Nanoparticles Provide a Targeted Version of Photothermal Therapy for Cancer

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(PhysOrg.com) -- Using easily prepared gold nanocages that are able to escape from the blood stream and accumulate in tumors, a team of investigators from the Washington University in St. Louis has shown that they can use laser light to kill human tumors in mice. The results of this study, which was led by Younan Xia and Michael Welch, have been published in the journal *Small*.

Though the use of gold nanocages to treat human cancer is still several years from clinical trials, the researchers are encouraged by their recent findings. "We saw significant changes in tumor metabolism and histology," says Dr. Welch, "which is remarkable given that the work was exploratory, the laser 'dose' had not been maximized, and the tumors were 'passively' rather than 'actively' targeted."

The nanocages themselves are harmless in the absence of light energy. "Gold salts and gold colloids have been used to treat arthritis for more than 100 years," says Dr. Welch. "People know what gold does in the body and it's inert, so we hope this is going to be a nontoxic approach."

Gold nanocages are hollow boxes made by precipitating gold onto silver nanocubes. The silver simultaneously erodes from within the cube, entering solution through pores that open in the clipped corners of the cube. Suspensions of the gold nanocages, which are roughly the same size as a virus particle, are not always yellow, as one might expect, but instead can be any color in the rainbow. The color of a suspension of nanocages depends on the thickness of the cages' walls and the size of

pores in those walls. Like their color, their ability to absorb light and convert it to heat can be precisely controlled. "The key to photothermal therapy," says Dr. Xia, "is the cages' ability to efficiently absorb light and convert it to heat."

The gold nanocages are colored thanks to a process known as surface plasmon resonance. Some of the electrons in the gold are not anchored to individual atoms but instead form a free-floating electron gas, Dr. Xia explains. Light falling on these electrons can drive them to oscillate as one. This collective oscillation, the surface plasmon, picks a particular wavelength, or color, out of the incident light, and this determines the color that a given gold nanocage takes in solution. The resonance — and the color — can be tuned over a wide range of wavelengths by altering the thickness of the cages' walls. For biomedical applications, Dr. Xia and his colleagues tuned the cages to absorb light at 800 nanometers, a wavelength that falls in a window of tissue transparency that lies between 750 and 900 nanometers, in the near-infrared part of the spectrum. Light in this sweet spot can penetrate as deep as several inches in the body (either from the skin or the interior of the gastrointestinal tract or other organ systems).

The conversion of light to heat arises from the same physical effect as the color. The surface plasmon resonance has two parts. At the resonant frequency, light is typically both scattered off the cages and absorbed by them. By controlling the cages' size, Dr. Xia and his collaborators tailor them to achieve maximum absorption. They also fine-tune the ability of the nanocages to remain in the blood stream by coating them with a biocompatible polymer known as polyethylene glycol (PEG).

In Dr. Welch's lab, mice bearing tumors on both flanks were randomly divided into two groups. The mice in one group were injected with the PEG-coated nanocages and those in the other with buffer solution. Several days later the right tumor of each animal was exposed to a diode

laser for 10 minutes. The team then employed several different noninvasive imaging techniques to follow the effects of the therapy. During irradiation, thermal images of the mice were made with an infrared camera. As is true of other animals that automatically regulate their body temperature, mouse cells function optimally only if the mouse's body temperature remains between 36.5 and 37.5 degrees Celsius. At temperatures above 42 degrees Celsius (107 degrees Fahrenheit) the cells begin to die as the proteins whose proper functioning maintains them begin to unfold.

Infrared images made while tumors were irradiated with a laser show that in nanocage-injected mice, the surface of the tumor quickly became hot enough to kill cells. In buffer-injected mice, the temperature barely budged. Indeed, in the nanocage-injected mice, the skin surface temperature increased rapidly from 32 degrees Celsius to 54 degrees C, while in the buffer-injected mice, the surface temperature remained below normal body temperature of 37 degrees Celsius.

To see what effect this heating had on the tumors, the mice were injected with a positron emission tomography (PET) contrast agent that is used to measure cellular metabolism. The tumors of nanocage-injected mice were significantly fainter on the PET scans than those of buffer-injected mice, indicating that many tumor cells were no longer functioning. Positron emission scans made after photothermal treatment showed that the tumors in buffer-injected mice were still metabolically active, whereas those in nanocage-injected mice were not. This specificity is what makes photothermal therapy so attractive as a cancer therapy. The tumors in the nanocage-treated mice were later found to have marked histological signs of cellular damage.

Despite these results, Dr. Xia is dissatisfied with passive targeting. Although the tumors took up enough gold nanocages to give them a black cast, only 6 percent of the injected particles accumulated at the

tumor site. He would like that number to be closer to 40 percent so that fewer particles would have to be injected. He plans to attach tailor-made ligands to the nanocages that recognize and lock onto receptors on the surface of the tumor cells. In addition to designing nanocages that actively target the tumor cells, the team is considering loading the hollow particles with a cancer-fighting drug, so that the tumor would be attacked on two fronts.

This work, which was supported by the National Cancer Institute, is detailed in the paper "Gold Nanocages as Photothermal Transducers for Cancer Treatment." An abstract of this paper is available at the journal's Web site.

Provided by National Cancer Institute

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