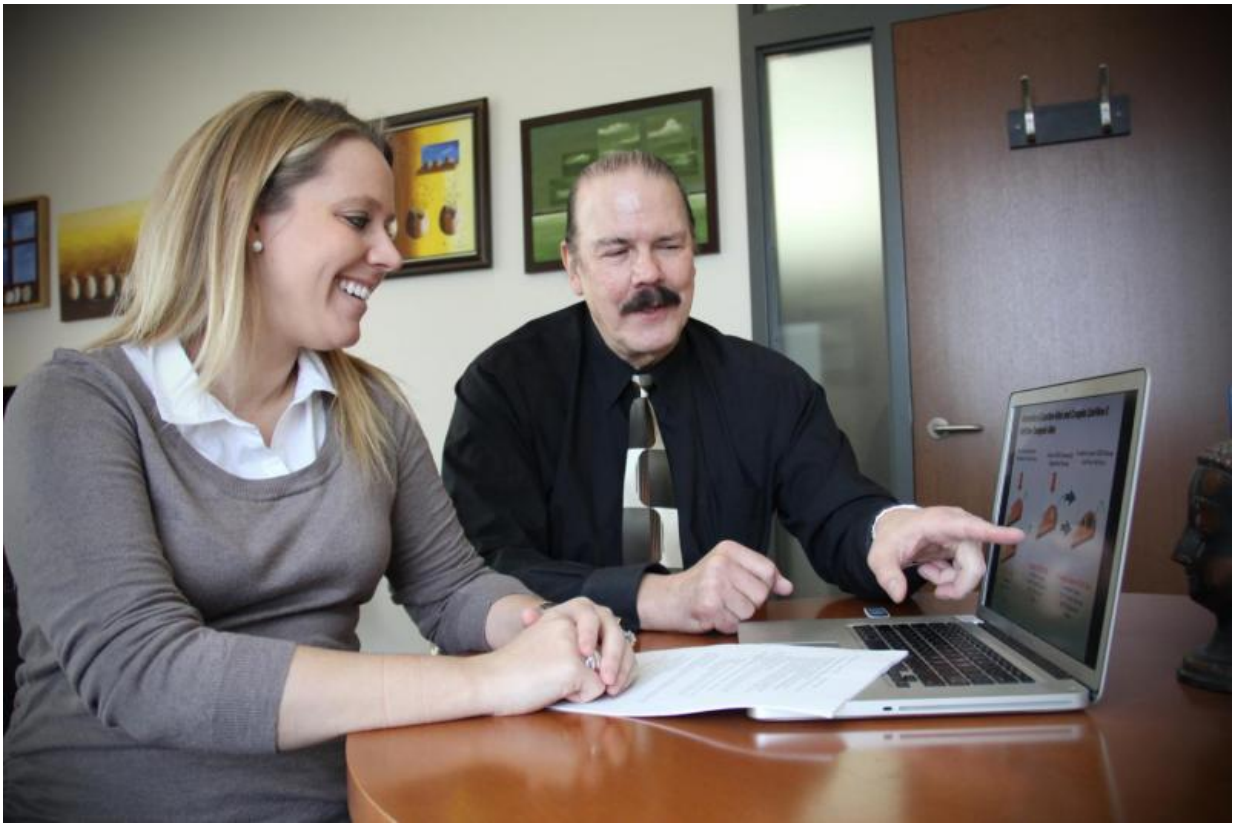
Common antibiotic part of a new potential pancreatic cancer therapy

June 1 2015



Bridget Quinn and Paul Fisher, M.Ph., Ph.D. Credit: VCU Massey Cancer Center

Despite surgical advances, pancreatic cancer continues to be one of the most deadly and difficult cancers to manage due to a lack of effective

therapies. However, VCU Massey Cancer Center and VCU Institute of Molecular Medicine (VIMM) scientists in the lab of Paul B. Fisher, M.Ph., Ph.D., are hoping to change that with a novel combination of an experimental drug and a common antibiotic that has shown promising results in preclinical experiments.

The results of these experiments were recently published in the journal *Cancer Research*. The researchers found a potent synergistic effect when they combined the drug Sabutoclax and the antibiotic Minocycline. The combination was significantly toxic to pancreatic cancer cells and disrupted tumor growth and extended survival in several types of advanced pancreatic cancer mouse models.

"Pancreatic cancer is so difficult to treat because it shows distinct genetic profiles among patients. This complexity contributes to its aggressive nature and resistance to conventional therapies such as chemotherapy and radiation therapy," says Fisher, Thelma Newmeyer Corman Endowed Chair in Cancer Research and co-leader of the Cancer Molecular Genetics research program at Massey Cancer Center, professor and chair of the Department of Human and Molecular Genetics at the VCU School of Medicine, and director of the VIMM. "The multiple in vitro and in vivo models that we used have varying genetic backgrounds and yet they all still show susceptibility to this novel and exciting therapeutic combination."

Sabutoclax is a novel drug that inhibits B-cell lymphoma 2 (Bcl-2) family proteins, which have been shown to be overexpressed in the majority of pancreatic cancers. Bcl-2 proteins play a key role in cell survival by protecting against a form of cell suicide known as apoptosis. Minocycline, a synthetic tetracycline-based antibiotic, has shown only limited success as an anti-cancer agent because it promotes the expression of pro-survival Bcl-2 proteins and, subsequently, can lead to inhibition of caspase-3 and caspase-9 activation downstream in the cell

death pathway. Caspases are enzymes that play key roles in apoptosis, necrosis and inflammation, and their activation is necessary for apoptotic cell death. However, studies have also shown that Minocycline is capable of inducing modest cancer cell death and growth inhibition in a variety of cancer types. The researchers hypothesized that Sabutoclax may negate Minocycline's Bcl-2 promotion and amplify its anti-cancer properties.

The synergistic effect of the two drugs completely eliminated Stat3 expression in pancreatic cancer cells. Stat3 is a protein that regulates a cell signaling pathway critical to tumor growth and development. Cell signaling pathways are a defined series of interactions between proteins that govern biological functions, initiated by receptors on the surface of cells. The researchers were able to reverse the lethal effects of the combination therapy by reintroducing activated Stat3 proteins.

VCU School of Medicine M.D.-Ph.D. student Bridget A. Quinn has played a critical role in advancing this novel therapeutic concept. In 2013, Quinn won an Excellence in Cancer Research Award at VCU Massey Cancer Center's annual Cancer Research Retreat poster session for her research into the anti-cancer effects of Sabutoclax and Minocyline.

"We hope to continue evaluating other tetracyclines in combination with Sabutoclax to determine if these anti-cancer effects extend outside of just Minocycline," says Quinn. "We would also like to determine if this combination is effective against other cancer types."

Provided by Virginia Commonwealth University

potential-pancreatic-cancer.html