ERA- CVD NEWSLETTER2

January 2018

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ERA-NET on Cardio Vascular Diseases (ERA-CVD)

Transnational call, 2017

"Mechanisms of Early Atherosclerosis and/or Plaque Instability in Coronary Artery Disease"

21 consortia were selected to submitted a full proposal which were reviewed by over **30** expert of which **12** also attended in the Scientific Evaluation Board (SEB) meeting in Rome

Finally **10** consortia are funded with around **8.5** million € for three years. These projects involve **39** reserach groups from altogether **21** countries..

More details at: http://www.era-cvd.eu

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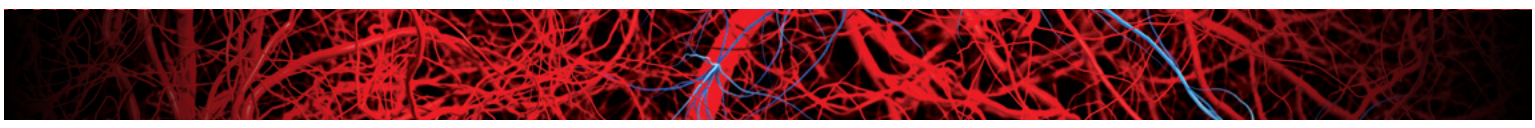

Gerard Pasterkamp

Hester den Ruijter

ENDLESS

Atherosclerotic plaque erosion leading to thrombus formation. The role of microparticles in ENDtheliaL transdiffErentiation, apoptoSiS and senescence.

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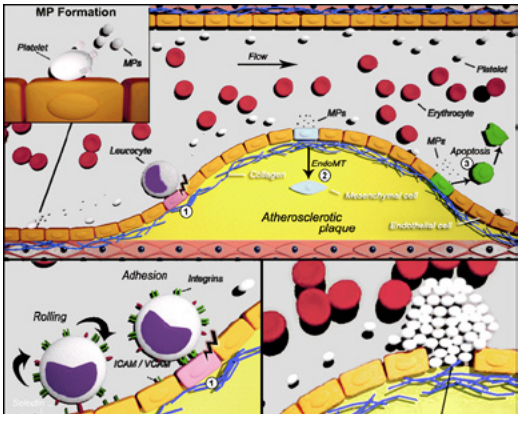
The community has faced an impressive drop in incidence of atherosclerotic diseases over the past two decades. Mortality rates due to myocardial infarctions have decreased by nearly 50%. There has also been a significant change in the underlying pathology of symptomatic atherosclerotic lesions. This drastic change mandates uncovering the mechanisms that accelerate a thrombotic event on top of a stable plaque.

Endothelial cells play a crucial role in the processes that promote luminal thrombosis. ENDLESS will unravel the mechanisms that lead to endothelial damage, explaining the thrombotic event that is superimposed on a stable plaque. Analyses will be executed in a sex-stratified manner, as thrombus on top of stable plaques has been described to be more prevalent in women. Ultimately, this may lead to the discovery of new mechanisms indicative of a healthy endothelium.



External triggers such as microparticles (MPs) and hormones activate endothelial cells (ECs). Activation will result in selectin, integrin expression and leucocyte attachment (1), EC transdifferentiation into mesenchymal cells (2) and/or apoptosis and senescence (3). These events will expose activated platelets to a thrombogenic surface and platelet aggregation on top of a non ruptured fibrous plaque.

Erik Biessen

AtheroMacHete

Macrophage heterogeneity in human and murine atherosclerosis: a therapeutic opportunity?

