Initial Training Network on Small Artery Remodelling (SmArteR)

Who are we?

We are a group of European academic institutes and enterprises who perform R&D in the field of small arteries. We aim to improve scientific understanding of the role of these blood vessels in cardiovascular disease, and to pave the way for new therapeutic options.

Our network started in 2009, funded by the Marie Curie training programme of the European Commission ('SMART') and was coordinated by Per Hellstrand from Lund University, Sweden. We continued on November 2013 based on a new Marie Curie grant ('SmArteR') and is coordinated by Ed van Bavel at the Academic Medical Center in Amsterdam, the Netherlands. SmArteR will run until early 2018.

These grants have allowed us to set up large research training programmes for Ph.D. students and young post-docs. It is our philosophy to share our research progress and available technology with the scientific community. While we cannot include new partners, we do allow participation in our network symposia and training events where possible, and we are always willing to help you with your questions and ideas on collaboration in this field.

You can contact us at smarter@amc.uva.nl, or via our website www.smallartery.eu

What are small arteries?

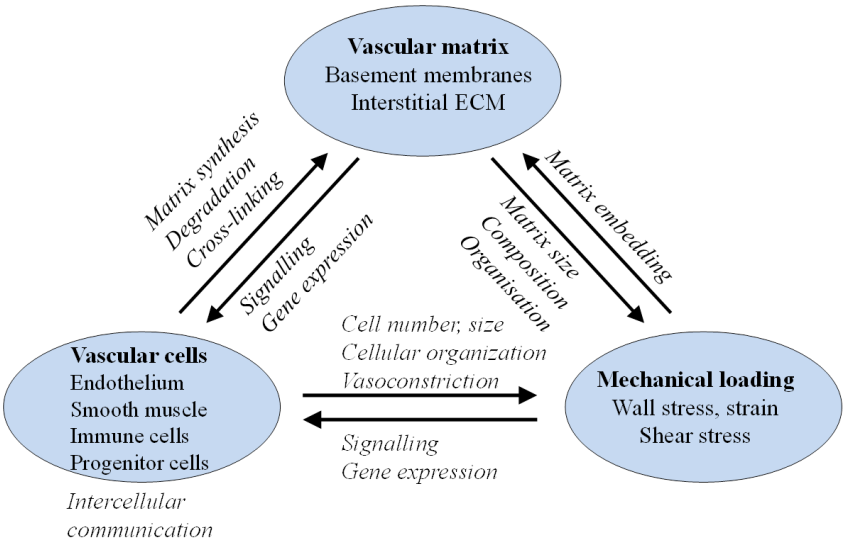
Our systemic arteries branch from the large aorta to increasingly smaller vessels, ending in the capillary bed that allows perfusion and oxygenation of all tissue in the body. This is an amazingly large network, containing hundreds of millions of blood vessel segments. Their diameter varies from 25 mm in the aorta to 0.01 mm in the most distal segments. In order to maintain blood flow through this network, a driving pressure is needed, which is the blood pressure generated by the heart. The ratio of pressure and flow is the resistance of this network.

It turns out that vessels of around 0.2 mm and smaller contribute to this resistance. Hence these vessels are called resistance arteries or small arteries. You cannot easily see them (on MRI or CT) or feel them (from the pulse). Yet they are there and they form the very vast majority of the arterial segments.

The small arteries have a very important task: to regulate local blood flow in each and every corner of our body. They do so by adjustments of their diameter. Quick functional changes are accomplished by contraction and relaxation of smooth muscle cells in the vessel wall. Chronic changes in the diameter result from reshaping of the vascular wall, where existing elements are reorganized, new elements are added, or elements are broken down. We call this vascular remodelling.

The regulation of the arterial diameter and wall structure is a continuous process of adaptation to changing needs, ranging from exercise to development of the body. This adaptation may malfunction: a too small diameter of the resistance vessels relates to insufficient tissue perfusion as well as hypertension.

The vascular wall consists of amongst others the vascular smooth muscle cells, endothelial cells that line the lumen, and elastic fibres and other extracellular matrix elements. Physical forces form an important part of the adaptation mechanisms of small arteries: blood pressure causes distension of the matrix elements, but also induces contraction of the smooth muscle cells and production of more cells and more matrix. Blood flow is sensed by the endothelial cells, which release factors such as nitric oxide that cause relaxation and remodelling towards larger diameters. Forces, cells and matrix therefore form a triangle of mutual effects that underlie vascular adaptation. We aim to unravel the functioning of this triangle.

