Photothermal Cancer Therapy Using Immunotargeted Nanoshells

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Introduction: Photothermal cancer therapy using immunotargeted nanoshells may enable the preferential destruction of cancer cells while minimizing damage to healthy tissue. Nanoshells possess an optical tunability that spans the visible to the near infrared (NIR) region [1]—a region where light penetrates tissues deeply. Conjugated with tumor-specific antibodies, NIR absorbing immunonanoshells could be systemically injected and preferentially bound to tumor sites. NIR light heats the tumor-bound nanoshells, thus destroying the tumor. *In vitro* and *in vivo* studies have confirmed the ability to selectively induce cell death with the photothermal interaction of nanoshells and NIR light. Previous studies have demonstrated the ability of PEG-coated nanoshells to passively accumulate at a tumor site through the leaky vasculature that is characteristic of neoplastic tumors [2] Complete regression of tumors has been observed in animals receiving systemic injections of nanoshells prior to NIR laser treatment [2]. Furthermore, the tissue damage from the NIR laser therapy is confined to the tissue region receiving both NIR absorbing nanoshells and laser irradiation [3]. Nanoshells can be targeted to cancer cells or the tumor vasculature by the conjugation of tumor-specific antibodies to the gold surface.

Methods: Gold nanoshells were manufactured as previously described [1,4]. Briefly, silica cores were fabricated by the Stöber method in which tetraethoxysilane is reduced in basic ethanol [5]. Following amine functionalization, gold colloid (~ 3 nm) was adsorbed to silica surface. Reduction of additional gold completes the shell. Nanoshells were evaluated by their optical absorption profiles and SEM. The nanoshells used in the following study had a 110 nm core diameter with a 10 nm thick gold shell and a peak extinction at ~820 nm. Anti-HER2 antibody was conjugated to the gold nanoshells through a bi-functional PEG linker, with an N-hydroxysuccinimide terminus for antibody coupling and a disulfide terminus for attachment to the gold surface.

In vitro, immunonanoshells were incubated with HER2-expressing SKBR-3 breast carcinoma cells. Unbound nanoshells were rinsed from the surface with PBS. Control cells were incubated with anti-IgG-conjugated nanoshells or PEG-coated nanoshells. After exposure to NIR light (820 nm, 1.55 W, 1.5 mm diameter spot, 7 min), the cells were incubated overnight at 37°C. Cell viability was assessed with calcein AM and ethidium homodimer staining Nanoshells were visualized by silver staining. Similar studies were completed targeting vascular endothelial growth factor (VEGF) receptor on human umbilical vein endothelial cells (HUVECs) to demonstrate feasibility of an anti-angiogenic strategy

To verify the ability to selectively destroy cancer cells when in close proximity with non-cancerous cells, a co-culture set-up was used. SKBR-3 cells and HDFs were grown separately on glass coverslips and placed adjacent to one another prior to nanoshell treatment. Anti-HER2 nanoshells were incubated over the combined cells. After rinsing away unbound nanoshells, the NIR laser was applied such that both SKBR-3 cells and HDFs were exposed simultaneously. Cells were later stained for viability.

Results / Discussion: Cell death was confined within regions receiving immunonanoshells and laser irradiation for all experiments. In the co-culture, HDFs continued to live after laser irradiation even though the adjacent SKBR-3 cells did not (Fig. 1). Silver staining verified the presences of nanoshells. Control nanoshells did not bind to the cells, as indicated by silver staining, and cells continued to be viable after irradiation.

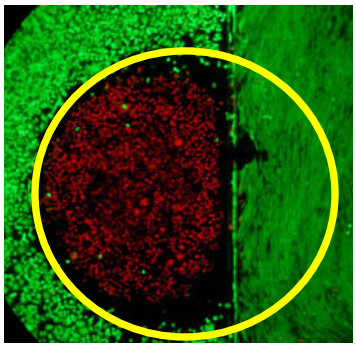

Figure 1. The NIR laser was applied as outlined in yellow. Within the laser spot, cancerous SKBR-3 cells on the left were destroyed while healthy HDFs continued to live.

Conclusions: Nanoshells show promise as a minimally invasive cancer therapy. Nanoshells are biocompatible and display selective photothermal destruction of tissue by absorption of NIR light. Antibody-conjugation may improve the cellular specificity of the nanoshell therapy.

References:

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