# In Vivo MR Imaging of Bone Marrow Cell Trafficking to Atherosclerotic Plaques

B. Qiu[1], P. Walczak[1,2], J. Zhang[1], F. Gao[1], S. Kar[3], J. W. Bulte[1,2], X. Yang[1]

[1]Radiology, Johns Hopkins Univ School of Medicine, Baltimore, MD, United States, [2]Institute for Cell Engineering, Johns Hopkins Univ School of Medicine, Baltimore, MD, United States, [3]Biomedical Engineering, Johns Hopkins Univ School of Medicine, Baltimore, MD, United States

## Introduction:

Recent studies have shown that hematopoietic bone marrow (BM) cells participate in the formation of different types of plaques, such as hyperlipidemia-induced atherosclerosis and transplant-associated vasculopathy (1,2). We attempted to use MRI to monitor, *in vivo*, trafficking of magnetically labeled BM cells to atherosclerotic lesions.

## Materials and Methods:

BM-derived cells from LacZ-transgenic mice were labeled with a superparamagnetic MR contrast agent, Feridex, and then transplanted into ApoE$^{-/-}$ recipient mice (n=25) with an atherogenic diet for approximately 7-9 weeks. The ApoE$^{-/-}$ mice were divided into different study groups with various treatments, including: (a) Group I with Feridex-labeled BM cell transplantation (n=10); (b) Group II with unlabeled BM cell transplantation (n=10); and (c) Group III with no BM cell transplantation (n=5). Approximately 13-15 weeks after BM cell transplantation, migrating Feridex/LacZ-BM cells to atherosclerotic lesions were monitored, *in vivo,* on a 4.7T MR scanner with a fast spin echo (FSE) sequence. To further valuate the detection of atherosclerotic lesions in the mouse aorta, *ex vivo* high resolution, 3D MR imaging of two isolated thoracic aortas was performed on a 9.4T and an 11.7T scanner with an FSE sequence. The MR images were subsequently correlated with (a) histology to grade the atherosclerotic lesions, and (b) histochemistry with Prussian blue and X-gal staining to detect Feridex- and LacZ-positive cells at the atherosclerotic tissues.

## Results:

Histological examination revealed formations of atherosclerotic plaques in 17 cases and neointimal hyperplasia in 8 cases. *Ex vivo* high-resolution MR imaging demonstrated details of plaque structure, which was correlated with histology confirmation (Fig. 1). In Group I with Feridex-labeled BM cell transplantation, *in vivo* MR imaging showed larger MR signal voids of the aortic walls (due to the "blooming" effect of Feridex) in four cases, in which Feridex- and/or LacZ-positive cells were detected with histochemistry. No such findings were visualized in the two control animal groups (Groups II and III)(Fig. 2). In the eight cases with intimal hyperplasia, no larger MR signal voids of the aortic walls were detected by in vivo MR imaging.

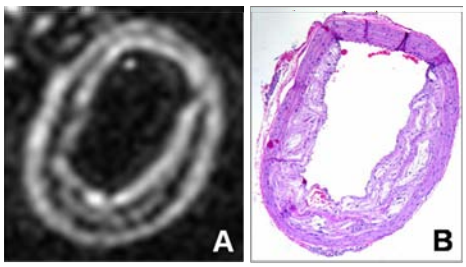


**Fig. 1.** (A) Cross-sectional view of an ex-vivo 11.7T MR image of the ApoE$^{-/-}$ mouse aorta, showing the thickened aortic wall due to the formation of hyperlipidemia-induced atherosclerotic plaque, which is confirmed by histology correlation (B, H&E, 10X).

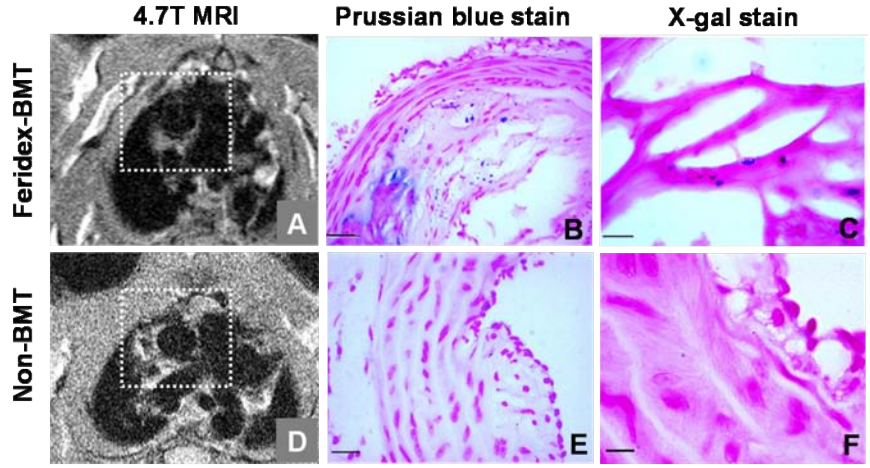


**Fig. 2.** (Upper panel) An ApoE mouse with Feridex-labeled BM transplantation (BMT) compared to a control ApoE mouse without BM cell transplantation (Low panel). (A) Cross-sectional view of an *in vivo* 4.7T MR image shows larger MR signal voids of the ascending aortic wall, while no such finding is visualized in the control aorta on D. Insets in A&D outline the ascending aorta. Histochemical staining with Prussian blue (B&E, 40X) and X-gal (C&F, 100X) detects Feridex- and LacZ-positive cells (blue colors on B&C) in the atherosclerotic lesion transplanted with Feridex/LacZ BM cells, which are not seen in the control tissue with no BM cell transplantation (in E&F).

## Conclusion:

We present a potential method of using MRI to monitor, *in vivo*, trafficking of magnetically labeled bone marrow cells to atherosclerotic lesions, which may provide a useful tool to guide the targeting of hematopoietic cells for gene therapy- or chemotherapy-based interventions in atherosclerotic cardiovascular disease.

**References:** 1) Krause D, et al. Cell 2001;105:369. 2) Sata M, et al. Nat Med 2002:8:403.