

High-resolution MR Angiogenesis Mapping with Integrin-targeted Ultralow Gadolinium-Manganese Nanocolloids

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Introduction: Molecular imaging of angiogenesis offers a unique opportunity to differentiate aggressive tumors from benign lesions, to guide diagnostic biopsy to minute lesions, to risk/benefit stratify patients for antiangiogenic inductive therapy, and to treat cancer and serially monitor early biochemical as well as subsequent anatomical changes.

Objective: We have previously demonstrated the effectiveness of gadolinium perfluorocarbon nanoparticles to target angiogenesis and generate sensitive and repeatable neovascular maps in minute tumors.(1) Although the risk of adverse effects from transmetallation of DOTA-coupled gadolinium on these nanoparticles is very low, the recent discovery of nephrogenic systemic fibrosis (NSF) has raised concern, which encourages us to find ways to eliminate or significantly lower the patient exposure risk. For PFC nanoparticles, the r_1 relaxivity of the construct is fully contributed by the incorporation of lipophilic gadolinium chelates into the outer phospholipid layer of the particle and is maximized by loading up to 100,000 Gd-DOTA per nanoparticle ($< 1/10^{\text{th}}$ the approved blood pool dose). (2) The objective of the present study was to utilize the particle core as a significant contributor to the overall r_1 , allowing the surface gadolinium concentration to be lowered markedly while retaining strong relaxivity. In this proof of concept study, we hypothesized that angiogenesis mapping could be achieved with 90% less surface gadolinium,(1) if the perfluorocarbon core was substituted with one of concentrated Mn(II) oleate suspended in polysorbate.

Methods: Gadolinium-Manganese oleate nanoparticles (GdMnOL NP) were synthesized as vascularly-constrained (150-250nm) phospholipid encapsulated nanocolloids. Briefly, manganese chloride tetrahydrate was reacted with sodium oleate (TCI chemical) in a mixture of ethanol-water-hexane for 14h maintaining the temperature at 80°C and 4h at ambient temperature to afford organometallic manganese. Organometallic manganese (30 mole%) was suspended with sorbitan sesquioleate as inner matrix, homogenized with 2.0% (wt/v) phospholipid surfactant containing 2.5 mole% gadolinium DTPA bisoleate chelate (GdDTPA-BOA). Angiogenesis imaging was evaluated using a Matrigel plug model in BALB/C mice. Anesthetized flank-shaven mice were injected SC with 1 ml of Matrigel containing 500ng FGF (+/- 100ng MCP-1) and 64U heparin. Neovascular development was allowed to proceed for 14 days. Mice were imaged in a clinical 3T MR scanner (Philips Achieva) with a SENSE-Flex-M coil using a high-resolution, T_1 -weighted, fat suppressed, 3D gradient echo sequence 2 hours post injection Gd/MnOL NP. The imaging parameters were: TR/TE = 51/3.9 ms, 40° flip angle, 4 NSA, 0.39 x 0.39 x 1 mm resolution, . A GdDTPA doped water standard was placed within the field of view of each image and used as a signal reference standard. High resolution, three-dimensional (3D) maps were reconstructed from the 3D image dataset to present the spatial distribution of neovasculature using MATLAB. The overall 3D structure of the tumor was displayed as a mesh surface plot using isosurface rendering and a smoothing filter. Enhancing voxels (i.e., 3 std. deviation increase over baseline) were overlaid in blue onto the tumor volume. The renderings were rotated in space to better appreciate the 3D distribution of neovascular enhancement.(1)

Results: ManOL core substitution added significant paramagnetic advantage over perfluorocarbon: $r_1 = 423,420 \pm 10564$ (s•mmol [nanoparticle])⁻¹ at 3.0T (25°C) with ionic r_1 of 14.6 ± 1.1 (s•mmol [Mn])⁻¹. The particulate r_2 was $2135,482 \pm 20543$ (s•mmol [nanoparticle])⁻¹ with an ionic r_2 of 70.7 ± 1.2 (s•mmol [Mn])⁻¹. This relaxivity was approximately 50% of that previously reported successful for imaging neovessel integrins with GdDTPA-BOA on PFC nanoparticles. However, addition of only 2.5 mole% GdDTPA-BOA into the surfactant of $\alpha_v\beta_3$ -targeted MnOL nanoparticles (GdMnOL) allowed robust 3D mapping of angiogenesis in the Matrigel plug model at 2 hours postinjection with 90% less GdDTPA-BOA than previously required (Fig 1).

Conclusion: These are the first data to illustrate rapid, high resolution angiogenic mapping using less than $1/100^{\text{th}}$ of the approved GdDTPA dose administered for blood pool imaging. By substituting the perfluorocarbon with MnOleate, the lanthanide use for angiogenesis molecular imaging could be reduced by at least 90%. This platform technology may be used for rapid, T_1 w molecular imaging of a broad array of pathological biomarkers with little or no adjunctive gadolinium, reducing the potential for NSF adverse effects.

1.Schmieder AH, et al. FASEB J 2008;22:4179-4189

2.Winter PM et al. Magn Reson Med 2003;50(2):411-416.

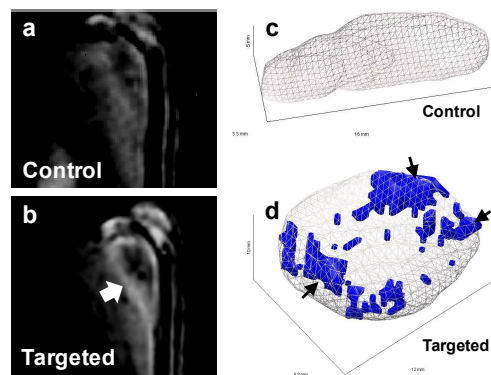


Fig. 1. MR single slice images (3T) in rats treated with control (a) and $\alpha_v\beta_3$ -targeted Gd/ManOL nanoparticles (b). (c) 3D neovascular maps of matrigel angiogenesis from control (c) and $\alpha_v\beta_3$ -targeted Gd/ManOL nanoparticle (d) images.