), a major coenzyme in energy generatione. In a previous mouse model of cardiac pressure overload, we were able to show the protective effect of diet supplementation of two vitamins, B12 and B9, stimulating the mitochondrial biogenesis pathways, or with nicotinamide riboside (NR), a recently characterized vitamin B3 which is a NAD+ precursor. Inasmuch as these treatments were given before the appearance of the first symptoms of HF in previous studies, we propose here to test the curative effect of a cocktail of these 3 B vitamins in symptomatic HF in mice. In a translational perspective toward clinics, we will also assess the impact of this vitamins cocktail in the context of standard medical HF care (β-blocker, ACE inhibitor). Finally, it is critically important to consider the sex differences in treatment of HF. Therefore our second aim is to compare the effect of the treatment between males and females that may differ according to the mitochondrial alterations in HF.

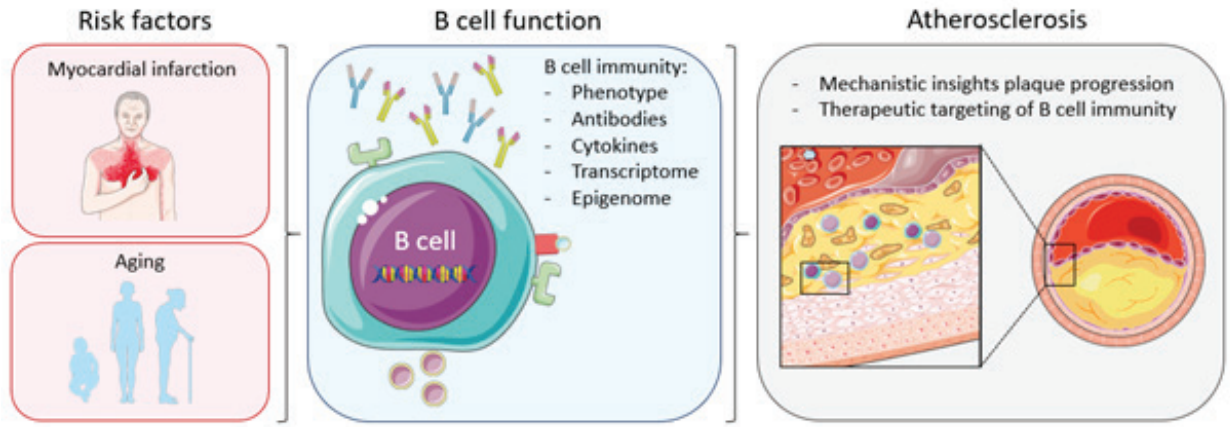
Amanda Foks

B-eatATHERO

The role of B cell immunity in accelerated atherosclerosis

Coordinator:
Amanda Foks, Leiden University (LACDR), The Netherlands
Contact:
a.c.foks@lacdr.leidenuniv.nl
Partners:
Dimitrios Tsiantoulas, Medical University of Vienna, Austria
Julia Polansky-Biskup, Charité Universitätsmedizin Berlin, Germany

Atherosclerotic cardiovascular disease is the leading cause of mortality and morbidity worldwide, and results in the formation of atherosclerotic plaques that upon rupture or erosion cause myocardial infarction (MI) and stroke. The recent clinical trial CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) has demonstrated the therapeutic value of immunomodulation in secondary prevention of atherosclerotic cardiovascular disease. This is very important as MI survivors are at a high risk for recurrent infarctions. Experimental studies have attributed this risk profile to accelerated atherosclerosis. However, the role of the immune system in this setting is not well understood. Here, we aim to investigate how major risk factors for secondary atherosclerotic cardiovascular disease, such as aging and history of MI, modulate B lymphocyte responses and thereby affect atherosclerosis progression. Our studies will employ atherosclerosis-prone mice and will include analysis of plaque specimens and peripheral B cell subsets from coronary artery disease patients. These studies will provide new insights for the development of precise therapeutic strategies, which will be particularly relevant for the secondary prevention of atherosclerotic cardiovascular disease.



