Nanoparticle Cocktail Targets and Kills Tumors

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A team of researchers from two of the National Cancer Institute's Centers of Cancer Nanotechnology Excellence have teamed up to develop a "cocktail" of different nanometer-sized particles that work in concert within the bloodstream to locate, adhere to and kill cancerous tumors.

This work, which was led by Michael Sailor, Ph.D., of the Center of Nanotechnology for Treatment, Understanding, and Monitoring of Cancer (NANO-TUMOR) at the University of California, San Diego, and Sangeeta Bhatia, M.D., Ph.D., of the MIT-Harvard Center of Cancer Nanotechnology Excellence.

"This study represents the first example of the benefits of employing a cooperative nanosystem to fight cancer," said Dr. Sailor of the work that was published in the Proceedings of the National Academy of Sciences.

In their study, the investigators developed a system containing two different nanomaterials that can be injected into the bloodstream. One nanomaterial was designed to find and adhere to tumors in mice and then sensitize tumor cells for the second nanoparticle, which kills the tumors. These scientists and others had previously designed nanometer-sized devices to attach to diseased cells or deliver drugs specifically to the diseased cells while ignoring healthy cells, but the functions of those devices, the researchers discovered, often conflicted with one another.

"For example, a nanoparticle that is engineered to circulate through a

cancer patient's body for a long period of time is more likely to encounter a tumor," said Dr. Bhatia. "However, that nanoparticle may not be able to stick to tumor cells once it finds them. Likewise, a particle that is engineered to adhere tightly to tumors may not be able to circulate in the body long enough to encounter one in the first place."

When a single drug does not work in a patient, a doctor will commonly administer a cocktail containing several drug molecules. That strategy can be very effective in the treatment of cancer, where the rationale is to attack the disease on as many fronts as possible. Drugs may sometimes work together on a single aspect of the disease, or they may attack separate functions. In either case, drug combinations can provide a greater effect than either drug alone, and that is the same finding that the investigators made with their nanoparticle cocktail.

Ji-Ho Park, a graduate student in Dr. Sailor's UC San Diego laboratory, and Geoffrey von Maltzahn, a graduate student in Dr. Bhatia's MIT laboratory, headed the effort to develop two distinct nanomaterials that would work in concert to overcome that obstacle and others. The first particle is a gold nanorod "activator' that accumulates in tumors by seeping through their leaky blood vessels. The gold particles cover the whole tumor and behave like an antenna and absorb otherwise benign infrared laser irradiation, which then heats up the tumor. The researchers found that as a tumor's temperature rose, it expressed a protein, known as p32, on tumor cell surfaces. The investigators took advantage of this finding by including a targeting agent that binds tightly to p32 on the outside of a second, "responder" nanoparticle. Much of the work developing the p32 targeting agent was done in the laboratory of Erkki Ruoslahti, M.D., Ph.D., of the Burnham Institute for Medical Research at UC Santa Barbara and a member of the NANO-TUMOR center.

The responder nanoparticles consisted of either iron oxide nanoworms or doxorubicin-loaded liposomes. While one type of the responder

nanoparticle improves detection of the tumor, Dr. Sailor explained, the other is designed to kill the tumor. The iron oxide nanoworms show up brightly in a medical magnetic resonance imaging, or MRI, system. The second type is a hollow, lipid-based nanoparticle loaded with the anti-cancer drug doxorubicin. With the drug-loaded responder, the scientists demonstrated in their experiments that a tumor growing in a mouse can be arrested and then shrunk. "The nanoworms would be useful to help the medical team identify the size and shape of a tumor in a patient before surgery, while the hollow nanoparticles might be used to kill the tumor without the need for surgery," said Sailor.

"This study is important because it is the first example of a combined, two-part nanosystem that can produce sustained reduction in tumor volume in live animals," said Sailor.

This work, which is detailed in a paper titled, "Cooperative nanomaterial system to sensitize, target, and treat tumors," was supported by the NCI Alliance for Nanotechnology in Cancer, a comprehensive initiative designed to accelerate the application of nanotechnology to the prevention, diagnosis, and treatment of cancer. An abstract of this paper is available at the journal's Web site.

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