Title: A biomimetic organ-on-chip model for vascular calcification

Introduction and project description: Vascular calcification, i.e. extraosseous mineral deposition in blood vessels, is a well-established marker of subclinical atherosclerosis and arteriosclerosis and, when occurring in coronary arteries, an independent predictor of future coronary heart disease. Although numerous studies have explored the associations between vascular calcification and various biochemical factors, a unifying mechanism that explains the initiation and development of this complex condition has not yet been unraveled. The role of genetic and environmental factors, which appears to vary from patient to patient, adds to the complexity of vascular disease. Clinical methods, often based on invasive angiography or non-invasive imaging techniques, are widely used for diagnosis of the vascular calcification. They, however, provide limited information for studying the underlying mechanisms, early-stage diagnosis, i.e., prior to (extensive) mineral formation, and drug development and screening. Current preclinical models for vascular calcification are also suboptimal for predicting the outcomes as they provide an oversimplified microenvironment that does not resemble many aspects of blood vessels such as dimension and shape, multicellularity and blood flow dynamics. Therefore, they do not represent the complexity of calcification of blood vessels, and consequently fail to reproduce extensive calcification that is usually seen in pathological conditions *in vivo*. Animal-based *in vivo* models, on the other hand, fall short in providing clinically translatable outcome. Hence, there is still a large unmet demand for reliable and predictive human *in vitro* models for pathological calcification of blood vessels, with non-invasive character and patient-specificity.

Recent advances in microfluidic and organ-on-chip technologies have resulted in the development of more complex human-based *in vitro* models for pathological conditions of blood vessels including calcification. However, existing organ-on-chip models have not yet succeeded to recapitulate the unique anatomical and biomechanical aspects of blood vessels combined with the complex biochemical and biological microenvironment that cells experience in the native vascular tissue, all of which have been individually shown to have great impact on calcification of blood vessels. Here, we aim to combine advanced bioengineering and microfabrication technologies with a patient-specific biological model to create a biomimetic organ-on-chip platform that resembles the anatomical, (bio)mechanical, biochemical and biological microenvironment of vessels in physiological and calcification conditions. The model(s) shall allow mechanistic studies to unravel the underlying mechanisms of pathological calcification in the cardiovascular system as well as the investigation of the role of various biological, chemical and mechanical factors in developing calcified regions in vessels. Additionally, the model shall enable the screening of new drugs or interventions to prevent or reverse calcification in blood vessels.

Work techniques: Microfluidic chip design, computational fluid dynamics simulation, microfabrication/chip fabrication (e.g., photolithography, soft lithography, chip bonding), operation of microfluidic chips, advanced cell culture (of primary and human induced pluripotent stem cells (iPSCs)), molecular biology techniques (e.g., immunocytochemistry, histology, quantitative real-time polymerase chain reaction, etc.), imaging (light and electron microscopy).

Your profile: You should have a master degree in bio(medical) engineering/biomedical technology or similar. Candidates from related disciplines with a major in the above-mentioned fields or in biomaterials, tissue engineering or similar are welcome to apply, too; also candidates with a pharmacy/pharmaceutical sciences/biological sciences background. Interest and already first experiences (e.g., through a master thesis) in some of the following areas, namely organs on chips, microfluidics and -fabrication, (patho)physiology of the cardiovascular system, primary endothelial and vascular smooth muscle cell and iPSC culture, molecular biology techniques and/or fluorescent and scanning electron microscopy, are essential for successful conduction of the PhD project. Good command of scientific English in terms of listening, speaking, reading and writing is indispensable. Our potential new colleague should have very good theoretical and good experimental skills, be creative/inspired, have good scientific writing skills and be ambitioned. As the project involves a close collaboration between two institutes, we are seeking for candidates who are motivated to work as part of a team in such a multidisciplinary environment.

What we offer: We offer an interdisciplinary and collaborative PhD project embedded into two highly international research institutions of the Faculty of Health, Medicine and Life Sciences of Maastricht University. The MERLN Institute for Technology-Inspired Regenerative Medicine is one of the worldwide leading research institutes in the biomedical engineering and tissue regeneration fields. The CARIM School for Cardiovascular Disease is one of the largest cardiovascular research institutions in Europe. Our modern laboratories include labs for materials synthesis and characterization, biofabrication/-printing, (clean room) micro- and nanofabrication, microfluidics, cell/tissue culture, histology, molecular biology, imaging/microscopy, all provided with latest state-of-the-art equipment.

Keywords: Vascular calcification, coronary heart disease, *in vitro* models, organs on chips, microfluidics, microfabrication.

Relation to Priority Majors highly recommended by the Chinese government: 重大新药创制 / Major New Drugs Discovery, 前沿技术 / Frontier Technologies, 新材料技术 / Advanced Materials Technology, **先**进制造技术 / Advanced Manufacturing Technology, **基**础研究 / Basic Research, 人类健康与疾病的生物学基础 / Biological Foundations of Human Health and Diseases, **材料**设计与制备的新原理与新方法 / New Principles and Methodologies for Materials Design and Fabrication

Pre-clinical and health

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Major publications (IF: 2021 impact factor; #Cit: number of citations since 2016 according to Google Scholar)**:**

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[2] M. R. Carvalho, et al., Colorectal tumor-on-a-chip system: A 3D tool for precision onco-nanomedicine, Sci. Adv., 2019, 5(5), eaaw1317. IF: 14.972; #Cit: 95
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[5] P. Petsophonsakul et al., Nicotine promotes vascular calcification via intracellular Ca^{2+}-mediated, Nox5-induced oxidative stress, and extracellular vesicle release in vascular smooth muscle cells, Cardiovasc. Res., 2022, 118(9), 2196–2210. IF: 13.081; #Cit: 6