Nanoparticles carry cancer-killing drugs into tumor cells

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Increased efficacy, lower drug toxicity in mice

University of Michigan scientists have created the nanotechnology equivalent of a Trojan horse to smuggle a powerful chemotherapeutic drug inside tumor cells – increasing the drug's cancer-killing activity and reducing its toxic side effects.
Previous studies in cell cultures have suggested that attaching anticancer drugs to nanoparticles for targeted delivery to tumor cells could increase the therapeutic response. Now, U-M scientists have shown that this nanotechnology-based treatment is effective in living animals.

"This is the first study to demonstrate a nanoparticle-targeted drug actually leaving the bloodstream, being concentrated in cancer cells, and having a biological effect on the animal's tumor," says James R. Baker Jr., M.D., the Ruth Dow Doan Professor of Biologic Nanotechnology at the University of Michigan, who directed the study.

"We're very optimistic that nanotechnology can markedly improve cancer therapy," says Baker, who directs the Michigan Nanotechnology Institute for Medicine and the Biological Sciences. "Targeting drugs directly to cancer cells reduces the amount that gets to normal cells, increases the drug's anti-cancer effect and reduces its toxicity. By improving the therapeutic index of cancer drugs, we hope to turn cancer into a chronic, manageable disease."

Results of the study will be published in the June 15, 2005, issue of

Cancer Research.

The drug delivery vehicle used by U-M scientists is a manmade polymer molecule called a dendrimer. Less than five nanometers in diameter, these dendrimers are small enough to slip through tiny openings in cell membranes. One nanometer equals one-billionth of a meter, which means it would take 100,000 nanometers lined up side-by-side to equal the diameter of a human hair.

Dendrimers have a tree-like structure with many branches where scientists can attach a variety of molecules, including drugs. In experiments reported in Cancer Research, U-M scientists attached methotrexate, a powerful anticancer drug, to branches of the dendrimer. On other branches, they attached fluorescent imaging agents and their secret ingredient – a vitamin called folic acid.

Folic acid, or folate, is an important vitamin required for the healthy functioning of all cells. But cancer cells, in particular, seem to need more than average amounts. To soak up as much folate as possible, some cancer cells display more docking sites called folate receptors on their cell membranes. By taking advantage of a cancer cell's appetite for folate, U-M scientists are able to prevent the cells from developing resistance to chemotherapeutic drugs.

"It's like a Trojan horse," Baker explains. "Folate molecules on the nanoparticle bind to receptors on tumor cell membranes and the cell immediately internalizes it, because it thinks it's getting the vitamin it needs. But while it's bringing folate across the cell membrane, the cell also draws in the methotrexate that will poison it."

In conventional chemotherapy, drugs like methotrexate must diffuse across a cell membrane to get inside cancer cells, according to Baker. It's a slow process and requires a high concentration of drug in the extra-

cellular fluid, which can damage normal cells and tissues.

When tested in laboratory mice that had received injections of human epithelial cancer cells, the nanoparticle-based therapy using folic acid and methotrexate was 10 times more effective at delaying tumor growth than the drug given alone. Nanoparticle treatment also proved to be far less toxic to mice in the study than the anticancer drug alone.

"In our longest trial, which lasted 99 days, 30 percent to 40 percent of the mice given the nanoparticle with methotrexate survived," says Jolanta Kukowska-Latallo, Ph.D., a U-M research investigator and first author of the study. "All the mice receiving free methotrexate died – either from overgrowth of the tumor or from toxic effects of the drug.

"We saw statistically significant tumor growth reduction in all the mice given targeted nanoparticle therapy, as opposed to mice receiving either free methotrexate or the dendrimer alone," adds Kukowska-Latallo. "Effectively, we achieved a 30-day tumor growth delay. Taking into account the length of a mouse's life, that is significant. One month for a mouse is about three years for a person."

Before they began to study the effects of targeted nanoparticle therapy on cancer, U-M scientists injected dendrimers with fluorescent tags into the bloodstream of laboratory mice to determine where they would be retained in the body. The results showed that the kidneys quickly filtered free nanoparticles from blood and eliminated them in urine. The researchers found no evidence that nanoparticles were able to leave the bloodstream and enter the brain. The nanoparticles did not appear to generate an immune response in mice in the study.

In future research, scientists at the Michigan Nanotechnology Institute will determine the maximum therapeutic dose, in research animals, of targeted nanotherapy with methotrexate, and complete other preliminary

studies in preparation for the first human clinical trial, which Baker says is scheduled to begin within two years.

Researchers at the Michigan Nanotechnology Institute also are planning to explore the use of nanotechnology-based therapies using other chemotherapeutic drugs. "There are many cancer drugs that are very effective, but they can't be used now, because they are too toxic," Baker says. "If these drugs can be delivered with a targeted nanoparticle system, we may be able to overcome the toxicity problem and provide a broader range of therapeutic agents for people with cancer."

By attaching different targeting molecules and different drugs to the nanoparticle, Baker believes scientists eventually will be able to develop effective therapies for many types of cancer, perhaps even personalized therapy for an individual's specific cancer.

The research was funded by the National Cancer Institute. The University of Michigan has filed a patent application on targeted nanoparticle technology. A licensing agreement is currently being negotiated with Avidimer Therapeutics, a biopharmaceutical company in Ann Arbor, Mich. Baker holds a significant financial interest in the company.

Other U-M collaborators in the research study are Zhengyi Cao, M.D., and Shraddha S. Nigavekar, Ph.D., U-M research associates; Istvan J. Majoros, Ph.D., research investigator; and Thommey P. Thomas, Ph.D., assistant research professor. Additional collaborators who were formerly with the U-M are Lajos P. Balogh, Ph.D., Kimberly A. Candido, and Mohamed K. Khan, M.D

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