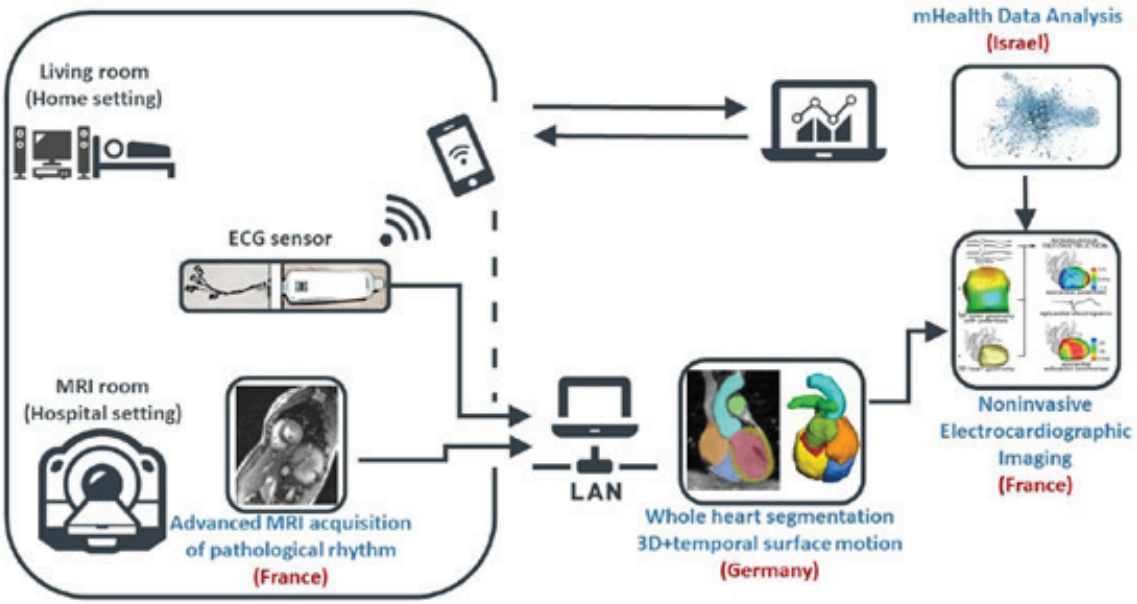
Julien Oster

MEIDIC-VTACH- Mobile

Electro-Imaging for the preDICtion of Ventricular TACHyarrhythmia

Coordinator:
Julien Oster, Inserm, U1254, Nancy, France
Contact:
julien.oster@inserm.fr
Partners:
Mattias Heinrich, University of Luebeck, Luebeck, Germany
Joachim Behar, Technion Israel Institute of Technology, Haifa, Israel

Patients suffering from heart failure are at risks of developing Ventricular Tachycardia (VT). VT is responsible for about 80% of the sudden cardiac deaths. There is a need to develop a better stratification of patients at risk of developing VT. The fusion of imaging and electrophysiology modalities, electrocardiographic imaging (ECGI) was recently introduced to enable a non-invasively visualisation of the cardiac electrophysiology. ECGI is an exciting avenue of research for several cardiovascular applications, including risk stratification for VT.
Our main objective is to develop a novel technique for the fusion of information provided by Electrocardiogram (ECG) data, mechanical information of the heart provided by Magnetic Resonance Imaging (MRI), and rhythm information provided by long-term portable ECG, which will be denoted mobile ECGI.

