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High magnetic relaxivity in a fluorescent CdSe/CdS/ZnS quantum dot functionalized with MRI contrast molecules

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Light emitting semiconducting quantum dots show great promise as solar cells, optoelectronic devices and multimodal imaging probes. Here we demonstrate successful grafting of a thiol-functionalised Gd^{III} MRI contrast agent onto the surface of core-multishell CdSe/CdS/ZnS quantum dots. The resulting nanoprobe exhibits intense photoluminescence and unprecedentedly large T_1 relaxivity of 6800 mM⁻¹s⁻¹ per nanoparticle due to secure implanting of ca. 620 magnetic centers per quantum dot unit.

Non-invasive imaging is essential for diagnosis and management of disease.¹ However, no single imaging modality can adequately characterise both anatomy and function due to the intrinsic limitations of each technique, mainly due to trade-offs between resolution and sensitivity.² Thus, magnetic resonance imaging (MRI)/fluorescence imaging hybrids are assumed to have clinical potential through combining the superior anatomical detail of MRI, with the sensitive molecular information of fluorescence imaging.³

Clinically approved MRI contrast agents are principally Gd-chelates based on DTPA (Magnevist®), DTPA-bis(methylamide) (OmniScan®) or DOTA (Dotarem®) ligands, where DTPA and DOTA are diethylene-triamine-pentaacetic acid and 1,4,7,10-tetraaza-cyclododecane-1,4,7,10-tetraacetic acid, respectively.⁴ Their role is to improve diagnostic sensitivity through decreasing longitudinal relaxation times (T_1) of neighbouring water protons, providing contrast that makes surrounding areas appear brighter.

Quantum dots (QDs) are bright fluorescent semiconductor nanocrystals with high photostabilities, large extinction coefficients, high photoluminescent quantum yields, and size-tuneable band gaps.⁵ They are attractive for a wide range of applications, including fluorescence imaging, solar cells, and optoelectronic devices.^{6,7} The most explored for such

applications are CdE QDs (E = S, Se, Te).⁸ Magnetic doping can unlock additional properties.^{9,10} Importantly, QD surfaces are highly amenable to organic functionalization, and thus can be tailored to allow increased solubility in water and coupling with biomolecules.¹¹

Anchoring clinically-relevant MRI contrast molecules onto QD surfaces is an attractive approach toward multimodal imaging due to increased resultant magnetic relaxivities, as a result of slower tumbling, and a higher loading of contrast agent.¹² Previous studies have indirectly attached Gd-DTPA and Gd-DOTA to QD surfaces via an intermediary silica,¹³ polymer,¹⁴ glutathione,¹⁵ or lipid layer;¹⁶ and through streptavidin-biotin interactions.¹⁷ In contrast, non-DOTA/DTPA Gd-chelates were directly attached to QDs through a bidentate thiol.^{18,19} This later procedure has involved several synthetic steps. A more straightforward route was reported by Lewis et al. for the covalent attachment to gold nanoparticles of an Eu(III) complex based on N,N'-bis(p-thiophenyl-amido)-diethylene-triamine-N,N',N''-triacetic acid (H₃L).²⁰

In this communication we report a luminescent and magnetic nanohybrid, QD@GdL, prepared by covalently binding GdL molecules to the surface of core-multishell CdSe/CdS/ZnS QDs (Scheme 1).

Scheme 1. Schematic illustration of hybrid synthesis through the covalent attachment of GdL to core-shell CdSe/CdS/ZnS QDs to form QD@GdL.

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QD@GdL has been characterised by several physical techniques, notably using high angle annular dark field scanning transmission electron microscope (HAADF STEM) imaging with energy-dispersive X-ray (EDX) spectrum imaging, electron paramagnetic resonance and magnetometry. Importantly, and for the first time, EDX mapping at close-to-atomic resolution is used to provide direct evidence that Gd(III) complexes are bound to the nanoparticle surface.

The H₃L ligand was synthesised according to a previously reported procedure that involved condensation of 4-aminothiophenol with DTPA-bis(anhydride) in anhydrous pyridine.²¹ Complexation of Gd³⁺ with H₃L was achieved via metathesis, which furnished GdL. Core-multishell CdSe/CdS/ZnS QDs were synthesised via the successive ionic layer adsorption and reaction (SILAR) method,²² and GdL was grafted to the QD surface via ligand exchange. Multidentate thiol ligands are often considered to produce largely stable coatings.²³ QD@GdL was isolated and washed through multiple rounds of centrifugation and was finally resuspended in methanol for optical studies (see the Supplementary Information for the synthesis of GdL, CdSe/CdS/ZnS QDs and QD@GdL). QD@GdL was also suspended in polar solvents such as phosphate buffered saline (pH 7.4) with a zeta potential of -21 ± 2.2 mV. Dynamic light scattering measurements revealed an increase in hydrodynamic radius of 3.3 nm after ligand exchange, consistent with grafting of GdL to the QD surface (Figure S2).

