A new biodegradable MR contrast agent with high kinetic chelation stability for cancer imaging

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Introduction:
Timely detection and accurate evaluation of cancer can greatly improve the therapeutic outcome and survival rate of cancer patients. Contrast-enhanced MRI has been used for clinical cancer diagnosis. Gd(III) based contrast agents are most commonly used in clinical application. However, the clinically used contrast agents are often non-specific for cancer imaging due to non-discriminated extravasation into normal tissues. Experimental macromolecular Gd based contrast agents showed better tumor selectivity because of tumor vascular permeability, but their increased tissue retention raises significant safety concerns. To address the slow-excretion of macromolecular contrast agents, we have designed and investigated a series of polydisulfide Gd(III) complexes as biodegradable macromolecular MR contrast agents. These polydisulfide Gd(III) complexes were synthesized based on the linear Gd(III) ligand, DTPA. Although the biodegradable macromolecular MRI contrast agents showed improved tumor selectivity and were readily degraded in vivo and excreted via renal excretion [1], the relatively poor kinetic chelation stability of linear Gd(III) chelates is a serious drawback for further development of such an agent. The macrocyclic Gd(III) chelates have shown much higher kinetic chelation stability than the linear chelates [2]. To further minimize the potential toxicity associated with the release of free Gd(III) ion from the contrast agents, it is beneficial to develop a new generation of biodegradable contrast agents based on the more stable macrocyclic ligand, DOTA. In this study, we have synthesized and characterized a polydisulfide Gd-DOTA as a new generation of biodegradable macromolecular Gd(III) contrast agents for cancer MR imaging. The effectiveness of the new agent for contrast enhanced MR cancer imaging was investigated in an orthotopic mouse breast tumor model.

Materials and Methods:
A polydisulfide Gd-DOTA (GODC) was synthesized by copolymerization of a monomer containing DOTA and a disulfide containing monomer, followed by Gd(III) complexation. The physicochemical properties of GODC, including molecular weight, Gd(III) content and relaxivities, were determined using size exclusion chromatography (SEC), inductive coupled plasma spectroscopy (ICP-OES) and the Bruker® Minispec relaxometer (1.5T, 60 Hz). The degradability of GODC was verified via in vitro incubation of the agent with plasma concentration of cysteine in PBS buffer at pH 7.4. The MR contrast-enhancment of the new biodegradable macromolecular contrast agent was evaluated in an orthotopic 4T1 mouse breast cancer model on a Siemens 1.5T MRI scanner using Magnevist® as a control. Statistical analysis was performed using a paired two-tailed Student's t-test.

Results:
The number average molecular weight and weight average molecular weight of GODC is 23.5 kD and 26.4 kD, respectively. The T_1 relaxivity of GODC was 8.33 $mM^{-1}s^{-1}$ per Gd at 1.5T. A decrease of molecular weight of GODC was observed at 30, 60, 120 and 240 minutes post incubation of cysteine. Figure 1 shows the T1-weighted axial 2D spin echo images of the tumor tissues of the mice bearing 4T1 breast cancer tumor before and after injection of the contrast agents. Prolonged and strong signals were observed in the tumor periphery after injection of GODC. In comparison, the control agent did not generate significant signals in tumor periphery. Figure 2 shows that GODC generated significantly higher signal enhancement in tumor periphery than the control agents for up to 30 minutes post administration.

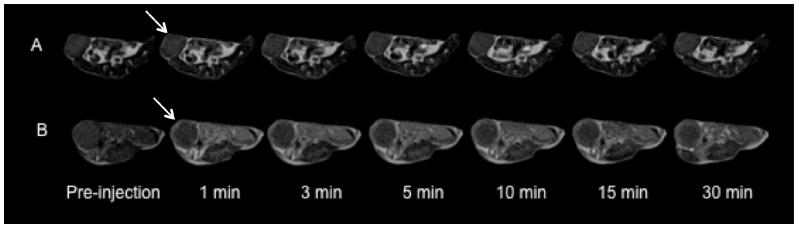

Figure 1. T_1-weighted axial 2D spin echo images of mice bearing 4T1 mouse breast cancer before and at different time points post injection of Magnevist® (A) and GODC (B) at a dose of 0.1 mmol-Gd/kg.

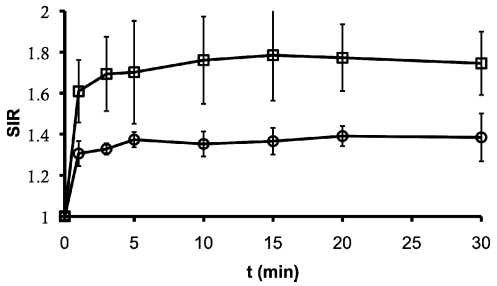

Figure 2. Signal intensity ratio (SIR) of tumor periphery of mice bearing 4T1 mouse breast cancer before and at different time points post injection of Magnevist® (circle) and GODC (square).

Conclusion:
We have designed and synthesized polydisulfide Gd-DOTA complexes, GODC, with kinetic stability as a safe and effective biodegradable macromolecular contrast agent for MR cancer imaging. Our preliminary results have shown that the agent can generate significant and prolonged MR signal enhancement in tumors, and be readily degraded. The newly developed agent is promising in clinical cancer diagnosis.

References:
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