Relationship Between Macrophage Content and MRI Signal Intensity of Atherosclerosis Using Gadolinium-Containing Immunomicelles Targeted to Macrophage Scavenger Receptor.

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Introduction and Purpose: Macrophages play a vital role in the pathogenesis of atherosclerosis. They are major sources of inflammation and LDL oxidation. Furthermore, the necrotic core of ruptured/thrombosed plaques often contains a high content of macrophages. Gadolinium-containing immunomicelles (gadolinium-marked micelles linked to a specific antibody targeting macrophages) have been shown to improve in-vitro and ex-vivo assessment of macrophages using MRI. We have also demonstrated the efficacy of macrophage-targeted immunomicelles to image atherosclerosis in vivo using ApoE knockout mice. The aim of the current study is to evaluate the relationship between macrophage content of atherosclerotic plaque and in vivo MRI signal intensity in the atherosclerotic aorta using immunomicelles as a contrast agent targeted to macrophages.

Methods: Immunomicelles, micelles and standard (Gd-DOTA or Gd-DTPA) MRI contrast agents were tested in ApoE KO mice. Mice were imaged at baseline with a 9.4T MR system. The mice were then imaged at intervals following a tail injection of immunomicelles (n=7), untargeted micelles (n=3) or standard agent (n=3). Immunohistochemistry, laser-scanning confocal microscopy, and standard pathology were performed to co-localize immunomicelles and plaque.

Results: Using untargeted micelles signal intensity (SI) increase in the aortic wall post-contrast was an avg of 1.5 ± 0.3 (enhancement of 50%) at 1-hr post-contrast, 1.35 ± 0.2 (35% enhancement) at 24-hrs post, 1.22 ± 0.2 (22%) at 48-hrs, 1.15 ± 0.12 (15%) at 72-hrs & 1.00 (0%) at 1-wk. Using **targeted immunomicelles** the signal intensity (SI) increase in the aortic wall post-contrast was an avg of 1.51 ± 0.3 (**enhancement of 51%**) at 1-hr post-contrast, **1.65 ± 0.2 (65% enhancement)** at 24-hrs post-contrast, 1.21 ± 0.2 (21%) at 48-hrs, 1.10 ± 0.12 (10%) at 72-hrs & 1.01 0% at 1-wk. **See Figure 1.** In the control ApoE group there was no significant enhancement. **Confocal microscopy showed co-localization of macrophages and NBD-chromophore-labeled immunomicelles in plaque (Figure 2).** Using the macrophage-stained confocal microscopy sections and IHC sections, there was a relationship between the number of macrophages per ROI (region of interest) and the MRI signal intensity observed on the imaged matched sections of the atherosclerotic aorta (R2=0.71 p=0.07). Analysis is ongoing with improving significance as we add more numbers to the total examined.

Conclusions: Immunomicelles show promising results in the in-vivo detection of atherosclerotic vascular disease using molecular MR imaging. There appears to be a relationship between macrophage content and MRI signal intensity using immunomicelles as the contrast agent. Immunomicelles may prove useful in detection of high-macrophage density typical of high-risk plaques.

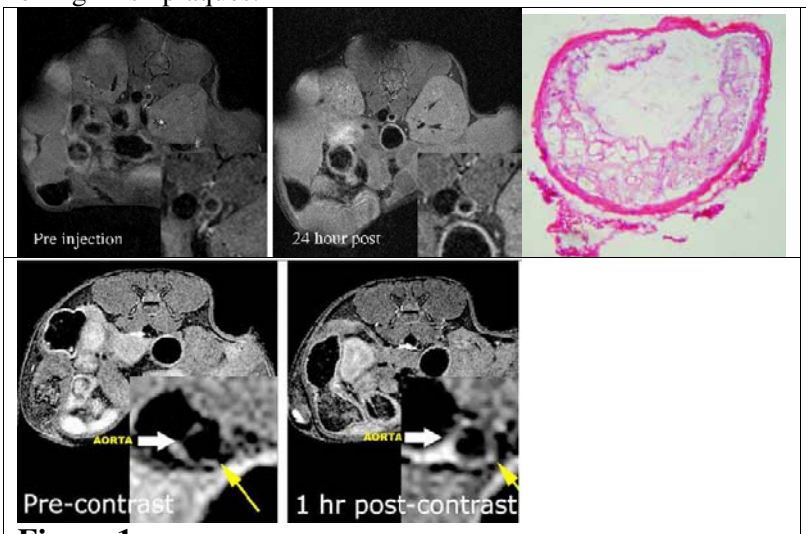

Figure 1

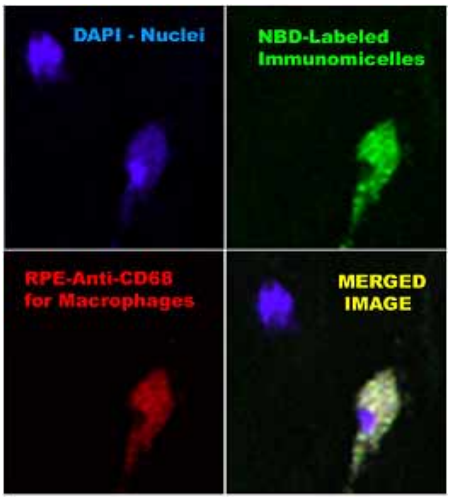

Figure 2