Integration of OCT Imaging and Photothermal Cancer Therapy Using Near Infrared Absorbing Gold Nanoshells

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Introduction:
Gold nanoshells, composed of a silica core nanoparticle surrounded by an ultrathin gold shell, are a new class of nanoparticles with tunable optical properties that can be designed to fall in the near infrared (NIR) [1]. We have previously shown that gold nanoshells accumulate in tumors due to the leakiness of the tumor vasculature and can induce photothermal ablation of tumors upon exposure to an external NIR laser source [2]. In the current studies, we sought to integrate nanoparticle-enhanced optical imaging of a tumor with photothermal ablation. Optical coherence tomography (OCT) is a relatively new imaging modality which provides subsurface imaging of biological tissue with micron-scale resolution based on scattering of NIR light. Because of their biocompatibility, optical properties, and nanoscale size, nanoshells are well suited for use as contrast agents in OCT imaging. Following OCT imaging of the tumors, higher intensity NIR light was applied to induce tumor ablation.

Methods and Materials:
Nanoshell Fabrication: Nanoshells were made as previously described. Briefly, silica cores are grown using the Stöber process [3]. The resultant silica nanoparticles were sized using scanning electron microscopy, SEM. Reaction of the silica nanoparticles with (3-aminopropyl) triethoxysilane provided amine groups on the surface of the core to allow for deposition of gold colloid. Gold colloid was prepared to a size of 2-4 nm using the method of Duff [4]. Gold colloid was mixed with the aminated silica particles to adsorb the very small colloid onto the surfaces of the larger silica nanoparticles to provide nucleation sites for reduction of additional gold. The gold shell was then grown by the reduction of gold from $HAuCl_4$ in the presence of formaldehyde. NIR absorption characteristics of the nanoshells were determined using a UV-Vis spectrophotometer. Pegylation was accomplished by addition of PEG-SH MW 5000 to nanoshells in DI water.
In vivo Cancer Therapy: Murine colon carcinoma cell line, CT-26, was grown subcutaneously on the right flanks of BALB/c mice. Tumors were allowed to grow to ~20 mm^2. For the treatment group PEGylated nanoshells were injected into the tail vein of the animals 20 hr prior to imaging and irradiation. One control group received a saline injection and subsequent laser treatment, and another control group was untreated. The tumors were imaged using the Niris Imaging System by topically applying glycerol for index matching and placing the probe directly on the skin. Images were captured at several locations on each tumor. After imaging, the tumors were exposed to higher intensity NIR light. Laser irradiation was accomplished using an 808 nm diode laser at a power density of 4 W/cm^2, spot size of 5 mm diameter for 3 min. Animal survival and changes in tumor size following treatment were monitored. Some mice from the nanoshell and PBS injection group were sacrificed and the tumors excised and sectioned. Silver enhancement stain was used to verify the presence on nanoshells in the tumor tissue. Figure 1(A) shows the tumor growth following treatment; (B) shows survival data following therapy. Figure 2 shows increase in OCT contrast for nanoshell treatment group compared to PBS.

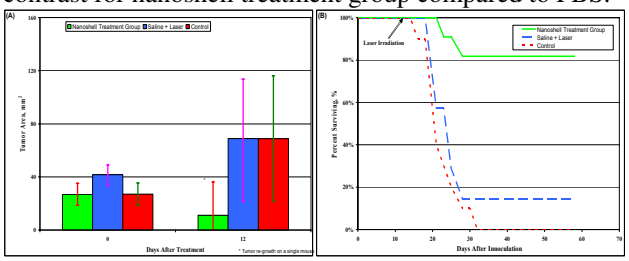

Figure 1: (A) Tumor size before and 10 days post treatment, (B) Survival data throughout study

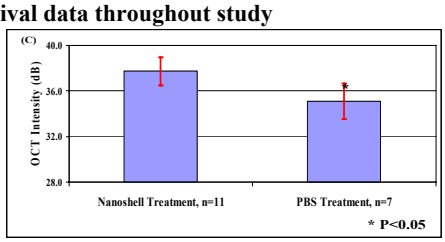

Figure 2: Quantification of the contrast increase of OCT images for tumors imaged after systemic nanoshell or PBS injection prior to therapeutic irradiation.

Results/Discussion:
OCT images of the tumors prior to irradiation shows overall higher contrast, indicative of higher scattering, in the tumors of mice that received systemic nanoshell injections compared to the mice receiving saline injections. Silver stained images show the presence of nanoshells in the tumors of mice injected with nanoshells compared to PBS injected mice. At the end of the 60 day study the survival rate of the nanoshell treated group was 82% compared to 14% of the PBS treated group and 0% for the untreated control.

Conclusion:
We have demonstrated in an *in vivo* model that the accumulation of nanoshells in the tumors can be imaged using commercially available OCT. This method will be refined and developed to improve the laser targeting of the tumors in the development of photothermal tumor ablation therapy using silica gold nanoshells.

References
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