Quantitative ^{19}F MRI and CT tracking of the Microencapsulated Stem Cells in 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: Microencapsulated stem cell (SC) impregnated with contrast agents offers a novel means to transplant mismatched SCs to avoid immunorejection and enable tracking using non-invasive imaging modalities. In this study, we first explore quantitative serial cell tracking using c-arm CT and ^{19}F-MRI of dual X-ray/MR-visible SC microcapsules (XMRCaps) in a rabbit peripheral arterial disease model (PAD) model using conventional clinical imaging systems.

Methods: XMRCaps were produced using a modified alginate-poly-L-lysine-alginate microencapsulation method impregnating 12% v/v perfluorooctyl bromine (PFOB) [1] and human or rabbit SCs for X-ray and ^{19}F MR visibility. *In vitro* validation studies were performed in an agarose phantom consisting of four layers of 50, 100, and 200 XMRCaps. C-arm CT images (dynaCT, Siemens Artis Zee, 240° scan angle; 0.5° increment; 0.36 µGy dose per pulse; 48 cm field of view) were acquired and reconstructed at 0.46 mm isotropic voxel size. ^{19}F 3T MRI was acquired with a flexible, 4-channel Tx/Rx ^{19}F coil using a 3D steady-state free precession pulse sequence (TrueFISP, Siemens Tim Trio, 4.1 ms repetition time; 2.0 ms echo time; 70° flip angle; 32 averages) in the coronal plane. Reference ^{1}H MRI was acquired with the system single channel body coil or the body matrix coil (6 channel phased-array) using a 3D gradient echo sequence (15 ms repetition time; 5.45 ms echo time, 0.45x0.45x1.5mm voxel size, 20° flip angle). *In vivo* c-arm CT and MRI studies were performed at one, two and three weeks after an intramuscular injection of ~3 ml human SC (XenoSC) or rabbit SC (AlloSC) XMRCap in the hindlimb of six rabbits using the identical imaging parameters as the *in vitro* studies. To test the repeatability of ^{19}F MRI, two imaging sets were acquired on the same day in one rabbit with the ^{19}F coil repositioned in between. To enhance repeatability of the *in vivo* studies, the flexible fluorine coil was constrained to a fixed geometry. Reference markers with known concentrations and volumes of PFOB were placed within the imaging field at the same depth of the injection sites relative to the coil to enable quantitation of XMRCap injection sites.

Segmentation of the injections sites (and reference markers) in the c-arm CTs and ^{19}F MRIs was performed with a thresholding algorithm (threshold=µ+6σ of the background noise). Relative fluorine concentration was then determined by averaging the integrated ^{19}F signal intensity over the segmented volume after normalization to the ^{19}F standards.

Result: Calculated CT and MRI XMRCap volumes in were highly concordant *in vitro* (y=0.8x+3.0, R^2=0.95) (Fig 1a). *In vivo* CT injection site volumes were 76% of MRI volumes; resizing the CT images to lower MRI resolution resulted in CT volumes more closely mirroring MRI volumes, i.e., 96%. ^{19}F MRI repeatability studies showed the volume and concentration measurement errors were <3% and <6%, respectively. For the AlloSC rabbits, *in vivo* XMRCap injection volume decreased 5 ± 5% each week and concentration increased 4 ± 9% each week, while the XenoSC rabbits had volume and concentration decreases of 30 ± 2% and 35 ± 17%, respectively, each week (Fig 1b, c).

Discussion: MRI provides accurate assessment of XMRCap volumes, which were slightly larger than CT due to partial volume effects with the larger MRI voxel size. *In vivo* XMRCaps injection site volumes in the ischemic environment of the PAD rabbit could be tracked on MRI and CT. However, only MRI was able to quantify the XMRCaps alterations in the fluorine concentration that reflect capsules degradation. In particular, decreases in XMRCap volumes with stable or increasing fluorine concentrations in animals that received allogeneic stem cells suggest better tolerance of allogenic microencapsulated cells than xenogenic stem cells.

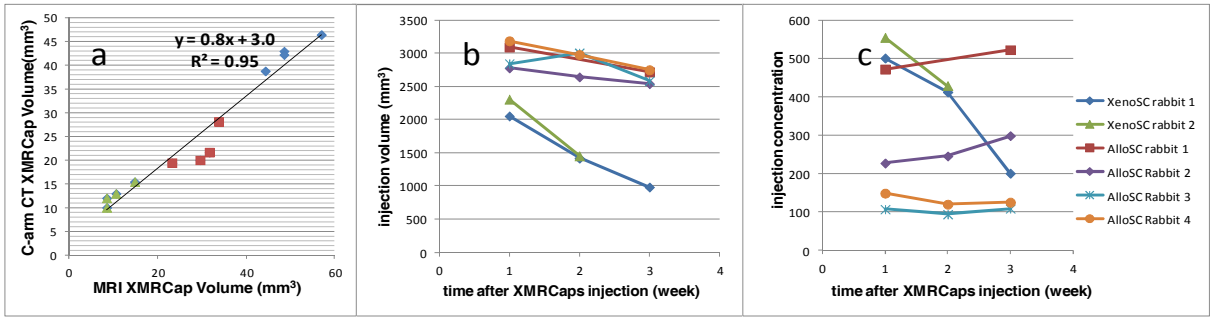

Fig1 (a) Correlation of the 200 (blue), 100 (red) and 50 (green) XMRCaps volumes in MRI vs. CT. (b) The XMRCaps injection volume in ^{19}F MRI images at one, two and three weeks after delivery. (c) Relative normalized fluorine concentration corresponding to the segmented volumes. The volume and concentration in AlloSC injections are more stable than the XenoSC injection over time.

REFERENCE [1] Barnett BP, et al. Radiology. 2011;258(1):182-91 [2] Liddell RP, et al. J Vasc Interv Radiol. 2005; 16(7):991-8

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