

# Dual-Purpose Nanoparticles Spot Residual Tumors, Improves Cancer Surgery

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(PhysOrg.com) -- The surest cure for cancer is to remove every last bit of a tumor through surgery. Unfortunately, for most cancers that is also the most difficult approach because of two problems: it is nearly impossible today to spot every last tumor in the body and it is often difficult to determine where a tumor stops and healthy tissue begins. A solution to both of those problems may be at hand in the form of a dual-purpose nanoparticle that penetrates tumor cells and lights them up using either fluorescence imaging or magnetic resonance imaging (MRI).

A team of investigators led by Roger Tsien, Ph.D., a member of the National Cancer Institute-funded Center of Nanotechnology for Treatment, Understanding, and Monitoring of Cancer at the University of California, San Diego, developed a dual-purpose nanoparticle that only enters cells coated with two proteins that tumor cells use to invade healthy tissue. Once the nanoparticles accumulate in tumor cells, they become readily visible using either MRI or a standard [fluorescence microscope](#). The researchers report that they can spot tumors as small as 200 microns in diameter, and that they can then remove even microscopic traces of [malignant tissue](#) by tracking the fluorescent signal the nanoparticles emit. Dr. Tsien and his colleagues report their work in back-to-back papers appearing in the [Proceedings of the National Academy of Sciences](#).

The investigators built their probe using a spherical polymeric nanoparticle known as a dendrimer. Dendrimers have numerous chemical linkages available on their surface, which enabled Dr. Tsien's

team to attach three different entities to each nanoparticle: an activatable cell penetrating peptide (ACPP); three molecules of the brightly fluorescent dye known as Cy5; and 15-30 molecules of gadolinium chelate, a potent MRI contrast agent, to each nanoparticle.

ACPPs are short, positively charged peptides linked by a cleavable molecule to a second negatively charged peptide. Positively charged peptides are well-known for their ability to penetrate cells, but in the inactivated state the linked negatively charged peptide blocks cell penetration. Cleaving the linker removes the negatively charged peptide, allowing the remaining positively charged peptide - and any attached cargo - to enter cells. In this case, the linker is cleaved only by one of two proteins - matrix metalloprotein-2 or matrix metalloprotein-9 - that are present in large numbers on the surfaces of tumor cells. As a result of this specificity, nanoparticles attached to this ACPP only enter tumor cells. Nanoparticles attached to a similar peptide, but one that cannot be cleaved, did not enter [tumor cells](#) and were cleared rapidly from the body.

When injected into animals bearing human tumors, the nanoparticles accumulated in tumors over 48 hours and were readily visible using whole body MRI. When the investigators were conducting this experiment, they noticed bright edges surrounding even small tumors. Upon closer examination using fluorescence microscopy, the researchers were able to clearly delineate the jagged edges of tumors.

Using the bright fluorescent edges as a guide, the investigators were then able to achieve more complete tumor removal than was possible without nanoparticle guidance. Tumor-bearing mice who received the [nanoparticles](#) prior to surgery had better long-term tumor-free survival and overall survival than did animals whose tumors were removed using traditional bright-light illumination. The investigators were documented using followup MRI that they had removed all tumors during surgery.

This work is detailed in two papers. The first is titled, "[Activatable cell penetrating peptides linked to nanoparticles as dual probes for in vivo fluorescence and MR imaging of proteases](#)," and the second it titled, "[Surgery with molecular fluorescence imaging using activatable cell-penetrating peptides decreases residual cancer and improves survival](#)."

Provided by National Cancer Institute

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