Stem cell tracking potential of Magnetic Particle Imaging compared with 19F Magnetic Resonance Imaging

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INTRODUCTION Stem cells have the potential to be used as treatment for regenerating cardiac and brain tissue, which both have limited self-healing capacities [1]. An important indicator for success of these type of treatments is cell fate: survival and engraftment of the stem cells. Localization of stem cells can be done by cell tracking; a process in which the cells are ‘labeled’ with a contrast agent or tracer material and a corresponding imaging technique is used to follow the stem cells, by scanning the body several times during several weeks.

The main modalities that are able to perform stem cell tracking deep inside the body (Single Photon Emission Computed Tomography, Positron Emission Tomography and Magnetic Resonance Imaging with T1 or T2 contrast agents) require at least 10,000 cells for detection, according to Nguyen (2014) [1]. Recently, fluorine-based MRI (19F MRI), has received more attention as a potential candidate for stem cell tracking even though sensitivity is still limited for clinical use [2]. Meanwhile, Magnetic Particle Imaging (MPI) has been shown to be useful for stem cell tracking as well [3]. A comparison between MPI and 19F MRI for stem cell tracking purposes has not yet been made. In this work, we aim to make a fair comparison between both techniques to determine which technique is most sensitive and therefore has the highest potential for future stem cell tracking research.

MATERIAL AND METHODS Sensitivity is here defined as the number of cells that is needed per voxel to be positively identified in an image. This detection limit depends on the physical sensitivity of the system and the amount of tracer that can be incorporated inside a cell through cell labeling.

For MPI, the detection limit of the system is tested by positioning 13 ‘point sources’ with small amounts of Resovist® (Bayer Schering Pharma AG, Leverkusen, Germany; 0.5 mmol Fe/m), ranging from 225 to 3600 ng Fe inside 50 g of chicken breast, five samples at a time. Scans have been performed with a 7 T/m Tesla system, built at UC Berkeley. Signal to Noise Ratio (SNR) is determined for all samples and a linear fit is obtained for a better estimate of the detection limit of the system, which we define to be three times the standard deviation of the background noise.

For 19F MRI, similar SNR experiments are performed with 13 samples (0.1 to 6.4 mol/l KF) in chicken breast with a Bruker 7 T small animal MRI scanner. Since point sources are harder to make for MRI due to local field inhomogeneity artifacts, instead volumes of 100 µl of diluted KF are scanned with a 90° Spin Echo sequence. Due to the bigger volume, several voxels should now contain maximum signal (resolution = 1x1x1 mm³), and averaging is done for four voxels containing the highest signal in one slice.

Cell uptake information was gathered for bone marrow-derived human mesenchymal stem cells (hMSCs; ATCC PCS-500-012, Manassas, VA). Uptake information of Resovist was already known [4], but labeling information of PFPE in hMSCs is limited and has been experimentally determined.

Normalization between experiments is done based on scanning parameters such as acquisition time and amount of voxels, which both affect the number of repetitions. Since cell labeling for MRI is done with an emulsified PFPE CS-1000 (Celsense Inc., Pittsburgh USA) with a shorter longitudinal relaxation time (T1) than KF, the detection limit was normalized for this factor as well. 1.5 x 10⁶ hMSCs are co-incubated with CS-1000 at 5 mg/ml for 24 hours. Labeling efficiency is determined in a 400 MHz NMR system with a known quantity of KF as a reference.

RESULTS An overview of the results is given in table 1. For MPI and 19F MRI, mass refers to the iron content in Resovist and fluorine content in KF and CS-1000 respectively. Note that for 19F MRI the detection limit is given for 19F in KF while cell loading is given for 19F in the emulsified PFPE.

Table 1: Overview of detection limits and cell loading.

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<th>MPI</th>
<th>19F MRI</th>
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<tr>
<td>Detection limit tracer (ng)</td>
<td>250-350</td>
<td>3800-5700</td>
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<tr>
<td>Cell loading (pg/cell)</td>
<td>78 [4]</td>
<td>41</td>
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CONCLUSION & DISCUSSION Loading of PFPE inside the hMSCs has been improved compared to existing literature [5], which has led to an improved detection limit of 19F MRI. Comparing sensitivity of MPI and 19F MRI is not straightforward. An interesting challenge is to normalize for scanning time, which is affected by repetitions, amount of voxels and T1 relaxation time. Despite these challenges and being in early stages of its development, MPI is found to be at least an order of magnitude more sensitive for cell tracking of hMSCs than 19F MRI. This would imply that MPI has tremendous potential to become the leading modality for tracking stem cells and thereby improve research towards stem cell therapy.

REFERENCES