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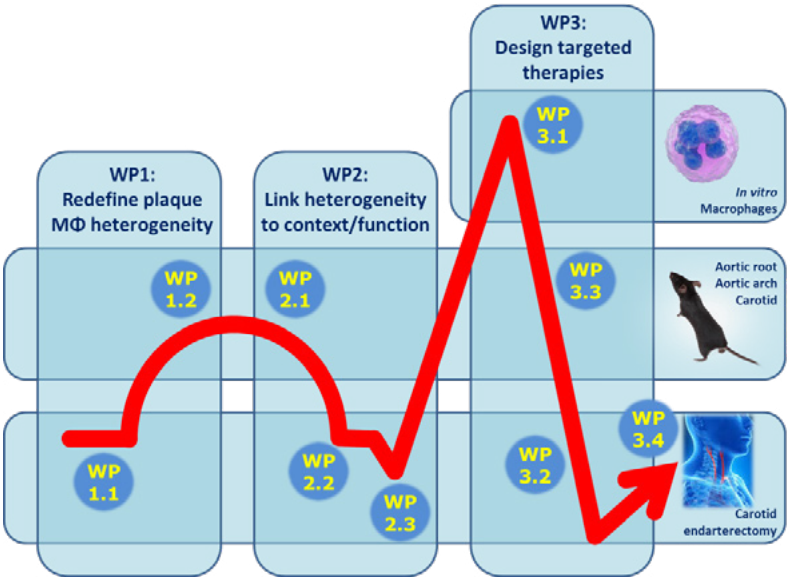
Atherosclerosis-related cardiovascular diseases are the prime cause of death worldwide. The most abundant immune cell type in plaque, the macrophage, is instrumental in its pathogenesis throughout the course of the disease. At AtheroMacHete, the aforementioned cross-disciplinary team will dissect the macrophage's transcriptional, ontogenic, and functional heterogeneity in atherosclerotic lesions in patients and in murine models of disease. Based on this unprecedented deep characterization we will identify essential gene programs and regulatory cues driving adverse macrophage functions in atherosclerosis. Finally, we will design and validate candidate drugs to target these cues in vitro, in murine models and, eventually, in the clinic. Together, AtheroMacHete is expected to pave the way to more precise anti-inflammatory treatment of cardiovascular diseases.



Jacob Fog Bentzon

SCAN

Subclinical atherosclerosis characterization: Nanoparticle-based molecular and cellular imaging

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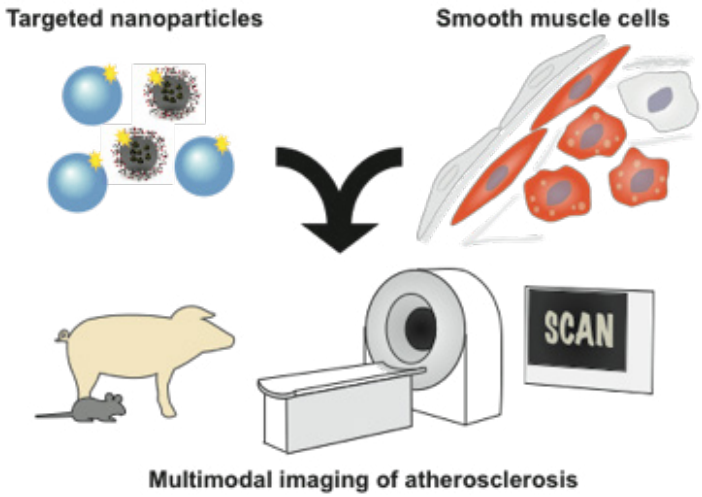
Molecular imaging of atherosclerosis can become a key tool to understanding the progression of atherosclerosis into clinical disease; identifying patients who need preventive therapy; testing the causal role of risk factors; and guiding the development of new drugs.

Partners in the present project have recently found that smooth muscle cells contribute much more abundantly to atherosclerosis than previously thought, and have developed two nanoparticle technologies that allow imaging of the vasculature across a range of modalities. In SCAN these competencies are brought together to develop multimodal imaging of atherosclerosis with nanoparticles targeted at smooth muscle cells.



