New cancer drug delivery system is effective and reversible

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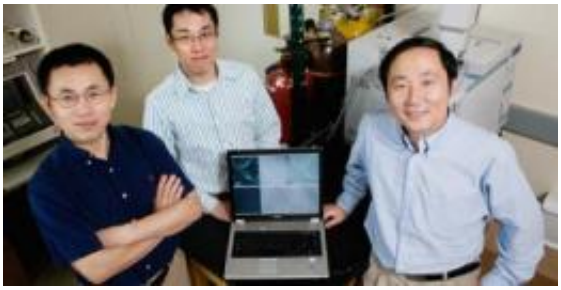

(From left) U. of I. materials science and engineering professor Jianjun Cheng, graduate student Rong Tong, chemistry professor Yi Lu and their colleagues developed a reversible method for delivering cancer drugs to breast cancer cells. Credit: Photo by L. Brian Stauffer, U. of I. News Bureau

For cancer drug developers, finding an agent that kills tumor cells is only part of the equation. The drug must also spare healthy cells, and - ideally - its effects will be reversible, to cut short any potentially dangerous side effects.

University of Illinois researchers report that they have assembled a new cancer drug delivery system that, in cell culture, achieves all of the above. The findings appear this month in the journal *Angewandte Chemie*.

The team began with the knowledge that small, membrane-bound compartments, called liposomes, are useful as drug-delivery vehicles.

When linked to molecules that target receptors on cancer cells, liposomes can enter and dump their cancer-killing contents into those cells.

Scientists have spent more than a decade trying to direct liposomes to specific cancer cells, with limited success. A common approach involves attaching an antibody to the liposome membrane. Ideally the antibody will bind to a cancer cell receptor so that it can deliver the liposome - and the cancer drug - into the cell.

Developing such antibodies is costly and time-consuming, however, and the process of attaching them to liposomes is difficult to control. Antibodies spur an immune response, requiring extra steps to create a useable therapeutic agent, and the ability of antibody-conjugated liposomes to bind to cancer cells can be inconsistent.

Some small molecules, such folate, a vitamin, also work as cancer cell targeting agents, but those now in use are not as good as antibodies at binding to cancer cells.

To solve the cell-targeting problem, the U. of I. team turned its attention to small molecules called aptamers.

"Aptamers are short strands of DNA or RNA; they are highly efficient binders, and are very easy to make, label and manipulate," said Zehui Cao, a postdoctoral researcher in the laboratory of chemistry professor Yi Lu, who led the study. Materials science and engineering professors Gerard Wong and Jianjun Cheng were co-principal investigators on the study with Lu. Graduate students Rong Tong (who is co-first author on the paper with Cao), Abhijit Mishra and Weichen Xu also worked on the study.

Lu's laboratory specializes in isolating aptamers that bind to specific

molecules and converting them into effective sensors and diagnostic agents. His team used an aptamer that binds to nucleolin receptors, which are found in abundance on certain breast cancer cells. The researchers then developed an effective method for attaching the aptamer to a liposome loaded with cisplatin, a drug that effectively kills cancer cells but has troublesome side effects when administered intravenously.

Tests in cells grown in the lab yielded promising results. Four days after they exposed the cells to the new drug-delivery system, 59.5 percent of the breast cancer cells had died, while less than 12 percent of breast cancer cells treated with cisplatin alone had died.

"By labeling a liposome that contains cisplatin with a cancer cell-specific aptamer, we have shown delivery of the drugs to cancer cells without significant damage to regular cells," Lu said, "making it possible to maximize the drug potency while minimizing its side effects."

This approach "integrates the advantages of small molecules and antibodies," said Cheng, who helped pioneer the use of aptamers as targeting molecules for drug delivery. "This is the first study to integrate the aptamers and the liposome."

Another advantage of using aptamers as targeting agents is that they are easily disabled. They readily bind to complementary DNA, which prevents them from interacting with cell receptors.

The new approach will be useful for many applications, Wong said. "What we're really doing here is coming up with a general toolbox to deal with a broad range of cancers."

"You can change aptamers to target a different type of cancer, you can change the therapeutic molecules to fight cancer or other diseases, and

you can reverse the dose," Cheng said. "That's a lot of tools in the toolbox. It has great potential."

Source: University of Illinois at Urbana-Champaign (news : web)