QD@GdL was imaged using HAADF STEM. The nanoparticles appear approximately spherical (Figure 1a) and are measured to be 8.4 ± 0.9 nm ($n = 301$) in diameter (Figure S3). EDX spectrum imaging is used to map elemental distributions confirming the Se-rich core and S-rich shell of the CdSe/CdS/ZnS QDs (Figure 1b) with Gd appearing peppered over the surface of all nanoparticles (Figure 1c). An EDX line-scan profile shows that the Gd signal is spatially co-localised with that of Cd, S, Zn and Se, supporting the successful grafting of GdL to the QD surface in QD@GdL (Figure 1d; and SI for additional EDX maps/spectra and quantification).

Ultraviolet–visible absorption spectroscopy of QD@GdL revealed an absorption profile displaying characteristic absorptions of both GdL and CdSe/CdS/ZnS QDs superimposed over one another (Figure 2a). The peak at 266 nm is ascribed to the π – π^* transitions of the thiophenylamide groups.²⁰ Photoluminescence spectroscopy and quantum yield (Φ)

measurements ($\lambda_{\text{exc}} = 400$ nm) revealed a ten-fold quenching of photoluminescence emission intensity for QD@GdL ($\Phi = 2.3\%$) compared with CdSe/CdS/ZnS QDs ($\Phi = 27.6\%$), due to thiol groups of GdL binding to the surface of the quantum dots (Figure 2b).^{22,24} The close proximity of carbonyl groups to the QD surface may also offer an additional quenching pathway.²⁵ Interestingly, the luminescence of the QD@GdL nanohybrid is still very intense, being comparable with that of the classic luminescent dye [Ru(bpy)₃]²⁺ ($\Phi = 2.8\%$ in aerated water). FTIR-spectroscopy provides further evidence for GdL functionalization of the CdSe/CdS/ZnS QD surface. The S–H stretch at 2569 cm^{-1} found in GdL is absent in QD@GdL, indicating that no free thiols are present. This suggests GdL is bound to the QD surface as S–Zn²⁶ (Figure S8). The C–H stretches observed in QD@GdL are tentatively assigned to irreversibly bound alkylamines.²⁷

The magnetic properties of solid state QD@GdL and GdL were measured by electron paramagnetic resonance (EPR) spectroscopy and SQUID magnetometry. The room temperature EPR spectrum of GdL shows a single resonance peak at 12300 G (34 GHz frequency), which is assigned to Gd³⁺ ($g = 1.99$; $S = 7/2$) (Figure 3a). The one-line pattern of the EPR spectrum indicates a negligible zero-field splitting (Zfs) for the 4f⁷ electronic configuration of Gd³⁺. The observed spectral broadening is most likely caused by intermolecular dipole-dipole interactions, as described by others.²⁸ QD@GdL shows a similar resonance peak due to Gd³⁺, indicating that the hybrid is paramagnetic (Figure 3a). The narrower linewidth is the effect of reduced dipole-dipole interactions as QD@GdL represents a more dilute spin system.

SQUID magnetometry measurements revealed the magnetic saturation (M_{sat}) 46 emu g^{-1} and 17 emu g^{-1} for GdL and QD@GdL respectively (Figure 3b). The lower saturation magnetisation for the hybrid is potentially due to it containing a lower proportion of paramagnetic material than pure GdL. In Figure S9, the magnetisation saturation curve for GdL has an asymptote of $6.96\text{ }\mu_{\text{B}}$ per Gd³⁺ as expected ($S = 7/2$; $g = 1.99$). A ratio of 1 QD unit to 620 ± 110 GdL molecules was calculated, by ICP-MS (ESI[†]). To support this ratio, the total M_{W} of the hybrid and the M_{sat} (Figure 3b) were used to calculate a magnetisation of $6.9\text{ }\mu_{\text{B}}$ per Gd ion, close to the expected value of $6.96\text{ }\mu_{\text{B}}$ (ESI[†]). With a ‘footprint’ for GdL previously calculated as 0.398 nm^2 ,²¹ it follows that a maximum of

Figure 1. HAADF STEM image (a) and corresponding EDX maps of S (red), Se (green) (b), and Gd (blue) (c), with a line-scan profile (d) from the positions indicated by the purple box in (a). The size of the box indicates the line-scan profile area, with the arrow indicating the scan direction.

