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Device hits pancreatic tumors hard with toxic four-drug cocktail, sparing the body

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A highly lethal cancer sometimes requires large doses of highly toxic drugs. However, a blitzkrieg approach can be unfeasible for some patients due to severe side effects. Now a powerhouse team of researchers at the University of North Carolina at Chapel Hill has revealed that an implantable device can deliver a particularly toxic cocktail of drugs directly to pancreatic tumors to stunt their growth or in some cases, shrink them - all while showing signs that the rest of the body would be spared toxic side effects.

"We use the device to hit the primary tumor hard," said UNC Lineberger Comprehensive Cancer Center member Jen Jen Yeh, M.D., who is also an associate professor in the department of pharmacology and the UNC School of Medicine department of surgery. "It's an exciting approach because there is so little systemic toxicity that it leaves room to administer additional drugs against cancer cells that may have spread in the rest of the body."

The work, published Feb. 8 in the *Proceedings of the National Academy of Sciences*, highlights the cocktail FOLFIRINOX, a combination of four chemotherapy drugs that has been shown to shrink tumors or halt their growth in nearly a third of pancreatic cancer patients. It's one of today's first-line treatments for pancreatic cancer, but it is not suitable for all patients due to its degree of toxicity when delivered through the bloodstream. The new device, currently tested in mice, delivers the drugs directly to the tumor, providing a viable alternative to sending this toxic cocktail through the bloodstream, limiting harsh effects throughout the

rest of the body.

"We are striving to get our device into clinical trials within the next several years," said Joseph M. DeSimone, Chancellor's Eminent Professor of Chemistry in UNC's College of Arts and Sciences and William R. Kenan, Jr. Distinguished Professor of Chemical Engineering at NC State University. "The prospect of halting tumor growth with our device, and potentially shrinking tumors, could help more patients qualify for surgery." Surgically removing a tumor is currently the best chance of cure for patients with pancreatic cancer, but only 15 percent of patients have operable tumors.

The findings are the latest for the researchers in the testing of the implantable device, which uses electric fields to drive the chemotherapy drugs directly into tumors. In a study published last year in *Science Translational Medicine*, the team showed, for the first time in animal models, that the device could be implanted on top of pancreatic tumors to increase the amount of the cancer drug gemcitabine reaching them. The tumors stopped growing and shrunk, providing more favorable conditions to remove the tumor and cure the disease.

The discovery was hailed as a big advance for the treatment of pancreatic cancer, which has a 75 percent mortality rate within a year of diagnosis - a statistic that has not changed in more than 40 years.

The latest study builds on last year's critical advance. Like the previous study, the device increased the amount of drug reaching the tumors, lowered drug concentration in the blood and significantly impacted tumor growth compared to intravenous delivery of the same drugs. But this time, the device was used with a more potent four-drug combination, making the treatment more effective while limiting unbearable side effects. The accumulation of drug in the tumor using the device was at least three times greater than when using IV

administration.

"The beauty of this device is that all of the drug delivery is focused locally, with low delivery to the rest of the body," said James D. Byrne, Ph.D., the paper's first author and a current medical student at the UNC School of Medicine. "If this works in humans, we hope the device can be used as a plug-and-play approach to delivering the latest, most promising drug regimens for patients who have a dire need for new and better treatments."

More information: Iontophoretic device delivery for the localized treatment of pancreatic ductal adenocarcinoma, *Proceedings of the National Academy of Sciences*, www.pnas.org/cgi/doi/10.1073/pnas.1600421113

Provided by University of North Carolina at Chapel Hill