

Euro Biopharma 2018: Enhancing T1 magnetic resonance imaging contrast with internalized gadolinium (III) in a multilayer nanoparticle- Oara Neumann- Rice University Applied Physics

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Multifunctional nanoparticles for biomedical applications have shown exceptional potential as contrast agents in various bi-imaging modalities, near-IR photothermal therapy, and for light-triggered therapeutic release practices. Over the past several years, numerous studies have been achieved to synthesize and enhance MRI contrast with nanoparticles. However, understanding the MRI enhancement mechanism in a multishell nanoparticle geometry, and managing its properties, remains a challenge. To systematically examine MRI enhancement in nanoparticle geometry, we have synthesized MRI-active Au nanomatryoshkas. These are Au core–silica layer–Au shell nanoparticles, where Gd(III) ions are condensed within the silica layer between the inner core and outer Au layer of the nanoparticle (Gd-NM). This multifunctional nanoparticle maintains its strong near-IR Fano-resonant optical absorption properties necessary for photothermal or other near-IR light-triggered therapy, while instantaneously providing increased T1 contrast in MR imaging by concentrating Gd(III) within the nanoparticle. Dimensions of Gd-NM revealed a strongly enhanced T1 relaxivity ($r_1 \sim 24 \text{ mM}^{-1}\cdot\text{s}^{-1}$) even at 4.7 T, substantially surpassing conventional Gd(III) chelating agents ($r_1 \sim 3 \text{ mM}^{-1}\cdot\text{s}^{-1}$ at 4.7 T) currently in clinical use. By varying the thickness of the outside gold layer of the nanoparticle, we show that the observed relaxivities are consistent with Solomon–Bloembergen–Morgan (SBM) theory, which takes into account the longer-range connections between the encapsulated Gd(III) and the protons of the H₂O molecules outside the nanoparticle. This nanoparticle complex and its MRI T1-enhancing properties open the door for future studies on quantifiable tracking of therapeutic nanoparticles in vivo, an important step for optimizing light-induced, nanoparticle-based therapies.

Multicomponent nanoparticle complexes have received great interest as theranostic agents (having both diagnostic and therapeutic functions) due to the exclusive properties that can be combined within a single nanostructure. These include intense near-IR (NIR) optical absorption due to a strong localized surface plasmon resonance, in vivo/in vitro stability, biocompatibility, facile surface conjugation chemistry, and their use as contrast agents in magnetic resonance imaging (MRI) applications. MRI is currently the most universally used biomedical imaging modality. It is a noninvasive technique with contrast versatility and high spatial and temporal resolution. There are two main types of MRI contrast agents currently in widespread clinical use. T2-weighted contrast agents locally modify the spin–spin relaxation process of water protons, generating negative or dark images (based on materials such as superparamagnetic Fe₃O₄ nanoparticles). T1-weighted contrast agents affect nearby protons through spin–lattice relaxation, producing positive (bright) image contrast [based on paramagnetic materials

such as Gd(III) and Mn(II)]. The ability of a contrast agent to change the longitudinal ($1/T_1$) or transverse ($1/T_2$) relaxation rate is measured as relaxivity, r_1 or r_2 , respectively, which is characterized as the change in reduction rate after the introduction of the contrast agent normalized to the concentration of the contrast agent. Despite their utility, T2 contrast agents also have several disadvantages that limit their use in clinical applications. They can cause a reduction in the MRI signal, which can be perplexed with other pathogenic conditions (such as blood clots and endogenous iron). In the case of tumor imaging, they can induce magnetic field perturbations on the protons in adjoining normal tissue, which can make spatially well-resolved diagnosis difficult. In contrast, T1 contrast agents increase the specificity and sensitivity of the MR image. Among the paramagnetic materials useful for T1 contrast MR imaging, Gd(III) is the most effective contrast agent currently available for clinical use. However, free Gd(III) ions have high toxicity, and Gd(III)-chelates currently in clinical use, such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and diethylenetriaminepentaacetic acid (DTPA), suffer from poor sensitivity ($r_1 \sim 3 \text{ mM}^{-1}\cdot\text{s}^{-1}$ at 4.7 T), rapid renal clearance, and lack of specificity due to their small molecular size. Considerable efforts have been devoted to the incorporation of Gd(III) onto or into nanoparticles that will enhance their sensitivity by increasing their specificity, prolonging circulation time, and reducing their toxicity. Furthermore, these nanostructured Gd(III) agents present enhanced relaxivity compared with free Gd(III) chelates due to both cumulative effect of the high number of Gd(III) ions per nanocarrier and the reduced global tumbling motion that enhance the r_1 of each nanocomplex.

Recently, we developed tunable plasmonic Au nanomatryoshkas (NMs), a metal-based nanoparticle consisting of a Au core, an interstitial nanoscale SiO₂ layer, and an outer Au shell. This nanoparticle possesses a strong optical extinction at 800 nm, resulting in strong local photothermal heating, which makes it a highly attractive candidate for NIR photothermal cancer therapy. Besides the biocompatibility and facile surface conjugation chemistry made feasible by its outer Au layer, this system has been shown to have several benefits compared with other NIR photothermal transducers. For example, tumor uptake of NM (~90-nm diameter) in a triple-negative breast cancer model was fourfold to fivefold higher than Au nanoshells (~150-nm diameter), and consequently NM demonstrated an improved photothermal therapy efficacy relative to nanoshells.

Here, we report a modification of NMs that transforms them into high-relaxivity MRI-active contrast agents. This was accomplished by incorporating Gd(III) into the interstitial silica layer of the NM structure. The geometry of this nanoparticle as

an MRI contrast agent is both surprising and counterintuitive. The T1 enhancement mechanism of molecular contrast agents, which typically consist of a single Gd(III) ion surrounded by chelating ligands, relies upon extremely close distances between the Gd(III) ions within the particle and nearby H₂O protons. Our layered nanoparticle strategy yields nanoparticle complexes with higher T1 relaxivities than molecular T1 contrast agents, but in this system, the Gd(III) ions are well-separated from the H₂O protons outside the nanoparticle. Our main goal was to calculate the influence of structural nanoparticle parameters such as the number of Gd(III) inside the particle, Au shell thickness, and surface functionalization on the relaxivity (r_1) of the Gd-NM, and to explicate the relaxivity mechanism. This study resulted in an optimized Gd-NM system with good T1 relaxivity at high magnetic field strength (4.7 T) and significantly enhanced T1 relaxivities compared with molecular contrast agents. Furthermore, an MRI T1-weight relaxivity mechanism of Gd-NM was elucidated by scientifically varying and controlling the layered nanostructure morphology.