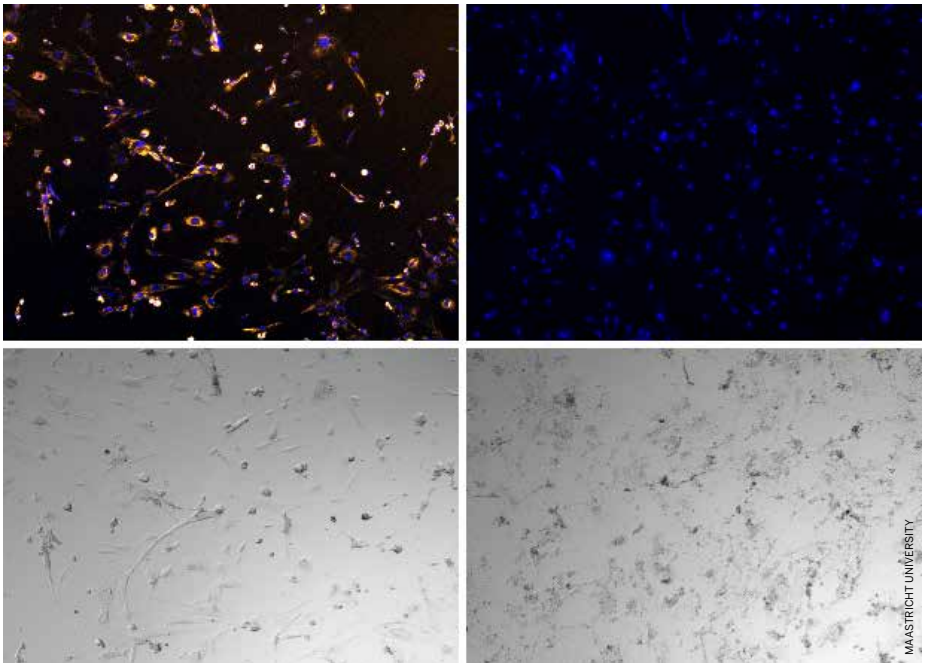

Left: calcifying cells treated with protein S Gla peptide; right: control.

A peptide against atherosclerosis

One of the leading causes of death worldwide is atherosclerosis. PhD student Anouk Gentier developed a peptide that can both trace and block calcifications in atherosclerotic plaques.

'Atherosclerosis is like a dam being built inside your arteries', says Anouk Gentier, PhD student at Maastricht University. 'This dam mostly consists of cholesterol, dying cells, scar tissue and microcalcifications. The latter is my study focus.'

Protein S

A microcalcification is like a ticking time bomb. Gentier: 'It increases the pressure the atherosclerotic plaque experiences. If rupture occurs, there could be nasty consequences, including stroke, myocardial infarction or necrosis of limbs. So, timely identification of these microcalcifications is essential.'
Gentier has found a way to do just that, and more. 'I am developing imaging agents that target microcalcifications even earlier than those currently used, like in PET imaging. We have the impression that these molecules actually inhibit the growth the microcalcifications.'
The molecule in question is a modified version of protein S Gla domain. Protein S is an endogenous anticoagulant and the Gla domain consists of multiple amino acids called glutamic acid. 'These glutamic acids are adjusted so that they carry two carboxyl (COOH) groups. These groups seem very important in the functioning of the peptide.'
Patient material was being used to test the peptide. Gentier: 'We get both healthy and diseased smooth muscle cells taken from patients that underwent surgery for their lesions in the University Hospital of Maastricht. These cells are then cultured, put upon a plate, and incubated with a medium enriched by either calcium, phosphate or both. We then treat them with either protein S Gla, bound to an imaging agent, in various concentrations or a negative control. Then we use a colorimetric assay to measure the number of microcalcifications formed.'

A microcalcification is like a ticking time bomb

Promising vesicles

Not only is the protein S Gla domain capable of detecting microcalcifications in the body. The peptide can also block the formation of these ticking time bombs. 'We see fewer microcalcifications in the treated cell cultures than in the negative control cultures', says Gentier. 'The exact mechanism of action is still unknown, but we think the peptide binds to the phosphatidylserine residues of the cell membrane of smooth muscle cells that are exposed to a calcifying environment. Through this binding the cells seem less prone to calcification.'
These findings may lead to a promising new treatment against atherosclerosis, hopes Gentier. She and her colleagues have ideas on how this could take shape. 'We have yet to finalise this, but we are planning on making extracellular vesicles in which we introduce both protein S Gla and annexin A2. The latter protein is known to have anti-inflammatory effects. So, we would have two ways to make atherosclerotic plaques less dangerous or even disappear.'
For a long time, doctors and researchers have assumed that microcalcifications inside an atherosclerotic plaque were stabilising the plaque. 'We now know it is quite the opposite, thanks to better tracers to monitor the process', says Gentier. 'And with this new endogenous tracer we can learn even more, and – as a big bonus – we can even treat the condition at the same time.' ●

Anouck Gentier is participating in the PhD Student Competition at the FIGON Dutch Medicines Days