

Nanoparticles for Cancer Treatment

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PARTICLES CAN BE ENGINEERED TO NANOMETER-SIZE (nm) which are only 1/1,000 the width of a single human hair. Nanoparticles made of gold display strong optical absorption.¹ A special type of gold nanoparticle called hollow gold nanoparticle has a core-shell nanostructure with unique characteristics, including small particle size (~40 nm in diameter), which is an ideal range for particles to be incorporated into living cells; hollow interior, which allows for higher drug loading capacity; and pure gold composition, which is associated with less toxicity.^{2,3} The hollow gold nanoparticles have been proven to convert optical energy into thermal energy, leading to overheating of the local environment around the light-absorbing species. This phenomenon is known as photothermal effect.⁴ We have developed a variety of applications of hollow gold nanoparticles in cancer diagnosis and therapeutics, including photothermal ablation therapy, photoacoustic tomography, and light-controlled drug release.

PHOTOTHERMAL ABLATION THERAPY

Photothermal ablation therapy is a therapeutic modality in which the light-absorbing nanoparticles are utilized to burn the tumor cells.⁵ The heat produced can lead to localized temperatures far above the threshold temperature (~330 K) that causes irreversible cell death.⁶ By varying the core radius and shell thickness, the optical absorption of hollow gold nanoparticles can be fine-tuned to the **near-infrared (NIR)** region.² Absorbance of NIR light is desirable because it causes minimal thermal injury to normal tissues and deeper tissue penetration, to several centimeters.⁷ We have applied this so called “targeted delivery” technology in order to increase the nanoparticles’ ability to enter the cancerous cells. In a mouse-bearing melanoma model, the surface of hollow gold nanoparticles was coated with small peptide NDP-MSH, a potent agonist of melanocortin type-1 receptor, which is overexpressed in melanoma cells.⁸ Following intravenous injection the NDP-MSH modified nanoparticles were actively located and drawn into cancer

cells through the cell membrane. NIR light beamed into tumors with targeted nanoparticles destroyed 66 percent of the tumors, but only destroyed 8 percent of tumors treated with untargeted nanoparticles.⁸ (Figure 1) Because of the specific accumulation of nanoparticles in tumor but not in normal tissues, the efficiency of photothermal ablation therapy was vastly improved and side effects were reduced by decreasing the laser dose duration and volume.

PHOTOACOUSTIC TOMOGRAPHY

Photoacoustic tomography is a hybrid technology that visualizes the internal distribution of optical energy deposition in biological tissues through the detection of laser-induced ultrasonic waves.⁹ Photoacoustic tomography provides higher

spatial resolution than traditional optical imaging in deep biological tissues because ultrasonic scattering in such tissues is two orders of magnitude less than optical scattering. The hollow gold nanoparticles can increase photoacoustic signals because of their light excitation in the NIR spectral region, where the signal ratio of gold nanoparticles to hemoglobin is high and contrast to endogenous chromophores is great.¹⁰ Recently, we developed peptide-based hollow gold nanoparticles to target integrins that are overexpressed in both glioma and angiogenic tumor blood vessels. The targeted nanoparticles permitted accurate photoacoustic imaging of inoculated U87 glioma in nude mice and mediated selective antitumor effect when mice were irradiated with an NIR laser.¹¹ These findings suggest potential

