Executive Summary

Prof. Bert Müller, Kantonsspital Basel

Project "Nanocontainers for local drug delivery to open heart vessels in case of heart attack"

Cardiovascular diseases are the main cause of mortality in Switzerland. Between 25 % and 50 % of the patients suffering from a heart attack die before they reach the high-technology environment of a hospital. The project should provide an encapsulation of a vasodilator to be administered in the ambulance. The infusion should deliver the vasodilator preferentially to the site of a critically occluded blood vessel to open the clogged arteries and avoid the negative side effects of systemic administration.

After a heart attack or stroke, an artery segment is occluded. The exact location of this stenosis, however, is usually unknown and we do not know any specific bio- or chemical mark-er, since inflammation is a common phenomenon in our body. As a consequence, we have proposed to take advantage of the endogenous wall shear stress significantly enhanced within the stenosed vessels. We have investigated this physical phenomenon and developed a nanocontainer that can transport the vasodilation drug through the blood vessel system and can release its cargo at constrictions as the result of the enhanced shear stress.

Our team discovered that lentil-shaped liposomes about 100 nm in diameter could be prepared from selected artificial phospholipids. These self-assembled nanocontainers provide enough space for a vasodilator including nitroglycerine and contains of a much tighter membrane than the natural phospholipids mainly due to a bilayer membrane interdigitation. The tightness leads to the non-spherical liposomes with defects in regions of high membrane curvature. The defects are even attenuated through mechanical stimuli such as shaking. Therefore, these nanocontainers are shear stress sensitive.

Our research team delivered the first proof-of-concept that mechanosensitive drug delivery is feasible. For this purpose, the Pad-PC-Pad liposomes were filled with a self-quenching dye, 5(6)-carboxyfluorescein. The dye release from the liposomes was monitored using fluorescence microscopy. The in vitro setup with an extracorporeal heart pump and polystyrene model showed a 20 % higher dye release through the constricted versus the model of the morphology of a healthy artery. The natural phospholipid liposomes used were insensitive.

For the appropriate modelling of the wall shear stress distribution using fluid dynamics one needs the detailed morphology of the arteries in health and disease. Together with partners from France, the team developed a protocol for the multimodal hard X-ray imaging of plaque-containing human arteries. This approach includes preparation steps such as decalcification and embedding, the imaging at laboratory and synchrotron X-ray sources, and a sophisticated treatment of the huge data sets. The approach is not restricted to blood vessels, but also reasonably applicable to other human or animal tissues.

In order to be sure enough that the vasodilator release takes place at the site of the stenosis, we have constructed micro-fluidic devices with well-defined shear stress values. In fact, the dye release was detected at the site of constriction.

Liposomal formulations, including the FDA-approved Doxil and AmBisome, are being recognized as foreign bodies and therefore cause complement activation. The in vitro and in vivo experiments we performed together Hungarian experts demonstrate a surprisingly low or even absent complement-activation-related-pseudo-allergy (CARPA) for the lentil-shaped, artificial liposomes.

The complementary expertise of medical doctors, physicists, and chemists was the prerequi-site to push forward this high-risk project. In the next step, the liposomes have to be further tailored to become effective within the diseased bodies of the numerous patients.