Copper Nanoparticles for T1-Weighted MR Molecular Imaging

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Background and Objective: With the potential to revolutionize diagnosis and treatment of cardiovascular disease, the benefits of MR molecular imaging using targeted contrast agents are multifold and are the focus of much research. Sensitive detection of disease markers such as angiogenesis, fibrous plaque, and inflammation have been reported using a multitude of agents based on gadolinium, iron, manganese and other metals—each bringing certain benefits and limitations. The common challenge, however, is the sensitive detection of the weak signal from agents bound to sparse biomarkers. Some agents have shown promise by amassing large quantities of gadolinium per binding site; but the spectre of nephrogenic systemic fibrosis casts questions on the ease of translating any new Gd-based contrast agent to the clinic. Therefore, the current objective is to develop and characterize a new soft nanoparticle-based contrast agent platform comprising the organically-soluble small molecule copper oleate. The new agent should be targetable, exhibiting sufficiently strong longitudinal relaxivity to effect a detectable change in T1 at concentrations expected of in vivo targeted agents.

Methods: A colloidal suspension of lipid-encapsulated copper (II) oleate (CuOL) was prepared incorporating approximately 100,000 Cu atoms per nanoparticle (NP). For the initial proof-of-principle experiments, the particles were functionalized for targeting by including biotin on the outer membrane. Size and surface charge were measured. The colloidal suspension was serially diluted and imaged at 3T using Look-Locker inversion recovery and CMPG-like multi spin echo techniques to measure R1 and R2, respectively, from which relaxivities (r1 and r2) per particle were calculated. To demonstrate targeting, acellular fibrin clots were grown on a suture using fresh human plasma. The clots, targeted via biotinylated antibody, were treated with targeted or non-targeted (i.e., control) CuOL agent, washed repeatedly, and imaged at 3T with T1w gradient echo.

Results: Nanocolloidal suspensions of CuOL were prepared successfully with a mean particulate size of 217nm and zeta potential of -13mV. The r1 and r2 per particle was $62315\pm2977(s\cdot mmol\ [NP])^{-1}$ and $161683\pm5328(s\cdot mmol\ [NP])^{-1}$, respectively. Successful targeting of fibrin clots was achieved, causing marked T1 enhancement on the treated clots, whereas the control clots exhibited low signal on T1-weighted scans (figure).

Conclusion: This work is the first demonstration of a targeted MR molecular imaging contrast agent based on copper. Strong r1 per particle allows detection, even at low biomarker concentrations. The in vitro results suggest that the nanoparticles concentrate enough CuOL to have substantive R1 changes in vivo. Moreover, based on previous technology, this platform has the potential of carrying drug with an image-based measurement of targeted delivery.

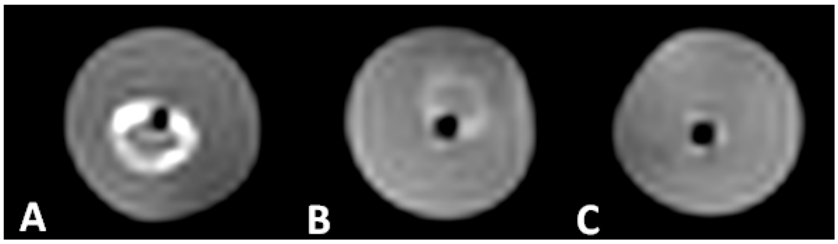

Figure. *In vitro* fibrin clot imaging at 3T. Copper nanoparticles targeted to fibrin cause the ~5mm diameter clot grown on a suture to enhance brightly on (A) T1-weighted MR. The clot treated with non-targeted copper nanoparticles (B) shows minimal enhancement, and the untreated clot (C) is imperceptible.