Dual functional graphene quantum dots for targeted multimodal imaging and therapy

Shizhen Chen[1], Yuqi Yang[1], Qing Luo[1], and Xin Zhou[1]

[1]*National Center for Magnetic Resonance in Wuhan, Wuhan Institute of Physics and Mathematics, Wuhan, Hubei, China*

Introduction Nano-constructs that can achieve multimodality imaging and drug delivery combine the strengths of each modality together with therapy. We developed a multifunctional nanoprobe incorporating graphene quantum dots, Gd^{3+} and a typical anticancer drug doxorubicin for magnetofluorescent bioimaging and drug delivery purposes(Fig 1). Our experiments demonstrated that such targeted nano-constructs significantly enhanced *in vivo* MRI contrast in rats with non-small cell lung tumor, and its relaxivity was ~16 times higher than that of current clinical MRI contrast agents (e.g. Gd-DTPA), on a "per Gd" basis. Fluorescent imaging also showed that the nano-constructs specifically accumulated in lung cancer cells by a receptor-mediated process, and were nontoxic to normal cells. Moreover, the anticancer drug is delivered preferably to cancer cell nuclei with synergistic therapeutic effects, as determined by diagnostic imaging during therapy.

Materials and Methods Water soluble GQDs were fabricated by chemical oxidation and cutting graphene oxide in a mixture of concentrated H_2SO_4 and HNO_3. To selectively target cancer cells, hyaluronan (HA) was further modified to the GQDs-DOTA composites. After chelated with Gd^{3+}, the formed GQDs-Gd composites can generate MR contrast on T_1 proton relaxation time weighted sequences. Thus, a combined fluorescence and magnetic resonance imaging can integrate the advantage of high-resolution 3D fluorescent imaging with non-invasive magnetic resonance imaging as well as selectively targeting of cancer cells.

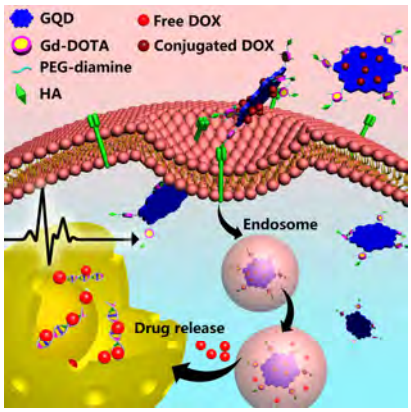

Fig. 1. Schematic representation of the multifunctional GQDs nanoprobe.

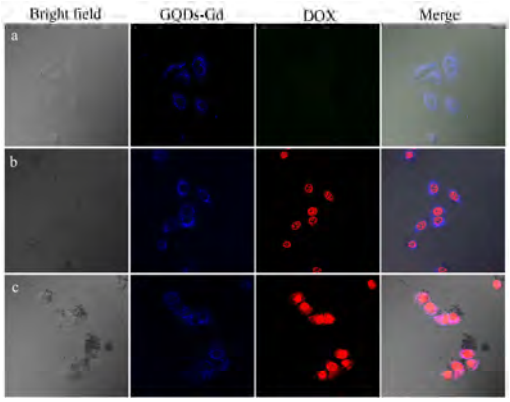

Fig.2. Fluorescence microscopy images of A549 cells incubated with 50 μg/mL (A) GQDs-Gd , (B) DOX/GQDs-Gd (m:m = 1:2), (C)DOX/GQDs-Gd (m:m = 1:1).

Results and Discussion Localization of GQDs-Gd and DOX/GQDs-Gd in the intracellular space was assessed via fluorescence confocal laser scanning microscopy (CLSM) analysis. As shown in Fig. 2, the synthesized nanoparticles were delivered into human lung cancer A549 cells to directly demonstrate the cellular uptake of GQDs and the release of DOX. The ability of nanoprobe to target lung cancer and be detected in MRI was tested in transgenic mice. Uninjected mice showed no change in T1relaxation time and no hyperintense signal in the tumor region. (Fig. 3 and Fig. 4) The tumors from mice injected with targeted DOX/GQDs-Gd showed a significant shortening in T_1 relaxation time hyperintense signals and in the tumor region which reveals the ability of targeted DOX/GQDs-Gd to provide contrast enhancement in MRI for disease detection or monitoring of drug delivery.

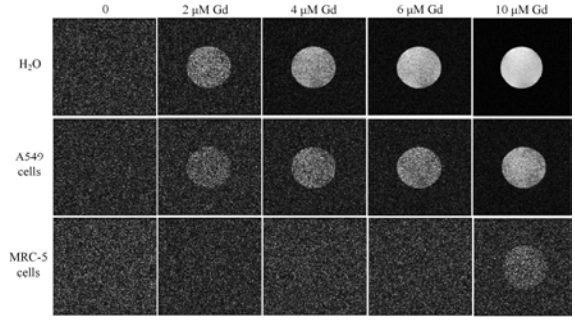

Fig. 3. T_1-weighted MR images of GQDs-Gd in water, A549 cells and MRC-5 cells with different Gd concentration.

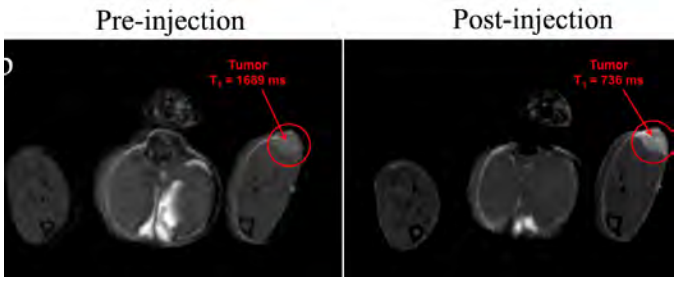

Fig. 4. In vivo T_1-weighted MRI:(a) No hyperintense signal was detected without injection. (b)Hyperintense signals were detected injected with DOX/GQDs-Gd after 2h.

Conclution In conclusion, we have developed a multifunctional nanoprobe of DOX/GQDs-Gd-HA for dual-modal bioimaging and drug-loading capacity as a result of our studies. Compared to previous multimodality contrast agents, the proposed nanoprobe integrates the advantages of a high-yield synthesis route and label-free fluorescence to harvest a biocompatible product with no toxic agents. Our method achieves the goal of synthesizing biocompatible nanoparticles with excellent chemical stability, intense fluorescent emission, and good MRI contrast for multimodality imaging.