A Novel Dual-Modality MRI/PET Probe

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Introduction

About 70 million Americans suffer from one or more types of cardiovascular disease, which are the major, primary or contributing causes of death in the United States (58% of all deaths). Current methods for imaging disease are geared towards identification of advanced disease with significant stenosis and indirectly image the lumen, rather than the lesion. We describe development of targeted contrast agents that will enable *in vivo*, combined Positron Emission Tomography (PET) and Magnetic Resonance (MR) imaging of early atherosclerosis and restenosis. We propose to use the high sensitivity of PET to first locate regions of potential blockages of the blood vessel, which then can be probed at higher resolution by using MRI. Interest in multimodality imaging has surged in recent years and multimodality probes will play a pivotal role in clinical molecular imaging of the future.

Methods and results

The contrast agent is targeted to macrophages, one of the earliest cellular components of developing plaques. Macrophages are labeled through the macrophage scavenger receptor A using an MRI contrast agent derived from scavenger receptor ligands. The agent is based on a maleylated bovine serum albumin (mal-BSA) with a conjugated 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) ligand system, that can tether both paramagnetic Gd^{3+} and a positron emitter, *e.g.* $^{64}Cu^{2+}$. Conjugation of 18 Gd-DOTA groups per molecule resulting in relaxivity of 31 $mM^{-1}s^{-1}$, which is comparable to literature values for similarly substituted proteins. Incorporation of ≥0.1 μCi/ml $^{64}Cu^{2+}$ shows sufficient activity for imaging by PET.

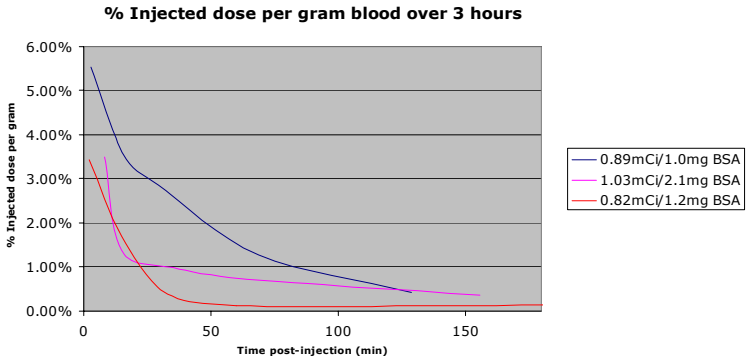

Figure 1. Clearance of agent from the blood stream.

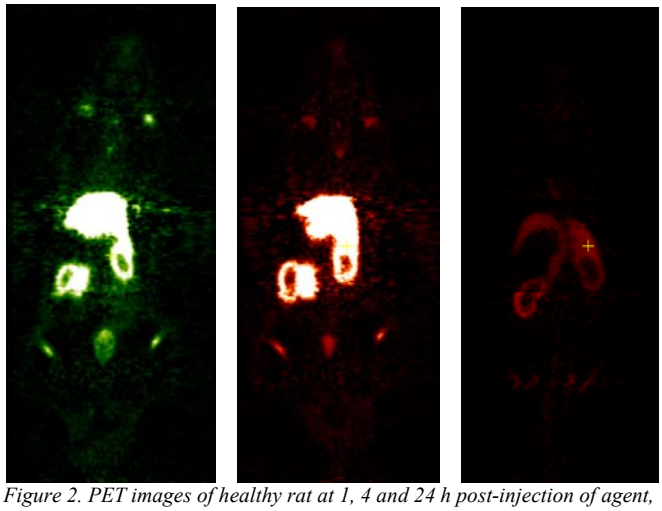

Figure 2. PET images of healthy rat at 1, 4 and 24 h post-injection of agent, showing high activity in the liver and kidneys.

Experiments in cultured cells demonstrate receptor-mediated uptake of the probes by macrophages, and show measurable contrast in MR image. The agent is rapidly cleared from the blood (Figure 1). Biodistribution studies in rat models show clearance of the contrast agent by kidney and liver, which decreases to low levels by 24 hours (Figure 2). Imaging of atherosclerotic plaques in transgenic ApoE knock-out mice and rats with balloon angioplasty injured vessel walls will give further information of the *in vivo* PET and MR imaging capabilities.

Conclusions

This novel MRI contrast agent has been combined with features for plaque lesion detection using PET, allowing the application of only one contrast agent for imaging using both these non-invasive modalities. Also the performance of this contrast agent, in this case targeted towards vascular inflammation, may give possibilities for tracking of other inflammatory diseases such as tumor immunotherapy and transplant acceptance using MRI/PET.