Figure 2. (a) Ultraviolet–visible absorption spectra of GdL (orange), CdSe/CdS/ZnS QDs (red) and QD@GdL (purple) in methanol. (b) Photoluminescence spectra ($\lambda_{\text{exc}} = 400 \text{ nm}$) of CdSe/CdS/ZnS QDs (red) and QD@GdL (purple). All spectra are corrected for instrument response.

of 550 ± 130 GdL complexes are able to bind to the surface of $8.4 \pm 0.9 \text{ nm}$ CdSe/CdS/ZnS QDs. Therefore, a ratio of 1:620 QD:GdL is a sensible estimate.

It was possible to use magnetic resonance imaging (MRI) to visualise solutions of QD@GdL. The T_1 relaxivity (r_1) was calculated from a linear fit of the measured $1/T_1 \text{ (s}^{-1}\text{)}$ against Gd^{3+} concentration (mM) at 42.5 MHz (1 T, PBS buffer, 300 K) (Figure 4a). The r_1 value for GdL and QD@GdL were calculated as $5 \text{ mM}^{-1}\text{s}^{-1}$ and $11 \text{ mM}^{-1}\text{s}^{-1}$, respectively. The reported r_1 value for QD@GdL was comparable to previously reported values for GdL functionalized Au nanoparticles ($10 \text{ mM}^{-1}\text{s}^{-1}$, 1.5 T, 293 K).²⁹ The literature relaxivity value for Gd-DTPA is $3.3 \text{ mM}^{-1}\text{s}^{-1}$ (1.5 T, water, 310 K).³⁰ The increased r_1 value for QD@GdL was attributed to the slower tumbling of GdL once immobilized upon the QD surface, and reduced mobility for nano-objects.³¹ Considering there are 620 ± 110 GdL complexes per QD, it follows that the r_1 value per particle is $6800 \pm 1300 \text{ mM}^{-1}\text{s}^{-1}$. This is higher than previously reported relaxivity values per particle for any Gd complex covalently attached to QD surfaces: $900 \text{ mM}^{-1}\text{s}^{-1}$ and $2523 \text{ mM}^{-1}\text{s}^{-1}$ at 35 MHz (0.81 T),¹⁸ and $655 \text{ mM}^{-1}\text{s}^{-1}$ at 60 MHz (1.4 T).¹⁹

Figure 4b shows T_1 weighted MR images of QD@GdL and GdL at varying Gd^{3+} concentrations measured at 127.7 MHz (3 T, PBS buffer, 300 K). QD@GdL showed a mean $47.4 \pm 10.7 \%$ increase in signal intensity compared to GdL (Figure S10), thus confirming QD@GdL as an improved contrast agent.

Figure 3. (a) Q-band EPR spectroscopy of solid state QD@GdL (purple) and GdL (orange) performed at room temperature. (b) Magnetisation (emu.g^{-1}) saturation curve of GdL and QD@GdL at 2K and 4K.

Conclusions

In conclusion, a magnetic and luminescent heterosystem, QD@GdL, was prepared through covalently binding a thiol-functionalised Gd(III) complex to the surface of core-multishell CdSe/CdS/ZnS quantum dots, and the structural, optical, and magnetic properties were characterized. High T_1 magnetic relaxivity values of $6800 \pm 1300 \text{ mM}^{-1}\text{s}^{-1}$ per QD at 42.5 MHz (1 T, 300 K) are reported: more than double that for similar previously reported QD systems.^{18,19} This improved behaviour is associated with the slower tumbling of the molecules strongly bound to the surface of the quantum dots through well-positioned thiol arms, and the high number of magnetic molecules attached to each nanoparticle.

Thus, we show that controlled functionalization of core-multishell quantum dots, which carry remarkable photo and chemical stabilities, with magnetic lanthanide complexes, is an effective approach toward luminescent magnetic probes for multimodal imaging. We anticipate that similar composites will be formed with other transition metal chalcogenites, and with mixed lanthanide complexes bearing both magnetic and luminescent properties, making possible to expand the luminescence spectrum of multimodal probes over a large optical scale. Combination of magnetic and optical properties into one entity may also be attractive for magneto-optoelectronic applications.

Figure 4. (a) Plot of $1/T_1 \text{ (s}^{-1}\text{)}$ as a function of Gd^{3+} concentration (mM) at 42.5 MHz (1 T, 300 K) in PBS buffer (pH 7.4). (b) T_1 weighted MR images at 3 T (127.74 MHz) of QD@GdL and GdL in PBS buffer at varying Gd^{3+} concentrations.

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Conflict of interest

The authors declare no conflict of interest.

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