Tracking of intravenously injected magnetically labelled progenitor cells in a mouse stroke model by high field MRI

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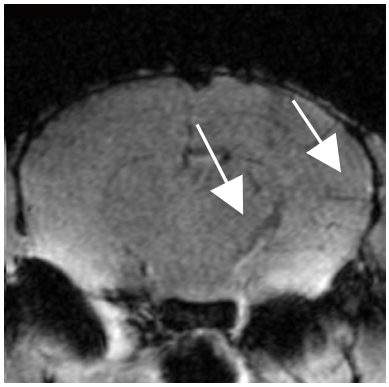
Objectives - Recent studies suggest a positive role for stem cells in the regeneration of tissue following an ischemic insult. We hypothetize that spleen derived mononuclear cells (MNC's) are actively recruited from the blood stream by signals released from ischemic brain tissue. In order to monitor migration of intravenously injected progenitor cells by high field MRI, we magnetically labeled primary culture spleen derived MNC's with Very-Small-Superparamagnetic-Iron-Oxide-Particles (VSOP).

Materials and Methods – MNCs were isolated from transgenic GFP expressing mice and magnetically labelled with VSOP. 30 mice were treated with both 30 min and 60 min middel cerebral artery occlusion (MCAO) for stroke induction. 1×10^6 magnetically labelled cells were injected into the tail vein at various time points after MCAO. T2 and T2* weighted images were taken of mouse brains before cell injection and up to five weeks after cell injection at 7T. For MR-histological correlation, Prussian Blue staining was performed for the magnetic label, and confocal microscopy for GFP fluorescence.



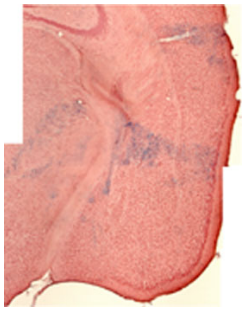


Figure 1. **Typical T2* hypointensities after developing in the first 48 h after MCAO with corresponding histology.** T2* weighted MRI conducted at day four after cell transplantation. T2*-weighted image shows a hypointense shaded region bordering the ischemic tissue developing in the first 48 hrs to 4 days following VSOP labeled MNC injection. Prussian blue positive cells are found in areas of T2*-weighted hypointense signal changes

Results – 24 hrs after stroke induction, ischemic tissue appeared hyperintense in T2 weighted images, whereas, ischemic tissue did not show any significant effect on T2* weighted images. Four days after cell treatment, several regions of shaded hypointense signal in the T2* weighted images appeared in the borderzone of the hyperintense (T2w) ischemic areas. Histologically, clusters of iron positive MNC's as well as numbers of single cells were found to be closely correlating to the MR signal changes seen in T2* weighted images. Fluorescence microscopy revealed GFP positive cells in correlation to both the iron-positive cells and the T2* hypointensities. These correlated signals were found in the ischemic tissue and in brain regions surrounding the ischemic tissue.

Conclusion - The results show that *in vivo* tracking of systemically injected labeled stem cells appears possible by the use of high field MRI combined with an efficient labeling method. Our results demonstrate the arisal of shaded hypointense regions around ischemic tissue and in other brain regions in T2* weighted images three to four days following cell injection. These signal changes seeme to reflect accumulations of systemically injected cells in the ischemic brain.