Multimodal imaging of atherosclerosis

Erik Stroes

OPERATION

Elucidate monocyte phenotype to predict arterial wall inflammation

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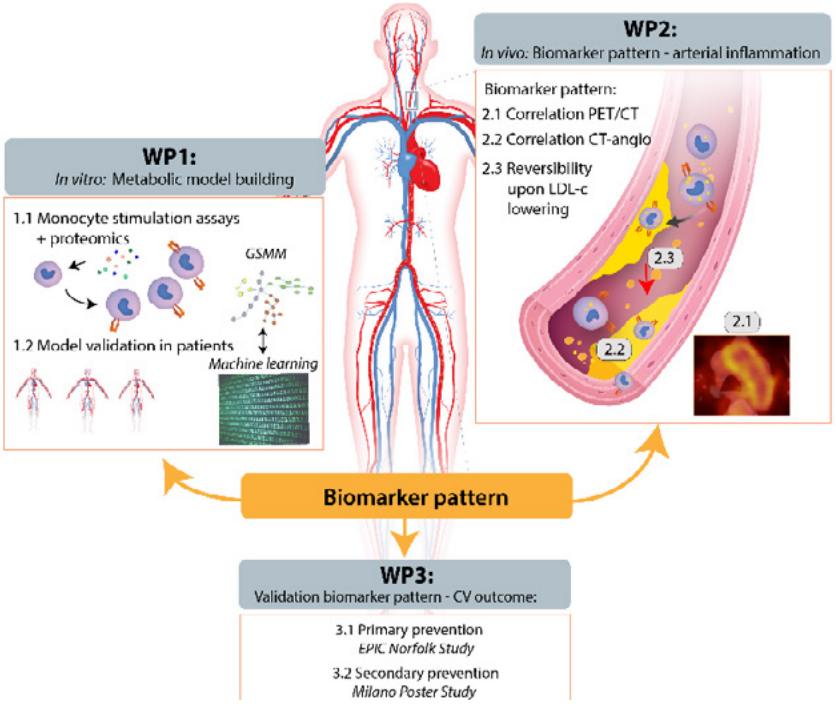
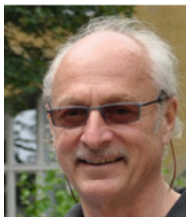
A.K.Groen, AMC, The Netherlands (Associated partner)

Patients at increased cardiovascular risk currently receive lipid-lowering treatment, resulting in a modest risk reduction of 30%. Recently, direct targeting of inflammation (using an antibody against IL1 -antibody) was also found to reduce cardiovascular risk, particularly in patients with increased inflammatory activity. Although anti-inflammatory treatment should ideally be given to these 'inflammatory' patients, biomarkers predicting arterial wall inflammation are, unfortunately, unavailable. At OPERATION project, we will use genome-scale metabolic modelling of plasma immune cells, combined with plasma protein screening, by using proteomics, in order to design a 'biomarker pattern' correlating with arterial wall inflammation. Subsequently, advanced machine-learning technology will be applied to optimize this biomarker pattern, followed by validation of predictive value in both primary and secondary prevention setting.





Andreas Habenicht

PLAQUEFIGHT

Fighting Atherosclerotic Plaques in Coronary Artery Disease Via Targeting Neuroimmune Interfaces

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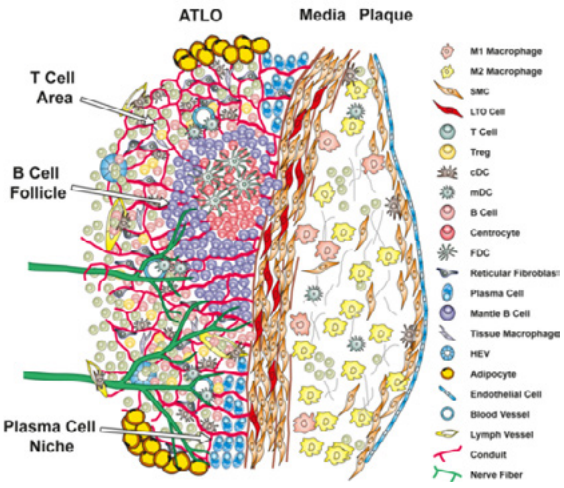
Atherosclerosis is a chronic inflammatory condition of the arteries and the most deadly disease worldwide. Despite international research efforts, there is no causal therapeutic approach to treat the disease and pathophysiological mechanisms underlying atherosclerosis largely remain to be identified. The PLAQUEFIGHT consortium will focus on the principal question whether the disease affects the nervous system and vice versa. This possibility arose in our unpublished studies as we observed newly formed nerve axon networks in the connective tissue coat (the adventitia) of diseased artery segments. Moreover, the affected adventitia segments are heavily infiltrated by inflammatory cells which are directly associated with axons. This project will examine the morphology and impact of the nervous system on the arterial wall and on disease progression using a variety of mouse models and diseased human tissues including the coronary arteries. A major aim of the project is **to** identify the nature of interactions between arterial wall immune cells and the nervous system in attempts to develop new therapeutic targets.



