Two-drug combination shows promise against one type of pancreatic cancer

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Maria Zajac-Kaye, Ph.D., an associate professor in the College of Medicine's department of anatomy and cell biology, and Rony François, an M.D./Ph.D. student who works with her, found a new drug combination that inhibits one form of pancreatic cancer tumor and kills its cells. Credit: Mindy Miller, University of Florida Health

One form of pancreatic cancer has a new enemy: a two-drug combination discovered by UF Health researchers that inhibits tumors and kills cancer cells in mouse models.

For the first time, researchers have shown that a certain protein becomes overabundant in pancreatic neuroendocrine tumors, allowing them to thrive. They also found that pairing a synthetic compound with an existing drug provides a more effective anticancer punch than a single drug. The findings were published recently in the *Journal of the National Cancer Institute* by a group that includes Rony A. François, an M.D./Ph.D. student working with Maria Zajac-Kaye, Ph.D., an associate professor in the UF College of Medicine's department of anatomy and cell biology.

Finding new treatments is critical because less than 5 percent of patients with pancreatic neuroendocrine tumors respond to everolimus, the most commonly used pharmaceutical, François said. Neuroendocrine tumors, which form in the hormone-making islet cells, account for 3 percent to 5 percent of pancreatic malignancies and have a five-year survival rate of about 42 percent, according to the National Cancer Institute. Pancreatic neuroendocrine tumors are increasingly common, which medical experts and researches have attributed to better diagnostic imaging, an aging population and heightened awareness of the disease stemming from the 2011 death of Apple Inc. co-founder Steve Jobs.

Zajac-Kaye's group discovered that a single protein is behind the process that allows pancreatic neuroendocrine tumors to thrive. The protein, known as focal adhesion kinase, or FAK, activates an enzyme called AKT, which helps islet cells in the pancreas to survive. But when islet cells begin turning into tumors, the FAK protein gets overproduced, researchers found. This overabundance of the protein allows tumors to resist chemotherapy and evade efforts to kill them off.

After identifying FAK's role in tumor development, François started looking for ways to get it in check. One idea was finding something to make the antitumor drug everolimus more effective.

"Once we figured out that FAK was important, we started looking for drug combinations that would increase efficacy," he said.

Among the substances they tested was a synthetic, small-molecule compound known as PF-04554787. During lab testing, the compound "markedly inhibited" the growth of three human pancreatic cancer cell lines five days after treatment and induced the death of pancreatic cancer cells. Researchers

then tested its effectiveness on human pancreatic cells that had been implanted in mouse models. Daily doses of the compound reduced tumor volume by about 50 percent after 25 days, they found.

Next, researchers paired the compound with everolimus. While everolimus can extend some patients' lives by holding tumors in check, it does little to make them regress and is not effective for many people. François wondered if the synthetic compound would make everolimus more effective. It did, with the two-drug combination killing off pancreatic cancer cells more effectively than everolimus alone. In testing on two mouse cell lines, the drug combination reduced the viability of cancer cells by about 50 percent when compared with everolimus alone, according to the findings.

That an existing drug can be made more effective is especially encouraging because the synthetic compound that was paired with everolimus is already undergoing human clinical trials, Francois said.

"This is important because we're focused on everolimus, a drug that is already approved, non-toxic and given to patients. Anything that we can

do to make it better represents a big improvement," François said.

The findings also have potential uses for most other types of solid tumors, including those affecting the lungs and ovaries, because the same protein and enzyme are involved, François said. Next, researchers would like to study how the two-drug approach works in humans, although no clinical trials have yet been designed or scheduled.

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