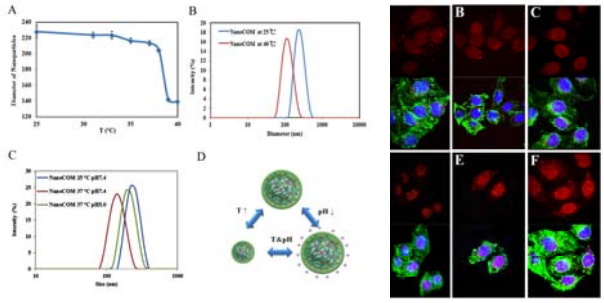
Preparation of Thermal/pH Dual Responsive Nanocarriers for Near Infrared Laser Guided Tumor Targeted Chemo/Photothermal Therapy

Ying Bi, Hui Gao, Aiping Lan, Yi Hu, Jun Chen*
Key Laboratory for Biomedical Effects of Nanomaterials&Nano Safety,
Institute of High Energy Physics, Chinese Academy of Sciences, Beijing, China.

Statement of Purpose: Nanomedicine possesses the great potential to improve tumor targeting and reduce adverse effects majorly ascribed to the enhanced permeability and retention (EPR) effect. This feature of "precision guided bomb" greatly benefited for the development of diverse therapeutic strategies besides the chemotherapy. Furthermore, the combined applications of diverse tumor therapeutic approaches with different drugs and mechanisms can thus be implemented with potential advantages (e.g., synergistic effects and reversal of drug resistance). In this presented work, we prepared chitosan/PNIPAAm encapsulating carbon nanotubes nanovehicles to execute chemo/photothermal combination therapy. And it was hypothesized that the enhanced tumor targeting was ascribed to the programmed stimuli sensitivity of the asprepared nanovehicles induced augment of EPR effect, which was straightforwardly contributed to the improvement of the therapeutic effects.

Methods: (materials and analytical procedures used)
The pristine single-walled carbon nanotubes (SWCNTs) were truncated to the length of ~100 nm. chitosan-g-oleic acid copolymer was synthesized to disperse the SWCNTs in the aqueous solutions. Subsequently, the nanovehicle of CS/PNIPAAm@CNT was obtained by the radical polymerization of PNIPAAm, crosslinkers, and CS@CNTs under vigorously stirring. Then the nanoparticles were characterized by the UV-vis spectrometry, IR spectrometry, SEM, Dynamic laser scattering.
DOX was loaded to the nanoparticles by dissolve-dry process followed by the extensive dialysis. The drug-loading efficiency, content, and the near infrared laser, pH, temperature-responsive drug release were characterized by the UV-vis spectrometry.
The confocal laser scanning microscopy was used to investigate the tumor cell inhibition rate of DOX-Nano and the intracellular drug release behavior.
To assess the potency of this combined therapy, we test it in an orthotopic bladder carcinoma model by challenging mice with intravesical implantation of MB49 cells. In the following days, mice were i.v. injected with PBS, DOX or DOX-Nano with or without NIR laser irradiation in bladder region at 30 min post-injection. The body weight was monitored every four days. On day 28 post-injection, mice were sacrificed and then tumor-bearing bladders were excised and weighed. Meanwhile, we analyzed serum chemistry level of mice after various groups at 28 days post-injection.

Results:



I II

Figure 1. I (A) The temperature dependent size change of three nanoparticles. (B) The hydrodynamic diameter change of nanoparticles monitored by the DLS at the different temperature. (C) The pH induced diameter change of nanoparticles. II Confocal laser scanning microscopy images of HeLa cells incubated with free DOX-Nano at pH 7.4 (A, D), DOX-Nano at pH 6.0 (B, E), DOX-Nano with NIR irradiation (C, F) for 15 min (A-C), 2 h (D-F).

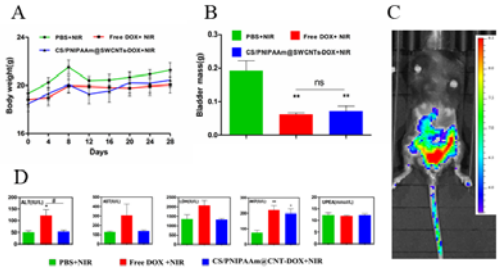


Figure 2.（A）Body weights of mice following various treatments indicated.（B）Tumor-bearing bladder mass in mice 28 days after intravenous injection of various formulation. (C) Representative live fluorescence imaging of C57BL/6 mice bearing MB49 tumors injection with Nano-Cy7.5 plus laser. (D) Serum chemistry levels including ALT, AST, LDH, AKP and UPEA in serum of tumor-bearing mice 28 days after i.v. injection of various formulations.

Conclusions: In summary, we have developed a new temperature/pH responsive intra-intercellular NP delivery system, which was composed of biopolymer-based nanogels with carbon nanotubes cores and crosslinked PNIPAAm-PEG shell. The obtained nanogels presented temperature/pH sensitive reversible swelling–shrinking capability, which was believed to be able to facilitate the tumor vessel penetration and tumor cells retention under NIR irradiation in-vivo. The in-vivo evaluation exhibited a safe and high efficient therapeutic effect. We believe that this strategy will provide the idea to explore more intelligent drug delivery nanoplatforms for high efficient tumor targeting therapy.