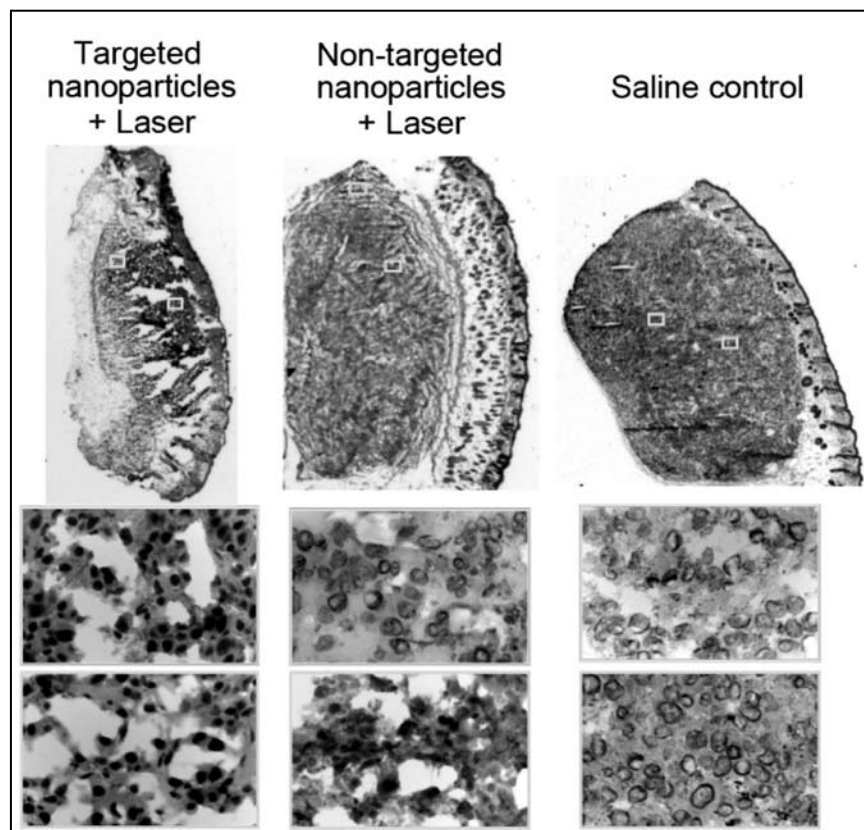


Figure 1. Photothermal ablation with targeted hollow gold nanoparticle-induced destruction of B16/F10 melanoma in nude mice. H&E staining of tumor sections 24 h after NIR laser irradiation. Tumor cells characterized by extensive pyknosis, karyolysis, cytoplasmic acidophilia, and degradation of the extracellular matrix of the tumor in mice treated with targeted nanoparticles plus laser. In mice treated with non-targeted nanoparticles plus laser, such features were observed mostly in areas close to the surface.

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applications of hollow gold nanoparticles as a novel diagnostic and therapeutic platform for 1) photoacoustic imaging for pretreatment diagnosis, real-time monitoring of treatment, as well as assessment of treatment outcome; and 2) photothermal ablation therapy of tumor cells under the guidance of photoacoustic imaging. Human malignant gliomas are characterized by their ability to infiltrate and invade surrounding normal brain tissues. Complete tumor resection is often limited by the surgeon's ability to distinguish residual tumor tissue from surrounding brain tissue. Tumors often recur because it is extremely difficult to remove infiltrating tumor cells without affecting vital brain functions. With this technique, it may be possible to achieve NIR laser treatment of the surgical bed through optical fiber for the eradication of residual brain tumor cells.

LIGHT-CONTROLLED DRUG RELEASE

The hollow gold nanoparticles can also act as vehicles to get the cancer cells to take the chemotherapy "bait". Because of their hollow interior, each hollow gold nanoparticle can load thousands of chemotherapy "baits". The drug-loaded nanoparticles are like a Trojan horse that can efficiently ferry "toxins" to the tumor cells. The hollow gold nanoparticles with high photothermal conversion efficiency can be exploited for controlled release of doxorubicin from the particles using NIR light as the external stimulus to trigger drug release.¹² Results from both cell and animal experiments showed that NIR light triggered release of doxorubicin from doxorubicin-loaded hollow gold nanoparticles in tumor sites offered temporally and spatially controlled release of the chemotherapeutic agent.^{12, 13} This increased the therapeutic efficacy and specificity. The nano-drug delivery system was also found to alter the pharmacokinetic disadvantages of the free drug, avoiding a burst exposure of a large amount of drug to vital organs such as the liver and kidney. In a future study, we will use the hollow gold nanoparticles to load the anticancer drug cisplatin. Conjugated with NDP-MSH peptide, the cisplatin-loaded nanoparticles will target melanoma. The combination of photothermal therapy and chemotherapy, with laser controlled drug release, may produce a synergistic

anticancer effect to overcome tumor regrowth and cisplatin resistance.

In summary, nanomedicine with hollow gold nanoparticles represents an innovative field with immense potential for improving cancer treatment. As illustrated in animal models,^{8, 10, 11, 13} the novel nano-drug delivery platforms have shown several potential advantages such as tumor targeting, optical imaging and controlled release strategies. Nanomedicine may generate a robust and efficacious therapeutic modality.

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