Quantitative ^{19}F MRI and CT Tracking of Microencapsulated Stem Cells in a Rabbit Peripheral Arterial Disease Model

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Target Audience: MR physicist interested in quantitative fluorine MRI; physician-scientists interested in cardiovascular applications of stem cell tracking.

Purpose: Nearly 12% of Americans suffer from peripheral arterial disease (PAD). Due to the severity of the disease, many are ineligible for conventional medical and surgical treatment. Microencapsulated stem cells (SC) offer a novel means to transplant mismatched SCs to avoid immunorejection and enable tracking using conventional imaging modalities. However, quantitative evaluation of cell fate has been elusive. Here we explore *in vivo* quantitative serial cell tracking of the volume and ^{19}F concentration of the dual X-ray/MR-visible SC microcapsules (XMRCaps) containing either human or rabbit SCs (XenoSC or AlloSC, respectively), using clinical c-arm CT and ^{19}F-MRI, in a non-immunosuppressed rabbit PAD model.

Methods: XMRCaps were produced using a modified alginate-poly-L-lysine-alginate microencapsulation method impregnating 12% v/v perfluorooctyl bromine (PFOB) [1] and XenoSCs or AlloSCs. Accuracy of volume and concentration measurements were performed in agarose phantoms consisting of five tubes containing a volume comparable to one *in vivo* injection (~0.5cc) of pure XMRCaps (n=3) or diluted XMRcaps (n=2). C-arm CT images (dynaCT, Siemens Artis Zee) were acquired and reconstructed at 0.3 mm isotropic voxel size. ^{19}F 3T MRI was acquired with a 4-channel Tx/Rx ^{19}F coil using a 3D TrueFISP (Siemens Tim Trio, TR/TE 4.1/2.0 ms TE; 70° flip angle; 32 averages) in the coronal plane. Reference ^{1}H MRI was acquired with the body matrix coil (6 channel phased-array) using a 3D gradient echo sequence (TR/TE 15/5.45 ms, 0.45x0.45x1.5 mm^3 voxel, 20° flip angle). *In vivo* c-arm CT and MRI studies were performed at immediately, one, and two weeks after an intramuscular administration of a total of 3ml of XMRCaps in the hindlimb (n=10) using identical imaging parameters as the phantom studies. To test the repeatability of ^{19}F MRI, images were acquired twice on the same day in one rabbit with the coil repositioned in between. Reference markers with known PFOB concentrations were placed within the imaging field at the same depth of the injections relative to the coil to enable field inhomogeneity and coil profile corrections.

Segmentation of the injection sites in the c-arm CTs and ^{19}F MRIs was performed in Matlab using a region grow and an Otsu thresholding algorithm respectively. An image morphology operation was performed to eliminate TrueFISP artifacts and smooth noise. XMR Cap injection site concentration were then determined by averaging the integrated ^{19}F signal intensity over the segmented volume after normalization to standards.

Result: The *in vitro* XMRCap volumes were highly correlated (0.003±0.03cc difference between CT and MRI). *In vivo* injection locations on CT and MRI were highly concordant (Fig 1a,b). ^{19}F MRI repeatability studies showed that the volume and concentration measurement errors were <3% and <6%, respectively. For the AlloSC rabbits, *in vivo* XMRCap injection volume and concentration decreased 0.2±24% and 7.4 ±17% each week, respectively, whilethe XMR volume increased 1.2±11% and concentration decreased 6.6±17% each week in the XenoSC rabbits (Fig 1c and d).

Conclusion: MRI provides an accurate assessment of XMRCap volumes *in vitro* compared to CT, which serves as the gold standard. *In vivo* XMRCaps injection site volumes could be assessed on MRI and CT. However, only MRI was able to quantify the XMRCaps ^{19}F volumes and concentrations without ionizing radiation. The similar trends of small changes in volume and concentrations of XenoSC and AlloSC microcapsule injections suggest that encapsulation is effective in preventing immunorejection of the mismatched SCs. Thus, the technique shows promise for assessment of patients after cellular therapy for PAD.

REFERENCE [1] Barnett BP, et al.Nat Protoc 2011 6(8)1142-51.

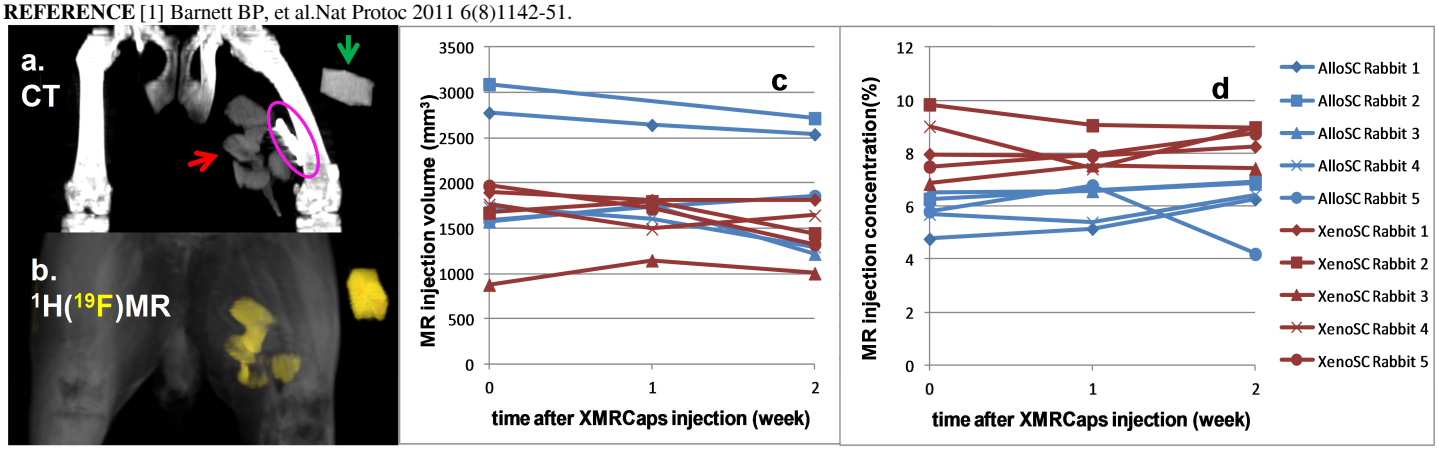

Fig1 (a) DynaCT image of a rabbit model of PAD (created by a platinum coil(purple)) acquired one week after XMRCap injection. Arrows denote and the injection sites (red) and the standard marker (green). (b) ^{19}F MR image (yellow) of the same rabbit as Fig 1a fused with gray scale ^{1}H MR image. (c) Segmented MR injection volume and (d) PFOB concentration of AlloSC rabbit (blue) and XenoSC rabbit (red) vs. time.

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