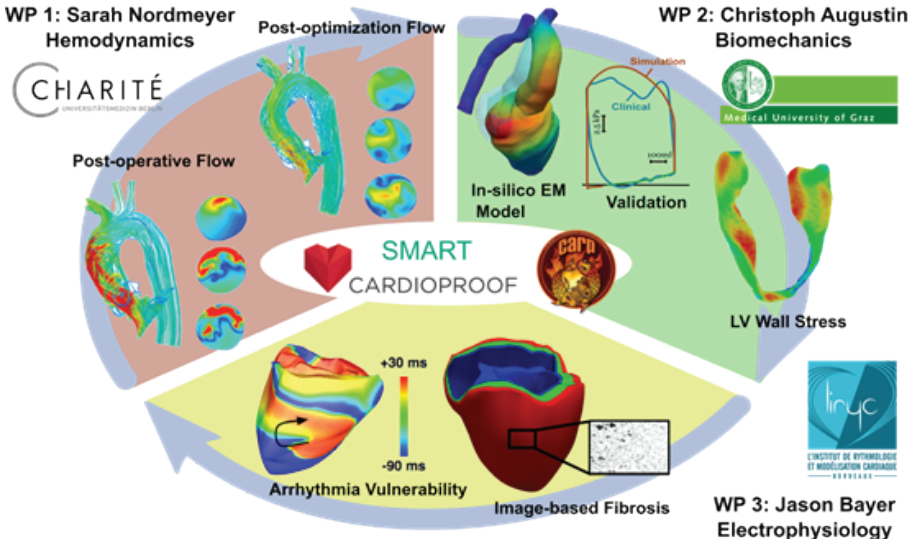


Christoph Augustin

SICVALVES

Multiscale modeling of Valvular Heart Diseases. Understanding the mechanisms of adverse remodeling to improve precision medicine

Coordinator:
Christoph Augustin, Medical University of Graz, Gottfried Schatz Research Center, Austria
Contact:
christoph.augustin@medunigraz.at
Partners:
Jason Bayer, University of Bordeaux, Bordeaux, France
Sarah Nordmeyer, Charité - Universitätsmedizin Berlin, Berlin, Germany



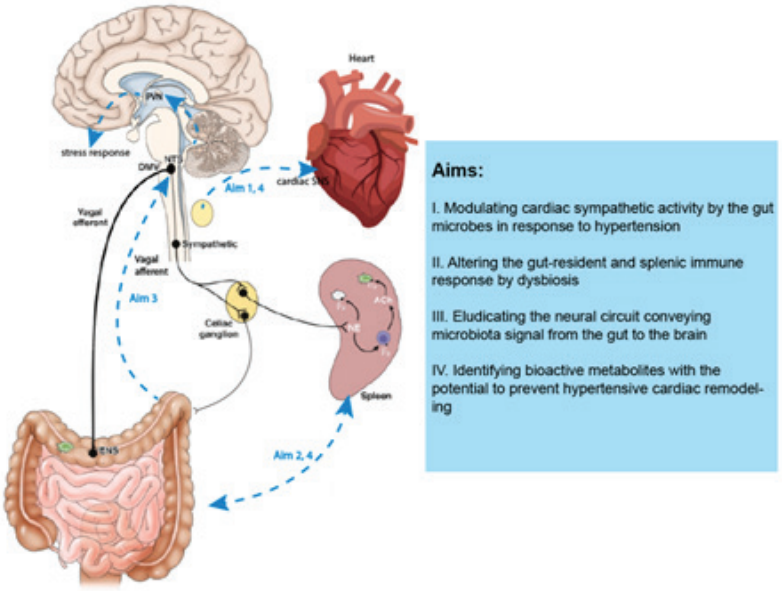
Valvular Heart Diseases (VHD) are chronic-progressive diseases that vary with gender and age. If left untreated, VHDs can cause malignant arrhythmias and severe heart failure. The existing guidelines for treatment are using only rough function parameters that fail to account for inter-individual variability. Nowadays, computational modeling has the potential to unveil important pathophysiological mechanisms and to contribute towards personalized precision medicine. Our objective is to use advanced models of the cell, tissue, and organ level in VHD to gain mechanistic insights about triggers of ventricular arrhythmias, diastolic, and systolic dysfunction and myocardial metabolic alterations and how these processes reinforce each other. Gender differences will be systematically taken into account, to improve diagnostics, risk assessment, and treatment planning of VHDs. Existing models of biomechanics, electrophysiology, and hemodynamics will be optimized for individual cases using a pool of data from our own previous trials. Model parameters will be calibrated under pre- treatment conditions and models will be validated by comparing model predictions of acute post- treatment conditions against clinical data. Finally, longer term follow up data of cases will be used to enable predictions of chronic outcomes.

