Researchers develop new drug delivery system for bladder cancer using nanoparticles

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A team of UC Davis scientists has shown in experimental mouse models that a new drug delivery system allows for administration of three times the maximum tolerated dose of a standard drug therapy for advanced bladder cancer, leading to more effective cancer control without increasing toxicity.

The delivery system consists of specially designed nanoparticles that home in on tumor cells while carrying the anti-cancer drug paclitaxel. The same delivery system also was successfully used to carry a dye that lights up on imaging studies, making it potentially useful for diagnostic purposes. The findings are published today in the journal *Nanomedicine*.

"We have developed a novel, multifunctional nanotherapeutics platform that can selectively and efficiently deliver both diagnostic and therapeutic agents to bladder tumors," said Chong-Xian Pan, principal investigator of the study and associate professor of hematology and oncology at UC Davis. "Our results support its potential to be used for both diagnostic and therapeutic applications for advanced bladder cancer."

Cancer of the bladder usually develops in the cells of the inner lining of the bladder. Survival rates are high if the disease is caught early, but it remains difficult to treat in advanced stages — when the tumor has grown outside of the bladder or metastasized to distant sites. It is the

fourth most common cancer in men; it occurs less frequently in women.

Paclitaxel is a drug used to treat advanced bladder cancer and other cancers, but it is associated with serious safety concerns. It can be toxic to bone marrow, leading to reduced levels of red and white blood cells, putting patients at risk of infection. In addition, because the drug is not readily soluble in blood, it is typically dissolved in castor oil, which has caused severe — and sometimes fatal — allergic reactions.

The drug delivery system used in this study makes use of nanoparticles called micelles developed by Kit Lam, professor and chair of the UC Davis Department of Biochemistry and Molecular Medicine and a co-author of the article. Micelles are aggregates of soap-like molecules that naturally form a tiny spherical particle with a hollow center. The researchers incorporated specific targeting molecules — called ligands — into the micelle structure. These ligands, developed by UC Davis researchers, were successfully shown in earlier studies to preferentially bind to bladder cancer cells derived from dogs and humans.

In addition to the cancer-targeting ligands, the micelles were loaded with paclitaxel. Experiments were run on mice receiving different dosages of the drug: the standard dosage currently used for therapy, and another dosage three times that amount. Mice receiving the standard dosage had significantly less tumor growth and longer overall survival compared to control mice who received a saline solution instead of drug therapy. Mice that received the high dosage took the longest time to develop a tumor and had the most days of tumor control. They also had nearly three times longer survival than mice that received drug therapy in the conventional way — without the use of the nanoparticle delivery system. The high dosage conferred few side effects and no deaths.

"The prognosis for advanced bladder cancer has not changed for three decades," said Pan. "Our findings have the potential to significantly

improve outcomes."

Mice used in the experiments were specially injected with human bladder cancer cells obtained directly from patients with the disease. This technique is believed to make the study results more clinically relevant than the more common method of using cancer cell lines that have been maintained in laboratories for research purposes for long periods of time. According to the study authors, the transplanted tumors were highly aggressive cancers.

In other experiments, the researchers loaded the bladder-cancer-homing micelles with a fluorescent imaging dye instead of paclitaxel. The imaging results proved that the micelles were targeting the bladder cancer cells and indicated that the technique may have clinical applications for diagnosis and monitoring therapy.

"These research findings are extremely exciting on many levels," said Ralph deVere White, director of the UC Davis Comprehensive Cancer Center and a study author. "We have very promising results using a novel technology that may offer a new approach to treating a variety of very difficult-to-treat cancers. I look forward to seeing this approach move forward in clinical trials."

Provided by UC Davis