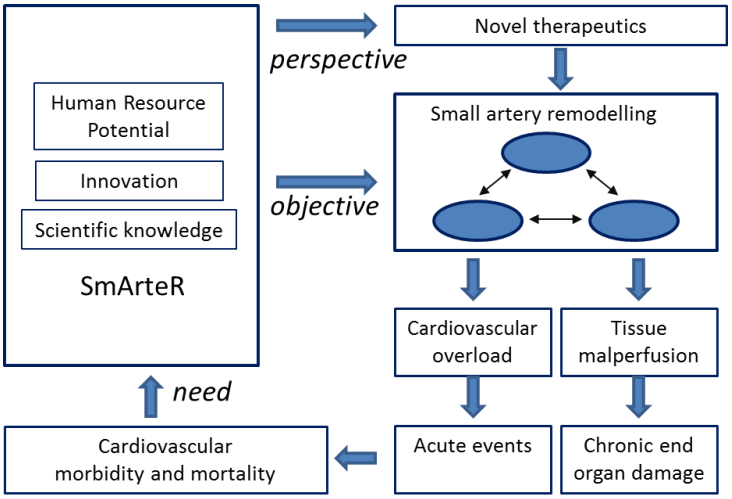


Why do we study small artery remodelling?

Cardiovascular diseases and their associated complications like stroke, heart failure or organ dysfunction currently account for 40% of deaths and impact significantly on costly long-term health care. This is a world-wide trend that is increasing at an alarming rate in European countries. Cardiovascular diseases are commonly associated with large vessel atherosclerosis; however, there is accumulating evidence that major disturbances occur in the small arteries that control tissue perfusion. In particular, these vessels undergo extreme reductions in their size and function in hypertension, aging, diabetes, obesity, and a sedentary life style, a process known as remodelling. Such changes manifest in malperfusion-related

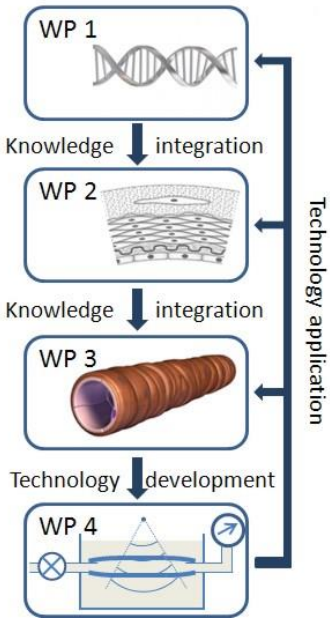
organ deterioration, including cognitive decline, heart failure and kidney failure. In addition, remodelling aggravates hypertension, which is a major risk for acute events, notably stroke and myocardial infarction.

Yet, despite this societal relevance, there is a marked paucity of research on this aspect of the vascular system. There is a consequent lack of innovation in diagnostic and therapeutic tools based on small artery remodelling. Our network will provide a wealth of information on small artery biology and potential therapeutic targets. New possibilities appear at the horizon, including inducible progenitor cell therapy, interference with micro-RNAs and personalised medicine. Hence, there is much to gain, but this will require a critical mass of interdisciplinary expertise on small artery remodelling. Our mission therefore is to train young scientists to become independent researchers and entrepreneurs in this rapidly growing field of small artery remodelling.



How do we study small artery remodelling?

We are studying small arteries on all levels of biological integration: molecular pathways (mechanosensitive gene expression, miRNAs), such as cell-matrix interaction and the role of pluripotent cells in the wall, regulation of vascular tone and remodelling, and development of novel technology on these vessels.



Specific experimental approaches use GFP-actin constructs and atomic force microscopy to detect actin dynamics, microarray and proteomics technology, progenitor cell isolation and culture. In addition, we run a number of techniques that are very specific for the study of small arteries. In the so-called 'wire myograph', these vessels are mounted as ring preparations, and tension generation by the smooth muscle cells is determined at a fixed distension. In pressure myographs, vessels are isolated and mounted on glass cannulas for pressurization and perfusion. In addition, we are able to maintain such pressurized segments under organoid culture, monitoring vascular remodelling *in vitro*. *In vivo* models include imaging of the microcirculation. This work is applied to a wide range of genetic and experimental models, e.g. hypertensive animals.

Our website www.smallartery.eu provides further details on the research teams and projects.

How can you contribute?

Ph.D. students seeking a position

The current Initial Training Network, SmArteR, will end early 2018, and there are no current positions available. We are actively seeking continuation of our network, and hope to be able to hire Ph.D. students in 2018. If you are interested, we suggest that you send an email to smarter@amc.uva.nl with your curriculum vitae and the request to remain updated on possible opportunities.

Vascular research groups

Formal involvement of new beneficiaries and partners in SmArteR is not possible, but we are happy to extend our network of informally collaborating laboratories. We are organising network events, such as workshops and summers schools, in which we can usually accommodate students from other laboratories, and we frequently invite speakers from other institutions for our meetings. Please see our website for further details of upcoming events.

Patient groups

Our research considers small arteries, which are of key importance for our health. Much of our work considers fundamental research questions that address the role of these vessels in cardiovascular health and disease. We are more than happy to answer any questions you may have on our research. Please send an email to smarter@amc.uva.nl!

Ed van Bavel
Coordinator of SmArteR