Suphansa Sawamiphak

Gut-brain-immune-HHD

Gut-brain interactions modulate immune response in Hypertensive Heart Disease

Coordinator:
Suphansa Sawamiphak, Max Delbrück Center for Molecular Medicine, Germany
Contact:
Suphansa.Sawawamiphak@mdc-berlin.de
Partners:
Daniela Carnevale, IRCCS Neuromed, Mediterranean Neurological Institute, Italy
Slava Epelman, Toronto General Hospital Research Institute, Canada
Tomasz Guzik, Jagiellonian University Medical College, Poland



Hypertension affects the remodeling of the heart through interactions between different organ systems, thus hindering mechanistic understanding of the disease and therapeutic advancement. In addition to the nervous and immune systems, the contribution of several microbes residing in the gut has recently been revealed to be strongly associated with hypertension. While the role of these microbes in pathogenesis of hypertensive heart disease is still unclear, recent findings suggest that they may be targets for much-needed novel preventive and curative interventions. This joint project aims to decipher the mechanistic relationship between gut microbes, neuronal and immune activity, and the disease progression from hypertension to damage of the heart. We will focus our investigation on microbiota-mediated modulation of neural activity and immune cell activation locally in the gut and distantly at the major lymphoid organ, the spleen, and the heart. To translate our findings to human pathology, we will perform in-depth characterization of microbiome and associated cardiac damage in hypertensive patients. Furthermore, neural circuitries relaying the microbiota signal from the gut to the heart will be elucidated. Vice versa, we will address the role of the central nervous system in the alteration of the gut barrier function, thereby contributing to dysregulated microbiota compositions and functions. Finally, we will identify novel bioactive metabolites with the ability to suppress neural hyperactivation and inflammation, thus preventing maladaptive remodeling of the heart in hypertension.

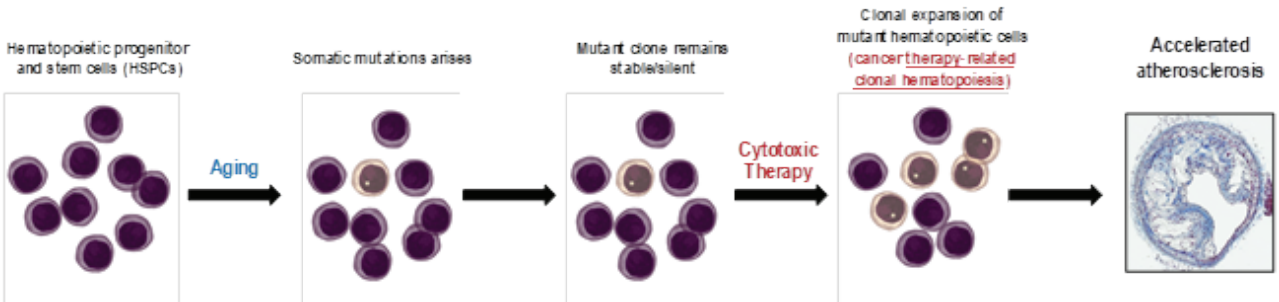
José J. Fuster

CHEMICAL

Cancer Therapy-Related Clonal Hematopoiesis as a Driver of Accelerated Atherosclerosis

Coordinator:
José J. Fuster, Centro Nacional de Investigaciones Cardiovasculares Carlos III, Spain
Contact:
josejavier.fuster@cnic.es
Partners:
Chloé James, INSERM 1034, Biology of Cardiovascular Diseases, France
Carolina Greco, IRCCS Istituto Clinico Humanitas, Italy

