Nanotech researchers prove two-step method for potential pancreatic cancer treatment

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A new method of microscopic drug delivery that could greatly improve the treatment of deadly pancreatic cancer has been proven to work in mice at UCLA's Jonsson Comprehensive Cancer Center.

The research team led by Drs. Andre Nel, professor of nanomedicine and member of the California Nanosystems Institute (CNSI), and Huan Meng, adjunct assistant professor of nanomedicine, published the results of their study in the journal *ACS Nano* online ahead of print and featured in the November 2013 print issue.

Pancreatic cancer (pancreatic ductal adenocarcinoma or PDAC) is a deadly disease that is nearly impossible to detect until it is in the advanced stage. Treatment options for it are very limited in number and suffer low success rates. The need for innovative and improved treatment of pancreatic cancer cannot be overstated, as its diagnosis over the years has often remained synonymous with a death sentence.

In the pancreas, PDAC tumors consist of cancer cells that are surrounded by other structural elements called stroma. The stroma can be made of many substances, such as connective tissue and pericytes, which block the access of standard chemotherapy in tumor blood vessels from efficiently reaching the cancer cells. These elements can reduce the effectiveness of the treatment.

The dual-wave nanotherapy method employed by Drs. Nel and Meng in their research uses two different kinds of microscopic particles

(nanoparticles) intravenously injected in a rapid sequence into the vein of the tumor-bearing mouse. The first wave of nanoparticles carries a substance that removes the pericytes' vascular gates to access the pancreatic cancer cells and the second wave carries the chemotherapy drug that kills the cancer cells.

Drs. Nel and Meng and their colleagues Dr. Jeffrey Zink, UCLA professor of chemistry and biochemistry and Dr. Jeffrey Brinker, University of New Mexico professor of chemical and nuclear engineering, sought to contain chemotherapy in nanoparticles that could more directly target pancreatic cancer cells, but they needed to find a way for those nanoparticles to get through the sites of vascular obstruction caused by the pericytes, which restricts access to the cancer cells. Through experimentation they discovered they could interfere with a cellular signaling pathway (the communication mechanism between cells) that governs the pericyte attraction to the tumor blood vessels. By making nanoparticles that effectively bind a high load of the signaling pathway inhibitor, they developed a first wave of nanoparticles that separates the pericytes from the endothelial cells (on the blood vessel). This opens the vascular gate for the next wave of nanoparticles, which carry the chemotherapeutic agent to the cancer cells inside the tumor.

To test this two-wave nanotherapy, the researchers used immuno-compromised mice that were used to grow human pancreatic tumors (called xenografts) under the mouse skin. With the two-wave method, the xenograft tumors had a significantly higher rate of shrinkage compared to those exposed to chemotherapy given the standard way as a free drug or carried in nanoparticles without first wave treatment.

"This two-wave nanotherapy is an existing example of how we seek to improve the delivery of chemotherapy drugs to their intended targets using nanotechnology to provide an engineered approach," said Nel, chief of the division of nanomedicine. "It shows how the physical and

chemical principles of nanotechnology can be integrated with the biological sciences to help cancer patients by increasing the effectiveness of chemotherapy while also reducing side effects and toxicity. This two-wave treatment approach can also address biological impediments in nanotherapies for other types of cancer."

Provided by University of California, Los Angeles