Choreography of the innervation of a diseased artery by the peripheral nervous system.

David Magne

MICROEXPLORATION

Exploring the effects of microcalcification on plaque vulnerability

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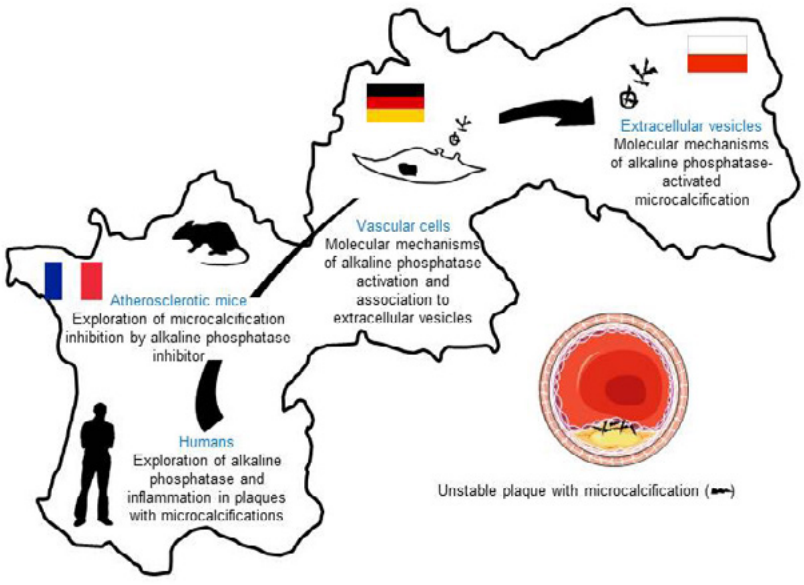
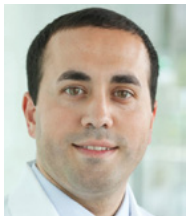
Calcification of atherosclerosis plaques has been known for decades, and the calcium score is today recognized as a reliable, independent predictor of acute cardiovascular events. However, the mechanisms leading to the deposition of calcium crystals in arteries, as well as their direct contribution to atherosclerosis plaque evolution and complications, remain obscure. Recent reports based on histopathological studies suggest that microcalcifications, forming in early lesions, are detrimental to plaque stability, but conclusive proof is still missing. The main objective of the MICROEXPLORATION project is to inhibit formation of microcalcifications in atherosclerotic mice, and analyze the evolution of the disease, focusing particularly on plaque inflammation and remodeling. We will use a new potent inhibitor of the key enzyme involved in calcification formation, alkaline phosphatase. Results of this research program may be useful to better understand the role of calcium deposition in atherosclerosis arteries, and help developing imaging technologies to detect microcalcifications and identify plaques at risks of acute complications.