Improvements in early cancer detection and treatment have drastically reduced cancer mortality, resulting in a growing population of cancer survivors. However, cancer survivorship is accompanied by a substantial increase in cardiovascular risk and mortality. Therefore, there is a great need to understand the specific mechanisms underlying the long-term cardiovascular side-effects of cancer therapies. Recent studies have shown that some acquired mutations in the hematopoietic system provide a competitive advantage that leads to the expansion of the mutant cell among the blood cell population. Unexpectedly, this phenomenon, called clonal hematopoiesis, has emerged as a new risk factor for heart disease. Furthermore, recent evidence suggest that the presence of certain clonal hematopoiesis-related mutations in blood cells is particularly frequent in survivors of solid cancers treated with cytotoxic therapies. Our collaborative project will test the hypothesis that acquired mutations that drive clonal hematopoiesis accelerate the development of atherosclerosis and therefore contribute to the increased cardiovascular risk observed in cancer patients and survivors. To test this novel hypothesis, we propose to use a multidisciplinary approach that combines experimental atherosclerosis studies in innovative animal models and DNA sequencing studies in cancer survivors.

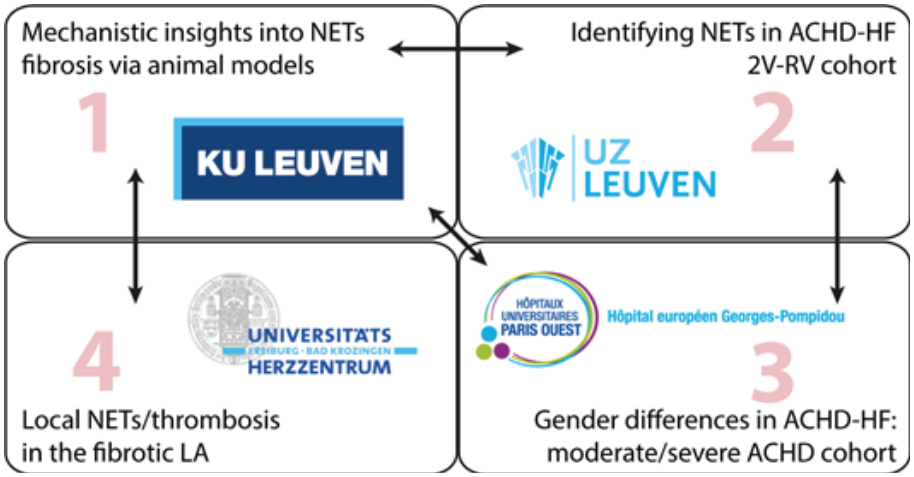


Kimberly Martinod

FIBRONETx

Casting NETs in the fibrotic heart

Coordinator:
Kimberly Martinod, KU Leuven, Belgium
Contact:
kim.martinod@kuleuven.be
Partners:
Alexander Van De Bruaene, KU/UZ Leuven, Belgium
Magalie Ladouceur, Hôpital Européen Georges Pompidou, France
Thilo Witsch, Universitäts-Herzzentrum Freiburg, Germany



Neutrophils can release their nuclear contents lined with granule proteins, creating fibrous DNA nets with antimicrobial properties, called neutrophil extracellular traps (NETs). NETs also promote thrombus formation by providing a scaffold for platelet and clotting factor binding. The release of NETs thus shifts from a protective, immune defense mechanism, to a process with pathological consequences. The early NET inducer peptidylarginine deiminase 4 (PAD4) contributes to cardiac fibrosis development during aging in mice. PAD4-deficiency and NET degradation similarly protected from aberrant collagen deposition and decline in cardiac output after injury. In humans, this type of decline in function is linked to progression to heart failure (HF) with poor prognosis, often due to an increase in cardiac fibrotic remodeling with an unknown cause. HF occurs when the heart cannot properly pump blood to the rest of the body. When heart muscle is damaged and tries to repair itself, widespread scar tissue (fibrosis) is left behind. The main goal of the FIBRONETx consortium is to investigate how NETs contribute to this process. We will: 1) Follow the downstream consequences of modulating NET formation, 2) Link NETs to functional imaging in congenital heart disease patients at high risk of developing HF, 3) Investigate the impact of gender and pregnancy on NETs and cardiac fibrosis, and 4) Correlate NETs with thrombosis markers in blood collected from within the fibrotic hearts of patients who are prone to developing strokes. With this project we aim to better elucidate HF pathogenesis and to provide insight into future diagnostic use of NETs in the context of HF and thrombosis.

