Design and testing of novel *in vivo* imaging probes for SPCCT and MRI

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Spectral photon-counting CT (SPCCT) is an emerging X-ray imaging technology that extends the scope of available diagnostic imaging tools. The photon-counting detector has the capability to detect K-edges and to distinguish simultaneously between different attenuation profiles, allowing multi-contrast agent imaging (1). Essentially, K-edge imaging offers exciting potential to transform CT into a true molecular imaging technology, but numerous challenges must be overcome for ultimate success in the clinic. Namely, SPCCT is relatively insensitive (10-1 to 10-3 mol/L). Therefore, the design of ideal contrast media that can provide maximum concentrations of suitable metals without toxicity is demanded (2). Lanthanides, most notably gadolinium, are predicted to afford an optimal signal level with SPCCT imaging. A number of Gd(III) chelates, routinely employed in clinical MRI practice, can find new diagnostic applications in SPCCT imaging without requiring extensive safety assessment. Molecular imaging of biological targets requires the specific accumulation of contrast media at the target site. However, the density of the molecular target might be inherently low, limiting the amount of contrast agent that can be accumulated and eventually the sensitivity of the imaging technique. An interesting approach to increase the concentration of contrast media at the target site is to link several Gd(III) chelates to the same targeting vector, in order to accumulate multiple copies of the contrast agent within a single target binding event. The aim of this project is to develop a novel bifunctional agent, carrying one functional group for the bioconjugation to targeting vectors and four Gd(III)-DOTA-like functions as contrast agent. This compound can be used as versatile building block to insert a pre-formed Gd(III)-multimer to biological targeting vectors (3). In particular, the tetramer has been used to label a tropoelastin-binding peptide. Tropoelastin may represent a promising imaging biomarker for non-invasive detection of atherosclerosis progression and lesion instability resulting in earlier diagnosis (4). Actually, dysfunctional matrix turnover, occurring in atherosclerosis progression, leads to the accumulation of monomeric tropoelastin rather than cross-linked elastin (5). Such Gd(III)-labelled peptide can be considered as a dual-modality molecular imaging probe, as it can be used both for K-edge imaging and MRI. In conclusion, this thesis is devoted to investigate the feasibility of monitoring lesion progression and rupture-prone plaques, in a pre-clinical level, by means of MRI (Fig.1) and SPCCT imaging.

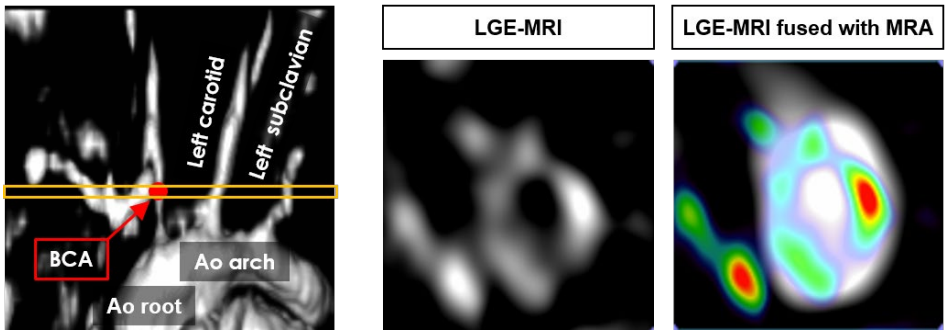

Figure 1: *In vivo* MRI (vessel wall enhancement) using the tropoelastin-binding contrast agent in an atherosclerotic apolipoprotein E-deficient mouse. MRI of the brachiocephalic artery (BCA) showed enhancement of the vessel wall after administration Gd_4-TESMA because of the presence of tropoelastin in the atherosclerotic lesion.

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