Since many years, a substantial amount of money from companies and private investors is going to research. Hence, valorisation of research supported by this money is gradually becoming mandatory from a socio-economical perspective. These groups expect a direct impact of this research or for it to be translated into value for their organisation. However, it is important to remain vigilant that research remains question-driven and not answer-driven. Thus, involvement of external parties providing funding should not influence the experimental results obtained and reported. Question-driven research might be valorisable but needs to a priory expand scientific knowledge. Being part of a knowledge-based economy, it should be possible, however, that external parties benefit from research. Although expanding scientific knowledge does not have a direct effect on society, its relevance in the scope of fact-based decision making can be of great value. Additionally, this knowledge is essential to remain a leader in innovation.

The key objective of this thesis was to gain further insights in the role of vascular smooth muscle cells (VSMC) in the development of both intimal and medial vascular calcification to find potential targets for holding or regressing vascular disease. Vascular calcification is gradually acknowledged as an important risk factor for developing cardiovascular disease. Cardiovascular disease is still the leading cause of death in the western world and has a vast impact on the financial cost of health care systems. Hence, the importance of cardiovascular research cannot be overestimated. The impact of cardiovascular disease is discussed into greater detail in chapters 1 and 2.

Chapter 3 investigates effects of smoking on development of microcalcification in atherosclerotic plaques. Smoking is one of the leading preventable causes of death worldwide, and quitting smoking is associated with a significant reduction in risk of developing cardiovascular disease. Our research identified nicotine as a major component of cigarettes increasing microcalcification of atherosclerotic plaques in smokers. Nicotine is well known to the general public as the addictive component of cigarettes making the process of smoking cessation a long and difficult one. Many different strategies for smoking cessation can be employed. As nicotine is the addictive component, a specific group of medications known as nicotine replacement therapy has been successfully used to assist people with smoking cessation. Although smoking cessation through nicotine replacement therapy impacts overall cardiovascular morbidity and mortality caused by smoking, our research presents a critical side note to reconsider nicotine replacement therapy. As microcalcifications greatly reduce plaque stability, the use of nicotine replacement therapy will still maintain nicotine blood levels. Hence, the development of microcalcification in plaques will not be reduced. This also indicates that reduction in cardiovascular morbidity may be less than what could be achieved. Thus, our research promotes the use of alternative smoking cessation therapies over nicotine replacement therapy.

Chapter 4 and chapter 5 elaborate on the role of Ucma, a recently discovered extra-hepatic vitamin K-dependent protein. Our research demonstrated that this protein is present in (calcified) cardiovascular tissue similar to MGP, another extra-hepatic vitamin
K-dependent protein involved in the inhibition of ectopic calcification. Previously, it was shown that a specific form of MGP (desphosphorylated and uncarboxylated MGP) serves as a biomarker for vascular vitamin K status and predicts vascular calcification in patients. The antibodies against MGP and the use of dp-ucMGP as a biomarker was patented and an ELISA was developed to measure circulating MGP levels. This patent and ELISA were developed within VitaK BV, a Maastricht University spin off. The patents and assay have recently been sold to IDS, an UK based company that markets biomarkers for cardiovascular disease. Also for Ucma, its use as a biomarker for cardiovascular disease has been patented. Based on this patent, a new company called GenoGla has been founded. These companies offer jobs and hence present themselves as a return-on-investment to society.

In **chapter 5** we have unravelled the role of Ucma in the development of vascular calcification and highlighted the BMP-2-pSmad1/5/8-β-catenin dependent-pathway as a potential mechanism through which Ucma has a protective effect. Although additional research is still required to turn this pathway into a potential diagnostic or therapeutic target. In the future this knowledge will be of importance to develop therapies for vascular calcification.

Finally, in **chapter 6** we focussed on the role of medial VSMC in the development of atherosclerotic plaques. Our results demonstrated that reduced medial VSMC in the vessel wall result in significantly larger, more vulnerable atherosclerotic plaques. This finding might have great clinical implications. Stents are often coated with anti-proliferative drugs to prevent restenosis. Our finding highlights the need to reconsider the coating of stents with agents inhibiting VSMC proliferation. Although there are short term benefits of this approach, the long term benefits remain questionable and may lead to accelerated atherosclerotic plaque formation in the affected area and hence translate to a larger atherosclerotic burden.