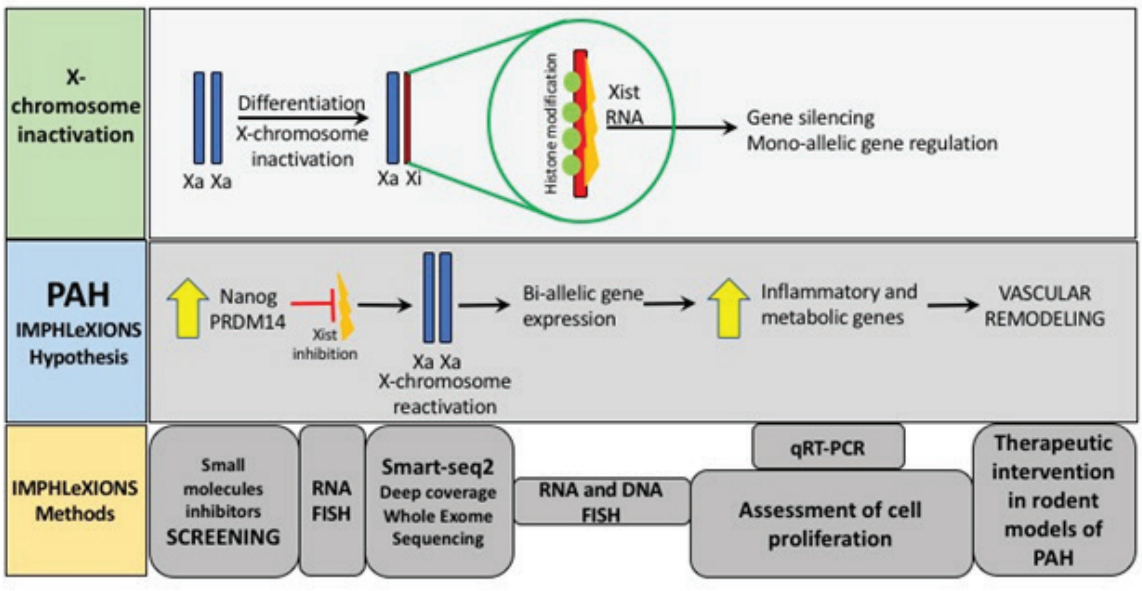
Roxane Paulin

IMPHLeXIONS

Inflammation and Metabolism in Pulmonary Hypertension are Linked to skewed chromosome X Inactivation: new therapeutic optiONS.

Coordinator:
Roxane Paulin, PhD, Quebec Heart and Lung Institute-Université Laval, Quebec, Canada
Contact:
roxane.paulin@criucpq.ulaval.ca
Partners:
Slaven Crnkovic, PhD, Ludwig Boltzmann Institute for Lung Vascular Research, Graz, Austria.
Konda Babu Kurakula, PhD, Max-Planck-Institute for Heart and Lung Research, Bad Nauheim, Germany

Pulmonary arterial hypertension (PAH) is a rare disease of increased blood pressure in lung vessels. It is fatal and affects at least twice as more women as males. Our consortium will follow a novel idea and use state-of-the art technologies to investigate why women are more at risk. Under normal conditions, in every female cell, one of the two X chromosomes is switched off. This inactivation process can, however, be imperfect and lead to the reactivation of silenced copies of genes, including ones that are involved in inflammatory and metabolic processes. Because PAH is associated with increased expression of inflammatory and metabolic genes, we hypothesized that reactivation of the silenced X chromosome genes could be one of the underlying reason for observed sex differences in PAH. We propose to measure X chromosome inactivation in 60 female PAH patients using single-cell RNA sequencing complimented with deep coverage whole-exome sequencing. We will investigate mechanisms behind defective X chromosome silencing, including the role of NANOG and PRDM14 overexpression in the regulation of XISt (a noncoding RNA that coats the inactive X chromosome). Finally, we will test tailored therapeutic approaches to restore proper X-chromosome inactivation and improve PAH.

