Nanoshell-Mediated Laser Ablation of Glioma: Biodistribution and Survival Studies in a Mouse Model of Glioma

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Statement of Purpose:

Glioblastoma multiforme is the most aggressive primary brain tumor, with only 5% of patients surviving 5 years after treatment.[1] Nanoshells composed of a spherical silica core and a gold shell heat upon exposure to a near-infrared laser, enabling thermal ablation of nearby cancerous cells.[2] Treatment of human glioma and medulloblastoma has been demonstrated with this technique *in vitro*,[3] and herein we report the extension of this work to an *in vivo* murine model. In a biodistribution study, gold content was measured in several organs following intravenous injection of nanoshells into mice bearing subcutaneous glioma tumors. A survival study was also performed, and the results showed significant improvement in survival when mice received nanoshell-assisted laser therapy.

Methods:

Nanoshell Synthesis and Stabilization

Nanoshells with 120 nm diameter silica cores and thin gold shells were synthesized as previously described [4] to produce 150 nm diameter nanoparticles with peak optical absorption at 800 nm (Figure 1a). Nanoshells were stabilized with a coating of poly(ethylene glycol) (mPEG-SH, Creative PEGWorks) and suspended in sterile phosphate buffered saline.

Nanoshell Biodistribution

Tumors were grown in NOD SCID mice by subcutaneous injection of 10^5 U373 human glioblastoma cells. When tumor diameter was 3-5 mm, 1.7×10^{10} PEG-coated nanoshells were delivered via the tail vein. At 6, 24, and 48 hours post-injection, mice were euthanized and tumor, liver, spleen, blood, brain, and muscle were collected for assessment of gold content by inductively coupled plasma-mass spectrometry (ICP-MS).

Treatment of Subcutaneous Glioma

A survival study was performed using NOD SCID mice bearing subcutaneous U373 tumors. PEG-conjugated nanoshells (1.7×10^{10}) or 100 µl saline was delivered intravenously when tumor diameter reached 3-5 mm. The nanoshells circulated for 24 hours, the time period shown to provide maximum gold uptake in the tumor by the biodistribution study. Tumors were externally irradiated with an 800 nm diode laser (4 W/cm^2, 3 min) and mice were monitored daily following treatment and euthanized when tumor diameter reached 10 mm.

Results:

The biodistribution study demonstrated that gold concentration increases in the tumor for the first 24 hours following tail-vein injection and stabilizes at ~50 ppm thereafter. The distribution of nanoshells to the tumor and the normal brain after 24 hours is shown in Figure 1b.

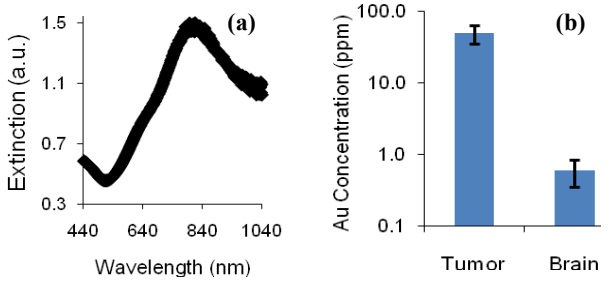

Figure 1. (a) Extinction spectrum of nanoshells. (b) Nanoshell concentration in tumor and normal brain 24 hours after intravenous delivery.

Tumor diameter was monitored daily following nanoshell delivery and laser irradiation. Four of seven mice that received nanoshell-assisted laser therapy experienced complete tumor regression without sign of re-growth for the entire study (overall survival = 57%). In contrast, median survival for the control group was only 12 days and none of the 8 mice survived past 24 days (Figure 2).

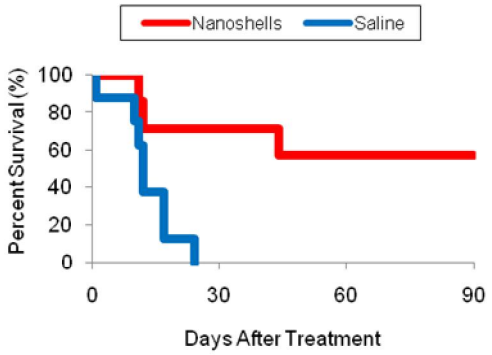

Figure 2. Survival following treatment with nanoshells or saline and laser irradiation.

Conclusions:

Nanoshell-assisted laser therapy was used successfully to treat glioma *in vivo*. PEG-coated nanoshells maximally accumulated within subcutaneous U373 tumors in mice 24 hours after intravenous delivery. Subsequent irradiation caused tumors to heat, leading to reduction in tumor size and improved survival. With further optimization of particle delivery and laser parameters, this technology could provide a highly effective treatment for glioma that reduces the risk associated with treatment of tumors situated near vital regions in the brain.

References:

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