Gd@(Carbon Nanostructures) as High Relaxivity Nanoprobes Magnetic Resonance Imaging

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Introduction:

Carbon nanostructures containing paramagnetic gadolinium exhibit unusually large proton relaxivities (efficacy), do not disassociate under physiologic conditions, and therefore may be useful as Magnetic resonance (MR) contrast agents (CAs).[1, 2] Our prior work shows that derivatized Gd@C_{60} metallofullerenes (gadofullerenes) and Gd@US-tubes (gadonanotubes) nanomaterials (Fig. 1) can serve as high-performance MRI CA probes with efficacies up to 100 times greater than currently used commercial clinical CAs. [1, 2] Recent studies have shown that, both fullerenes as well as single-walled carbon nanotubes can translocate into the interior of cells with minimal cytotoxicity, implying a potential application as an intracellular MRI probe.[3-5] In this paper, we report the first MRI phantom studies on these Gd@(Carbon Nanostructures) to examine their ability as potential nanoprobes for cellular MRI.

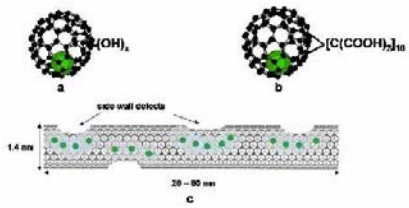

Figure 1. Depiction of (a) Gd@$C_{60}(OH)_x$, (b) Gd@$C_{60}[C(COOH)_2]_{10}$ and (c) a single Ultra short tube (US-tube) loaded with hydrated Gd^{3+} ions (Gd^{3+}_n@US-tubes). In the case of US-tubes Gd^{3+}-ion loading is likely through side-wall defects created by cutting full-length nanotubes to produce US-tubes (not to scale and Cl- anions and atoms attached to dangling C bonds not shown).

Materials and Methods: *Samples:* Vials of $GdCl_3$, gadofullerene (Gd@$C_{60}[C(COOH)_2]_{10}$), and gadonanotubes Gd@$C_{60}(OH)_x$, at 0.4 mM and 0.04 mM gadolinium concentrations were prepared as has been described previously.[1,2] Additional vials containing pure water, and 1% Sodium dodecyl sulphonate (SDBS) solutions were also included in the imaging section as a reference. *MRI Acquisition:* The samples were imaged on a 1.5T Philips MR imager. A quadrature head coil was used for signal reception. Following an inversion pulse, a series of gradient echoes were obtained at different inversion delay times, to map the regrowth of longitudinal magnetization. The imaging parameters of the segmented gradient echo readout were as follows: repetition time (TR)/echo time (TE)/flip angle: 10 msec/2.3msec/10°; the field-of-view and matrix sizes were chosen to yield an acquired voxel size of : 2 x 2 x 6 mm^3, that was reconstructed as a 1 x 1 x 6 mm^3 voxels using zero-filled reconstruction. The inversion pulse was repeated every 3580 msec, and the longitudinal recovery was sampled at 28 msec temporal resolution (128 time points). In addition to conventional magnitude reconstruction, phase corrected real images were also reconstructed.

Results / Discussion: Representative T_1 weighted MRI images of the vials are shown in Figure 2A. At 0.4 mM, and 0.04 mM concentrations, gadonfullerenes and gadonanotubes showed significant enhancements compared to commercially available Gd-based contrast agent at the same concentrations (Figure 2B).

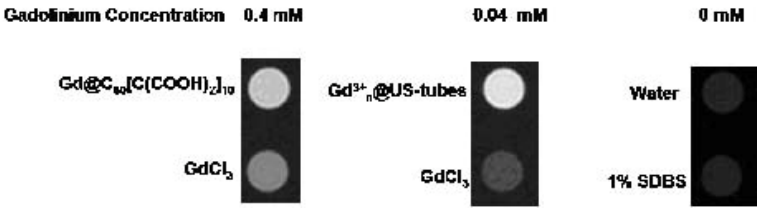

Figure 2: T_1 weighted MRI phantoms of the (a) Gd@$C_{60}[C(COOH)_2]_{10}$ and (b) Gd^{3+}_n@US-tubes solutions at 0.4 mM and 0.04 mM gadolinium concentrations, respectively, with a 1.5 T Philips MR imager. For comparative purposes MRI phantoms of pure water and 1% SDBS solutions are also shown.

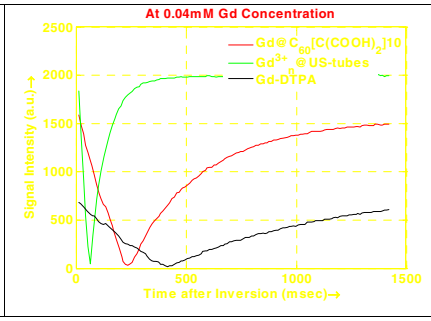

Figure 2B: Magnitude signal intensity curves for vials at the same Gd concentration of 0.04 mM. Note the substantially faster recovery for the nanoprobes compared to conventional Gd-based contrast agents.

The nanoprobes described appear to have desirable characteristics for cellular imaging. They are small, can cross the cell membranes, have low cytotoxicity, and induce high proton relaxivity. Therefore, the accumulation of CA probes derived from these materials within targeted cells could substantially boost MRI signal strength. For example, we estimate that each bundled (10 nm x 100 nm) gadonanotube probe with relaxivity r_1 = 170 $mM^{-1}s^{-1}$ per Gd^{3+} at clinical fields contains about a hundred Gd^{3+} ions to give an effective r_1 = 17,000 $mM^{-1}s^{-1}$ per probe. If only one thousand such probes were to accumulate within a single cell, the r_1 of the cell would be 17,000,000 $mM^{-1}s^{-1}$ (!) which should easily permit single-cell imaging.

Conclusions: In conclusion, MRI phantom studies on the Gd@(Carbon Nanostructures) show extremely large signal enhancement with intensities up to 100-150 times larger than pure water at modest concentrations of gadolinium. The ability of the nanoprobes to be internalized by cells could allow the first Gd^{3+}-based labeling of individual cells. This is area of ongoing research at our laboratory.

References:

1.Toth, E. JACS. 2005; 127:799-805. 2. Sitharaman, B. Chem. Commun. 2005;31:3915-3917.3. Dugan, L. L. PNAS. 1997; 94: 9434 - 9439. 4. Kam, N. W. S. JACS. 2004 126;22: 6850 - 6851. 5. Pantarotto, D. Chem. Commun. 2004; 1 16 - 17.