Mahir Karakas

Tanja Zeller

PREMED-CAD

PREcision MEDicine in Coronary Artery Disease

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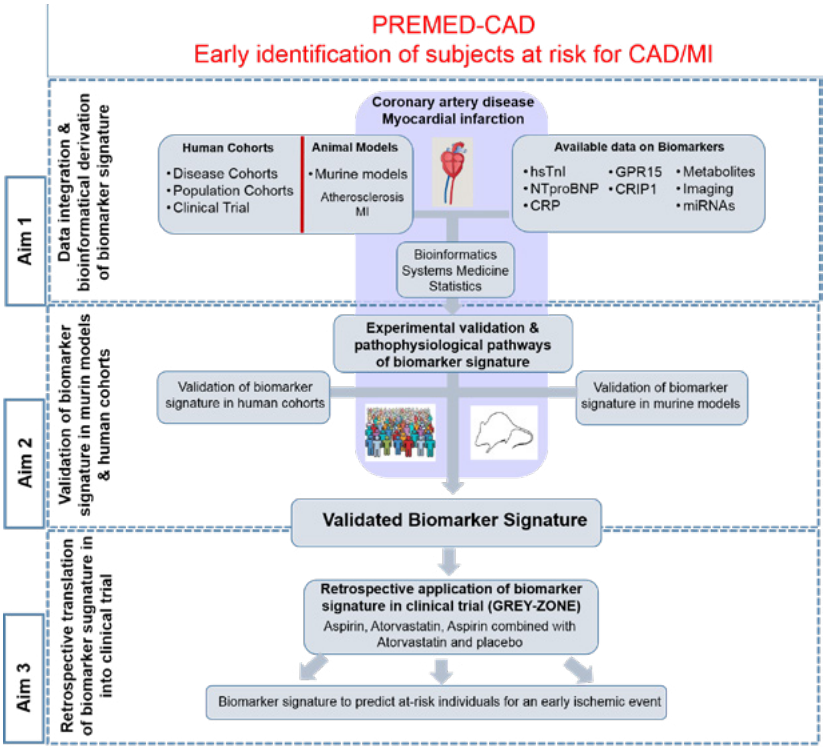
Cardiovascular disease represents the most prevalent cause of morbidity and mortality in the EU, and has an enormous socioeconomic impact. So far, existing tools have failed to adequately identify subjects at short-term risk for cardiovascular disease. Within this project, PREMED-CAD, we take an interdisciplinary and translational approach integrating knowledge and resources from cardiovascular epidemiology, imaging, bioinformatics, statistics and molecular biology. We integrate existing blood-based and clinical biomarkers into a biomarker signature and validate it in atherosclerosis-prone mouse models and human cohorts. Finally, we will translate the biomarker-signature in an ongoing large preventive clinical trial, comprising patients with subclinical ischemia.

The PREMED-CAD project will enable (i) the identification of novel tools for early recognition of individuals at immediate and short-term cardiovascular risk, (ii) exploration of the molecular pathophysiology and signature of myocardial ischemia in a comprehensive view, and (iii) the application of precision medicine to individuals at cardiovascular risk in a clinical trial.



Rune Hansen

XploreCAD

Advanced ex vivo analyses and multi-frequency ultrasound technology for improved evaluation and diagnosis of coronary plaque

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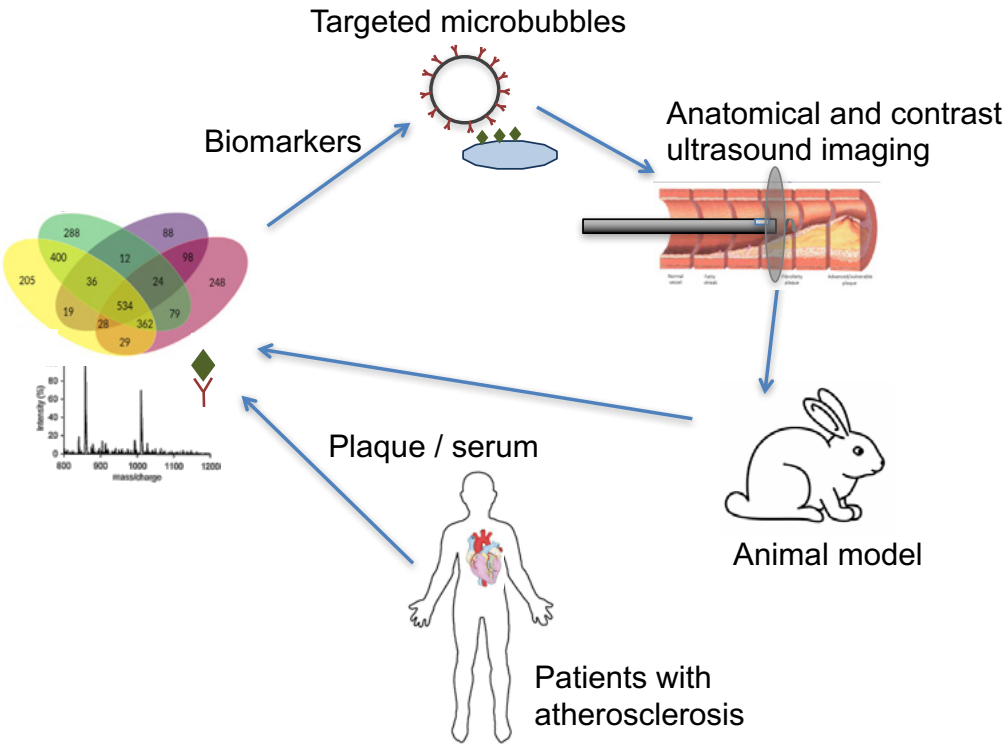
Atherosclerosis is considered a multifactorial disease with risk factors ranging from high-fat diet, hypertension, smoking, diabetes, to genetic susceptibility and other factors. Classic statin treatment has led to significant reduction of clinical events, but considerable residual risk of cardiovascular-related mortality still remains. By analyzing blood and plaque samples from both patient and animal models, the XploreCAD project will identify potential biomarkers of coronary artery disease that will be used in combination with novel ultrasound technology for improved imaging of coronary plaque. Expected results will lead to better understanding of the mechanisms related to plaque progression and plaque instability, and an improved imaging technique for plaque diagnosis.



