Title: Trimodal cell tracking in vivo: Combining iron- and fluorine-based MRI with MPI to monitor the delivery of mesenchymal stem cells and the ensuing inflammation

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Structured Abstract:

Introduction: The therapeutic potential of mesenchymal stem cells (MSCs) is limited as many cells undergo apoptosis following administration. Additionally, the attraction of immune cells (predominately macrophages) to the site of implantation can lead to MSC rejection. Many experimental studies of MSC engraftment have been conducted using histology, which provides detailed molecular and morphological information but is limited to the interrogation of a single time point and portion of tissue. We implemented a trimodal imaging technique to monitor the fate of transplanted MSCs and infiltrating macrophages in vivo. This technique combines iron and fluorine-19 (19F) based magnetic resonance imaging (MRI) with magnetic particle imaging (MPI).

Methods: MSCs were labeled with an ultrasmall superparamagnetic iron oxide (USPIO) nanoparticle (ferumoxytol) then implanted within the hind limb muscle of 10 C57Bl/6 mice. Control mice received unlabeled MSCs (n = 5). A perfluorocarbon agent was then administered intravenously for uptake by phagocytic macrophages in situ. 1 and 12 days later, the ferumoxytol-labeled MSCs were detected by proton (1H) MRI as a region of signal loss and MPI as a region of positive contrast. Perfluorocarbon-labeled macrophages were detected by 19F MRI. 1H/19F MRI was acquired on a clinical scanner (3T) using a dual-tuned surface coil and balanced steady state free precession (bSSFP) sequence.

Results/Discussion: The measured volume of signal loss (in 1H images) and MPI signal declined over 12 days, indicating the death and clearance of iron-labeled MSCs. 19F signal persisted over 12 days, demonstrating the continuous infiltration of PFC-labeled macrophages. Since MPI and 19F MRI signal are directly quantitative, we calculated estimates of the number of MSCs and macrophages present over time. Following the last imaging session, the muscle of these mice were collected and sectioned then stained with H&E (to locate MSCs), Perl's Prussian Blue (to identify iron in MSCs), and F4/80 immunostaining (to detect macrophages). This is the first study to demonstrate the ability to image macrophage infiltration in vivo using 19F on a clinical (3T) MRI system. This is also the first study to combine the use of iron- and fluorine-based MRI with MPI cell tracking.