Gold nanorods shed light on new approach to fighting cancer

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Researchers have shown how tiny "nanorods" of gold can be triggered by a laser beam to blast holes in the membranes of tumor cells, setting in motion a complex biochemical mechanism that leads to a tumor cell's self-destruction.

Tumor cell membranes often have an abnormally high number of receptor sites to capture molecules of folic acid, or folate, a form of vitamin B that many tumor cells crave. The Purdue researchers attached folate to the gold nanorods, enabling them to target the receptors and attach to the tumor cell membranes.

"The cells are then illuminated with light in the near-infrared range," said Ji-Xin Cheng (pronounced Gee-Shin), an assistant professor in Purdue's Weldon School of Biomedical Engineering. "This light can easily pass through tissue but is absorbed by the nanorods and converted rapidly into heat, leading to miniature explosions on the cell surface."

Scientists have recently determined that gold nanorods and other nanostructures can be used to target and destroy tumor cells, but it was generally assumed that cell death was due to the high heat produced by the light-absorbing nanoparticles. The Purdue team discovered, however, that a more complex biochemical scenario is responsible for killing the cells.

"We have found that rather than cooking the cells to death, the nanorods first punch holes in the membrane, and cell death is then chemically

induced, in this case by an influx of calcium," said Alexander Wei, an associate professor of chemistry at Purdue.

Findings are detailed in a research paper appearing Oct. 19 in the journal *Advanced Materials*. The paper, which appeared online last week, was written by doctoral students Ling Tong, Yan Zhao, Terry B. Huff and Matthew N. Hansen, along with Wei and Cheng.

The gold rods are less than 15 nanometers wide and 50 nanometers long, or roughly 200 times smaller than a red blood cell. Their small size is critical for the technology's potential medical applications: the human immune system quickly clears away particles larger than 100 nanometers, whereas smaller nanoparticles can remain in the bloodstream far longer.

Shining light on the gold nanorods causes them to become extremely hot, ionizing the molecules around them.

"This generates a plasma bubble that lasts for about a microsecond, in a process known as cavitation," Wei said. "Every cavitation event is like a tiny bomb. Then suddenly, you have a gaping hole where the nanorod was."

The gold nanorods also are ideal for a type of optical imaging known as two-photon luminescence, used by Cheng and his research group to monitor the position of nanorods in real time during tumor-cell targeting. The imaging technique provides higher contrast and brighter images than conventional fluorescent imaging methods.

In experiments with tumor cells in laboratory cultures, the nanorods attached to the cell membranes and were eventually taken up into the cells. The researchers found that it could take far less power to injure cells by exposing the nanorods to near-infrared light while they are still

on the membrane surface instead of waiting until the nanorods are internalized.

"This means that if you wait until the nanorods are inside the cell, then you really have to pump up the laser power, so localizing the nanorods on the cell membrane strongly influences their ability to inflict cell damage," Cheng said.

The findings suggest an optimal window of opportunity for applying near-infrared light to the nanorods for cancer treatment.

"We like to believe this opens the possibility of using nanorods for biomedical imaging as well as for therapeutic purposes," Cheng said.

The Purdue researchers observed that light-absorbing nanorods cause the formation of membrane "blebs, " similar to severe blistering. These blisters, however, are not produced directly by the high heat generated by the nanorods.

"The blebbing is triggered by the nanorods, but it's really caused through a complex biochemical pathway - a chemically induced process," Cheng said. "Extra calcium gets into the cell and triggers enzyme activity, which causes the infrastructure inside the cell to become loose, and that gives rise to the membrane blebs."

Researchers used a calcium-sensitive fluorescent dye to back up their argument that calcium influx caused the tumor cell death. When the nanorod-bearing tumor cells were maintained in a calcium-free nutrient medium, no blisters were formed if the nanorods were exposed to near-infrared light. But when the researchers added calcium to the medium, the blebbing took place immediately.

Although the technique offers promise for a new cancer treatment, it is

too early to determine when it could be in clinical use, said Wei, who is collaborating with the National Cancer Institute to determine the suitability of the functionalized gold nanorods for future clinical studies.

Source: Purdue University