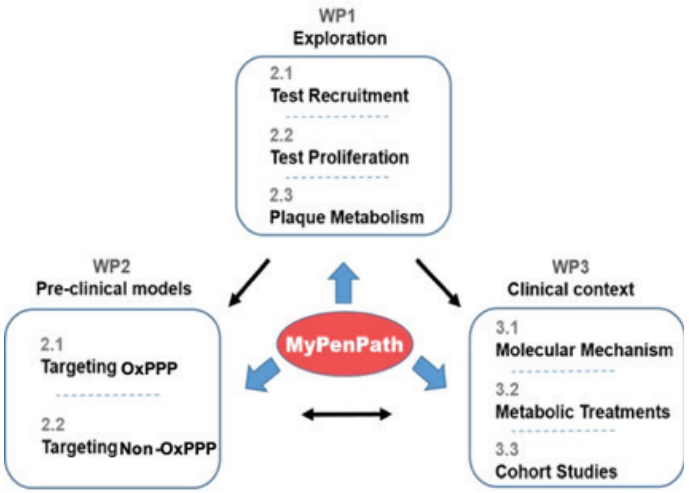


Stoyan Ivanov

MyPenPath

The Role of the Pentose Phosphate Pathway on Myeloid Cell Activation and Atherosclerosis

Coordinator:
Stoyan Ivanov, INSERM U1065, Nice, France
Contact:
Stoyan.IVANOV@univ-cotedazur.fr
Partners:
Florian Kahles, University Hospital Aachen, Germany, Department of Cardiology, Angiology and Intensive Care Medicine
Arvand Haschemi, Medical University of Vienna, Department of Laboratory Medicine
Jan Van den Bossche, Amsterdam UMC, location VUmc, Department of Molecular Cell Biology and Immunology



Atherosclerosis is the main cause of myocardial infarction and stroke, contributing to the global burden of cardiovascular diseases (CVD). Immune cell dysregulation and chronic inflammation are major causes of atherosclerotic plaque development. Importantly, myeloid cell activation in CVD is paralleled by an increase in glucose utilization. The Metabolic Syndrome (MetS) is hallmarked by chronic inflammation and the dysfunction of key processes that regulate glucose metabolism, escalating the risk of atherosclerosis. Thus, myeloid cell metabolic rewiring could have major implication in MetS, characterized by a gender-dependent nutrient overload and a dysregulated metabolic state, associated to insulin resistance and type 2 diabetes. We hypothesize that metabolic dysfunction in atherosclerosis reprograms glucose utilization in immune cells, leading to their expansion and activation in the plaque.

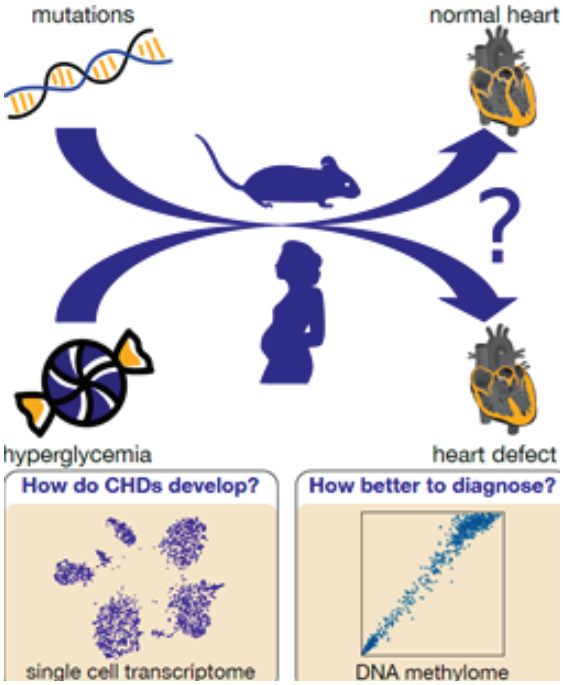
This consortium associates interdisciplinary and key expertise to investigate the contribution of glucose metabolism, and in particular the balance between glycolysis and the pentose phosphate pathway (PPP), in immune cell functions during atherosclerosis. We will define the contribution of glycolysis and the PPP to immune cell migration, proliferation and activation in atherosclerosis using mouse genetic models and pharmacological inhibitors. Moreover, in a translational approach, our consortium will bring together human cohorts and expertise to delineate the impact of metabolic dysfunction on inflammation and CVD development in the clinical context.

