FeCo/Graphitic Carbon-Shell Nanocrystals as MRI Contrast Agents for Cellular and Vascular Imaging

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Introduction: We have recently developed and tested new FeCo/graphitic carbon-shell (FeCo/GC) nanocrystals with interesting properties for MRI. The following summarizes these properties (advantages): (1) highest magnetization [1] among all magnetic materials, allowing a lower dosage for high contrast; (2) non-toxic due to encapsulating graphite carbon shell; (3) superparamagnetic up to 20 nm or higher and smallest size synthesized is down to 2–3 nm (i.e. wide size range to work with); (4) potential as highly sensitive T_2^* contrast agent used for cell labeling; (5) potential as intravascular T_1 contrast agent; (6) easy manipulation of the surface to modify bio-distribution; (7) high optical absorbance in near-infrared (NIR) for potential optical manipulation which can provide photothermal therapy guided by MRI [2]. Below, we show experimental results demonstrating some of these properties and potential applications.

Methods: All MRI experiments were conducted using a GE 1.5 T Excite whole-body scanner. **(1) *r_1, r_2 measurements:*** We used aqueous solutions of FeCo/GC nanocrystals, Feridex and Magnevist at various concentrations to measure and compare r_1 and r_2. To estimate r_1 and r_2, the T_1 and T_2 were measured using an IR sequence and an SE sequence. T_1 and T_2 values were then extracted through nonlinear least-square fits to the inversion recovery curve and the spin-echo decay curve respectively. T_1 and T_2 weighted SE images of the samples were also collected. ***(2) Cell imaging with T_2^* contrast:*** To test the material's potential as a T_2^* agent for cell labeling and imaging, mesynchymal stem cells (MSC) were labeled with the 7 nm FeCo/GC-nanocrystal and imaged. For the T_2^* -weighted imaging of the MSCs, a GRE sequence was used with a 100 ms T_R, 10 ms T_E, and 30° flip angle. ***(3) In-vivo vascular imaging with T_1 contrast:*** To test the material's potential as an intravascular T_1 agent, 4 nm FeCo/GC-nanocrystal solution was injected into a rabbit. 4 ml of 3 mM solution was injected four times in 10 min intervals. T_1-weighted images (fat-suppressed 3D SPGR sequence with 33 ms T_R, 4ms T_E, and 45° flip angle) were acquired before and after each injection. The total dosage of the four injections was 9.6 μMkg^{-1} (the rabbit weighed 5 kg), which is less than 10 % of the recommended dosage of Magnevist injection (100 μMkg^{-1}).

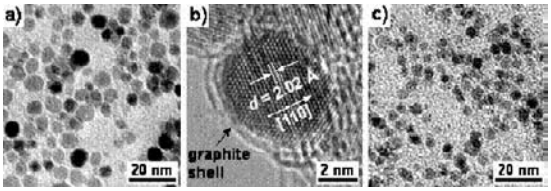

Figure 1: TEM micrographs of FeCo/GC nanocrystals: a) TEM and b) HRTEM images of 7 nm nanocrystals. c) TEM image of 4 nm nanocrystals.

sample	r_1 [$mM^{-1}s^{-1}$]	r_2 [$mM^{-1}s^{-1}$]	r_2/r_1
7 nm FeCo/GC	70	644	9.2
4 nm FeCo/GC	31	185	6.0
Feridex	10	104	10.4
Magnevist	4.5	4.5	1.0

Table 1. T_1 and T_2 relaxivities r_1, r_2, and r_2/r_1 ratios for PL-PEG-functionalized FeCo/GC nanocrystals, Feridex and Magnevist.

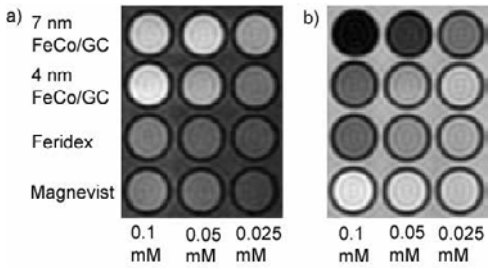

Figure 2. Images of various contrast agents at three metal concentrations generated using a) T_1- and b) T_2-weighted SE sequences.

Results: The r_1, r_2 measurement results (Table 1) and the T_1, T_2 weighted images (Fig. 2) show that the relaxation properties of FeCo/GC are superior to those of Feridex and Magnevist. The cellular imaging results (Fig. 3) confirm that stem cells can be labeled with FeCo/GC and that the sensitivity is higher than that of Feridex. Preliminary vascular imaging results (Fig. 4) show both the T_1 effect and the potential as an intravascular agent since the contrast does not leak out into the muscle for at least 30 min.

Discussion: Cell proliferation studies show no sign of toxicity. Five in-vivo rabbit studies have been conducted so far and no apparent sign of negative impact due to the contrast injection has been observed.

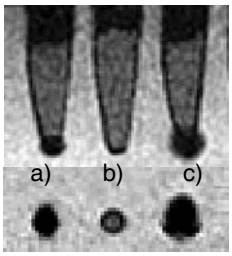

Figure 3 T_2^* weighted Images of a) Feridex-, b) non-, c) 7 nm FeCo/GC-labelled MSC pellets.

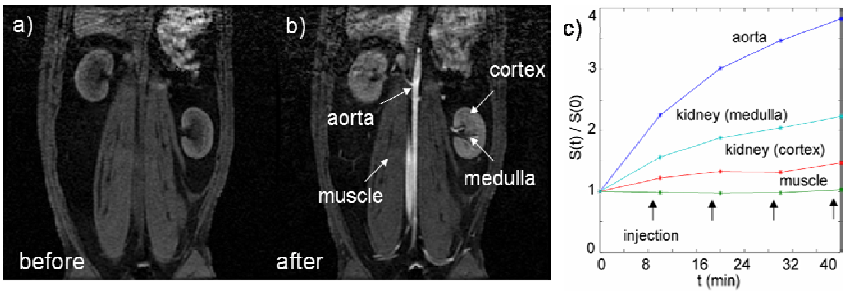

Figure 4. In-vivo images of a rabbit a) before contrast injection b) 30 min after the initial injection. c) Signal intensity curve before and after each injection. Note that the signal intensity keeps increasing in the aorta (blood pool) while there is no signal intensity change in the muscle.

Conclusion: FeCo/GC nanocrystals show great promise as a T_2^* agent for cellular imaging as well as an intravascular T_1 agent, due to their high relaxivities and nano-scale structures.

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References: [1] Hutten, A. et al., J. Biotechnol. 112, 47−63 (2004). [2] Kam, N.W. S. et al., Proc. Natl Acad. 101 Sci. USA **102,** 11600−11605 (2005).