Nanoparticles home in on brain tumors, boost accuracy of surgical removal

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Like special-forces troops laser-tagging targets for a bomber pilot, tiny particles that can be imaged three different ways at once have enabled Stanford University School of Medicine scientists to remove brain tumors from mice with unprecedented accuracy.

In a study to be published online April 15 in Nature Medicine, a team led by Sam Gambhir, MD, PhD, professor and chair of radiology, showed that the minuscule nanoparticles engineered in his lab homed in on and highlighted brain tumors, precisely delineating their boundaries and greatly easing their complete removal. The new technique could someday help improve the prognosis of patients with deadly brain cancers.

About 14,000 people are diagnosed annually with brain cancer in the United States. Of those cases, about 3,000 are glioblastomas, the most aggressive form of brain tumor. The prognosis for glioblastoma is bleak: the median survival time without treatment is three months. Surgical removal of such tumors — a virtual imperative whenever possible — prolongs the typical patient's survival by less than a year. One big reason for this is that it is almost impossible for even the most skilled neurosurgeon to remove the entire tumor while sparing normal brain.

"With brain tumors, surgeons don't have the luxury of removing large amounts of surrounding normal brain tissue to be sure no cancer cells are left," said Gambhir, who is the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research and director of the Molecular

Imaging Program at Stanford. "You clearly have to leave as much of the healthy brain intact as you possibly can."

This is a real problem for glioblastomas, which are particularly rough-edged tumors. In these tumors, tiny fingerlike projections commonly infiltrate healthy tissues, following the paths of blood vessels and nerve tracts. An additional challenge is posed by micrometastases: minuscule tumor patches caused by the migration and replication of cells from the primary tumor. Micrometastases dotting otherwise healthy nearby tissue but invisible to the surgeon's naked eye can burgeon into new tumors.

Although brain surgery today tends to be guided by the surgeon's naked eye, new molecular imaging methods could change that, and this study demonstrates the potential of using high-technology nanoparticles to highlight tumor tissue before and during brain surgery.

The nanoparticles used in the study are essentially tiny gold balls coated with imaging reagents. Each nanoparticle measures less than five one-millionths of an inch in diameter — about one-sixtieth that of a human red blood cell.

"We hypothesized that these particles, injected intravenously, would preferentially home in on tumors but not healthy brain tissue," said Gambhir, who is also a member of the Stanford Cancer Institute. "The tiny blood vessels that feed a brain tumor are leaky, so we hoped that the spheres would bleed out of these vessels and lodge in nearby tumor material." The particles' gold cores, enhanced as they are by specialized coatings, would then render the particles simultaneously visible to three distinct methods of imaging, each contributing uniquely to an improved surgical outcome.

One of those methods, magnetic resonance imaging, is already frequently used to give surgeons an idea of where in the brain the tumor

resides before they operate. MRI is well-equipped to determine a tumor's boundaries, but when used preoperatively it can't perfectly describe an aggressively growing tumor's position within a subtly dynamic brain at the time the operation itself takes place.

The Gambhir team's nanoparticles are coated with gadolinium, an MRI contrast agent, in a way that keeps them stably attached to the relatively inert spheres in a blood-like environment. (In a 2011 study published in Science Translational Medicine, Gambhir and his colleagues showed in small animal models that nanoparticles similar to those used in this new study, but not containing gadolinium, were nontoxic.)

A second, newer method is photoacoustic imaging, in which pulses of light are absorbed by materials such as the nanoparticles' gold cores. The particles heat up slightly, producing detectable ultrasound signals from which a three-dimensional image of the tumor can be computed. Because this mode of imaging has high depth penetration and is highly sensitive to the presence of the gold particles, it can be useful in guiding removal of the bulk of a tumor during surgery.

The third method, called Raman imaging, leverages the capacity of certain materials (included in a layer coating the gold spheres) to give off almost undetectable amounts of light in a signature pattern consisting of several distinct wavelengths. The gold cores' surfaces amplify the feeble Raman signals so they can be captured by a special microscope.

To demonstrate the utility of their approach, the investigators first showed via various methods that the lab's nanoparticles specifically targeted tumor tissue, and only tumor tissue.

Next, they implanted several different types of human glioblastoma cells deep into the brains of laboratory mice. After injecting the imaging-enhancing nanoparticles into the mice's tail veins, they were able to

visualize, with all three imaging modes, the tumors that the glioblastoma cells had spawned.

The MRI scans provided good preoperative images of tumors' general shapes and locations. And during the operation itself, photoacoustic imaging permitted accurate, real-time visualization of tumors' edges, enhancing surgical precision.

But neither MRI nor photoacoustic imaging by themselves can distinguish healthy from cancerous tissue at a sufficiently minute level to identify every last bit of a tumor. Here, the third method, Raman imaging, proved crucial. In the study, Raman signals emanated only from tumor-ensconced nanoparticles, never from nanoparticle-free healthy tissue. So, after the bulk of an animal's tumor had been cleared, the highly sensitive Raman-imaging technique was extremely accurate in flagging residual micrometastases and tiny fingerlike tumor projections still holed up in adjacent normal tissue that had been missed on visual inspection. This, in turn, enabled these dangerous remnants' removal.

"Now we can learn the tumor's extent before we go into the operating room, be guided with molecular precision during the excision procedure itself and then immediately afterward be able to 'see' once-invisible residual tumor material and take that out, too," said Gambhir, who suggested that the nanoparticles' propensity to heat up on photoacoustic stimulation, combined with their tumor specificity, might also make it possible for them to be used to selectively destroy tumors. He also expressed optimism that this kind of precision could eventually be brought to bear on other tumor types.

Provided by Stanford University Medical Center

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