Bernard Thienpont

DEFIANCE

Defining Environmental Factors Influencing and Affecting Neonatal Cardiac health through Epigenome profiling

Coordinator:
Bernard Thienpont, KU Leuven, Belgium
Contact:
bernard.thienpont@kuleuven.be
Partners:
Sonia Stefanovic, INSERM UMR1251 Marseille Medical Genetics, France
Anne-Karin Kahlert, UKSH, Germany



Congenital heart defects (CHD) are one of the leading causes for foetal and infant deaths worldwide. Apart from genetic factors, also nongenetic factors contribute to CHD. Studies have shown that factors such as maternal smoking, obesity and increased maternal age, maternal diabetes is also associated with an increased risk of having a child with CHD, though the underlying mechanism is still not fully understood. Therefore our aim is to gain a better understanding of the processes involved in the development of CHD due to high blood glucose during pregnancy.
We assume that epigenetic changes ,which modify the DNA and alter gene expression, play an important role in the development of CHD. For this reason, we will induce diabetes in female mice and examine the embryonic murine hearts of the pups by single cell sequencing and DNA methylation profiling. These results will be compared to the DNA methylation pattern and single cell transcriptome data of the cardiac tissue and blood of children with a CHD, whose mothers suffered from diabetes during their pregnancy.
Our results will enable a better risk prediction and might reveal new therapeutic targets for therapy and prevention, and may enble the development of a diagnostic tool based on methylation pattern in the blood to identify environmental factors contributing to CHD.

Bernard Thienpont

SCALE

Single Cardiomyocyte ALlelic imbalancE in hypertrophic cardiomyopathy (SCALE)

Coordinator:
Magdalena Harakalova, University Medical Center Utrecht (UMCU), Utrecht, The Netherlands
Contact:
m.harakalova@umcutrecht.nl
Partners:
Judith Montag, Hannover Medical School (MHH), Hannover, Germany
Fernando Dominguez, University Hospital Puerta de Hierro Majadahonda, Madrid, Spain
Eric Villard, The Hospital University Institute-Institute of Cardiometabolism and Nutrition (IHU-ICAN), Paris, France

Hypertrophic cardiomyopathy (HCM) is mainly caused by heterozygous mutations in sarcomeric genes. Patients express both the wild-type and the mutated allele. The fraction of the mutated allele differs between neighboring cardiomyocytes (CM) in cardiac tissue. This 'cell-to-cell allelic imbalance' is contributing to the disease. To address this problem, the members of the SCALE consortium will use patient-derived induced pluripotent stem cell (iPSC) differentiated to cardiomyocytes (CM) as well as a large collection of myectomy samples from HCM patients. We will isolate and analyze single cells by fluorescence-activated cell sorting (FACS) or laser microdissection (LMD). Allele specific RNA expression and chromatin modulation will be analyzed down to a single cell level to identify potential mechanisms underlying HCM development. Lastly, we will modulate the cell-to-cell allelic imbalance to minimize the functional mosaicism. To achieve this we will interfere with cultured CMs using compounds that might revert the allelic imbalance as possible treatment options.