Peter Verhamme

Jan Staessen

PROACT

Proteome analysis for the management of coronary artery disease

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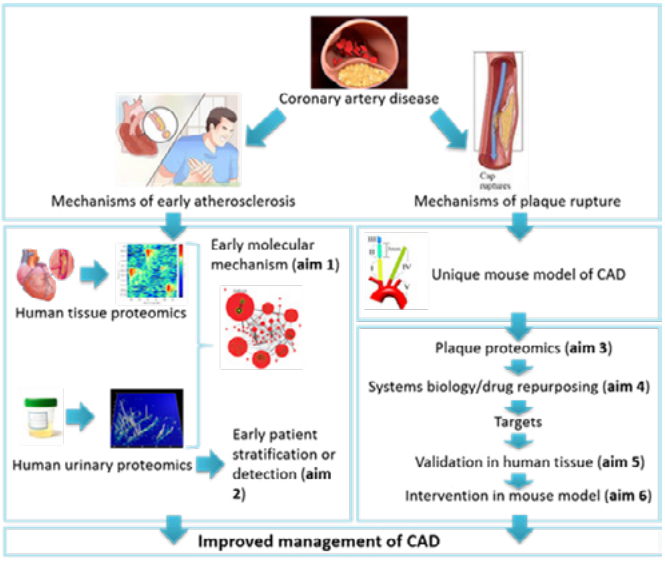
Coronary artery disease (CAD) is the leading cause of morbidity and mortality in developed countries. Although current diagnostic and therapeutic tools have significantly improved its management, the prevalence of CAD is still on the rise due to demographic transition and increased survival rates after myocardial infarction. The socio-economic burden of CAD is thus obvious and innovative methods that will improve its management are urgently needed. PROACT's task will be finding proactive disease management strategies. To do so, we will validate on a large scale urinary proteome biomarkers, allowing the early detection of CAD, while combining high throughput proteomics with systems biology, and integrating mouse and human data to systemically explore relevant pathways associated with plaque instability. Relevant molecular mechanisms of plaque instability will enable identification of novel therapeutic targets for stabilizing the atherosclerotic plaque. Therefore, cutting-edge technologies will be used to non-invasively detect the risk of developing CAD and an innovative systems-biology approach will generate potential therapeutic targets to treat plaque instability.



Heribert Schunkert

druggable-MI-genes

Utilising myocardial infarction genes for better treatment

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Coronary artery disease (CAD) is a major health threat for millions of people in the Western world. Recent work, sponsored in part by the EU, uncovered multiple genetic variants, each increasing CAD risk by a small extent. The precise mechanisms linking these genetic variants with the outbreak of disease, e.g. a heart attack, are often unclear.

The overall aim of druggable-MI-genes is to lay the foundation for a more precise and genomics-based prevention of coronary atherosclerosis and plaque stability.

At druggable-MI-genes we will first differentiate between genes/transcripts underlying genetic risk of myocardial infarction (i.e., unstable plaques), and stable CAD. Next, we will explore the molecular contexts of the most promising candidates, aiming to identify the so called key disease driver genes. In parallel, novel molecular mechanisms of plaque instability, will be further scrutinized for potential therapeutic interventions. Finally, translation to human pathophysiology will be achieved by interrogating unique biobanks of human atherosclerotic plaque material, as well as population-based samples of up to 500,000 individuals with genome-wide data and in-depth phenotypic characterization.

of individuals at risk (WP3). The overall aim of druggable-MI-genes is to lay the foundation for a more precise and genomics-based prevention of coronary atherosclerosis and plaque stability.