

## **PHILADELPHIA INTERNATIONAL MEDICINE® NEWS BUREAU**

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*Editors note: Research, new techniques and improved facilities by Philadelphia International Medicine hospitals and physicians may lead to new ways to treat some of our most challenging diseases. Below are just some examples from our hospitals.*

### **New Tool Helps Physicians Tailor Hormone Therapy for High-Risk Prostate Cancer Patients**

Philadelphia -- Using one of the largest databases of prostate cancer outcomes in the United States, Fox Chase Cancer Center researchers have developed a prediction tool that uses a patient's clinical information to estimate the benefits of adding androgen deprivation therapy of various durations to radiation therapy.

Such hormone therapy has been shown to help radiation kill prostate cancer cells and improve survival in men at a high risk of recurrence, but it is associated with significant side effects. Even in high-risk cases, the degree of benefit from the addition of androgen deprivation varies.

“Studies have generally lumped patients into three levels of risk, and physicians have recommended hormone therapy based on these studies,” said Niraj H. Pahlajani, MD, a resident in the radiation oncology department. “Our experience tells us that prostate patients can't be lumped together into broad categories and expected to respond the same way to treatment even when they fall into similar risk-categories. Fortunately, we've been able to generate a nuanced prediction tool that incorporates disease burden and individualizes treatment recommendations.

We can enter each patient's clinical information and estimate the probability of the cancer coming back using different durations of hormone therapy to determine the best course."

Dr. Pahlajani said similar tools exist to predict cancer treatment outcomes, but none are as personalized, nor have yet been used to estimate the gains from different lengths of hormone therapy. The Fox Chase researchers used two key factors derived from biopsies to identify the subtle differences among those at intermediate to high-risk of recurrence. "With this information, we're able to personalize each patient's treatment by quantifying the optimal duration of hormones based on his individual factors," Dr. Pahlajani said.

Dr. Pahlajani presented the study supporting the tool at the 50th annual meeting of the American Society for Therapeutic Radiology and Oncology.

*In addition to Dr. Pahlajani, co-authors include Brian L. Egleston, Mark K. Buyyounouski, David Y.T. Chen, and Eric M. Horwitz of Fox Chase Cancer Center, and Alan Pollack of University of Miami. The authors report no disclosures. Funding for this study was provided by the National Cancer Institute and Varian Medical Systems.*

### **Jefferson Scientists Deliver Toxic Genes to Kill Pancreatic Cancer Cells**

A research team, led by investigators at the Department of Surgery at Jefferson Medical College of Thomas Jefferson University and the Kimmel Cancer Center at Jefferson, has achieved a substantial "kill" of pancreatic cancer cells by using nanoparticles to successfully deliver a deadly diphtheria toxin gene. The findings – set to be published in the October issue of *Cancer Biology & Therapy* – reflect the first time this unique strategy has been tested in pancreatic cancer cells, and the success seen offers promise for future pre-clinical animal studies, and possibly, a new clinical approach.

The researchers found that delivery of a diphtheria toxin gene inhibited a basic function of pancreatic tumor cells by over 95 percent, resulting in significant cell death of pancreatic cancer cells six days after a single treatment. They also demonstrated that the treatment targets

only pancreatic cancer cells and leaves normal cells alone, thus providing a potential ‘therapeutic window.’ Researchers are targeting a molecule that is found in over three-quarters of pancreatic cancer patients.

“For the pancreatic cancer world, this is very exciting,” said the study’s lead author, molecular biologist Jonathan Brody, PhD, assistant professor, Department of Surgery at Jefferson Medical College of Thomas Jefferson University, who works closely with the Samuel D. Gross Professor and Surgeon, Charles J. Yeo, MD. “There are no effective targeted treatments for pancreatic cancer, aside from surgery for which only a minority of patients qualify. We are in great need of translating the plethora of molecular information we know about this disease to novel therapeutic ideas.”

Pancreatic cancer is the fourth leading cause of cancer-related mortality in the U.S., reflecting the generally short survival time of patients - often less than a year from diagnosis.

This approach was originally developed in ovarian cancer cells by study co-author Janet Sawicki, PhD, a member of the Kimmel Cancer Center, and professor at the Lankenau Institute for Medical Research. She and her group had recent success in reducing the size of ovarian tumors following treatment with diphtheria toxin nanoparticles.

The strategy is based on the fact that both ovarian and pancreatic cancer cells significantly over-express a protein found on the cell membrane, called mesothelin. The function of that molecule is unknown, but it is found in the majority of pancreatic tumors and ovarian cancer tumors. Other solid tumors also express mesothelin, but not at such a high rate.

“We don’t know completely why cancer cells repeatedly turn on mesothelin genes to produce these membrane proteins, but it gives us a way to trick the cell and hijack its machinery into making other more potent genes that will be detrimental to the cancer cells,” Brody said.

To do that, the researchers devised an agent that consists of a bit of mesothelin DNA connected to the gene that produces the toxin from diphtheria, a highly contagious and potentially deadly bacteria, which is now controlled through childhood DPT vaccination. “Naked” DNA is then coated in a polymer to form nanoparticles that are taken up by the cancer cells.

Inside the cells, the agent performs its trickery. The nanoparticles biodegrade and the cell machinery senses genetic material from mesothelin. It activates the diphtheria toxin gene, which then turns on production of the toxin which allows the toxin to then do its work on the cancer cells, Brody said. Within 24 hours of delivery, the toxin disrupted production of protein machinery by over 95 percent, and within six days, a number of cancer cells die or are arrested.

“The cancer thinks it is turning on mesothelin and once it gets started reading that genetic code, it can’t stop, so it will read the bacteria’s DNA and produce the toxin which shuts down protein production in the cancer cells” said Brody.

“It worked well in our cell culture models and now we are moving into pre-clinical experiments,” Brody says.

The agent will not attack normal cells because the molecular machinery needed to turn on mesothelin is not found in normal cells, Brody says. Additionally, Sawicki has modified the diphtheria DNA to ensure that toxin that might be released from dying cancer cells is not taken up by healthy, normal cells.

The researchers are now perfecting even more stringent measures to ensure safety. “We can’t help being hopeful,” Brody said. “Our findings suggest that such a strategy will work in the clinical setting against the majority of pancreatic tumors.”

## **Penn Researchers Use Honeybee Venom Toxin to Develop New Tool for Studying Hypertension**

Researchers at the University of Pennsylvania School of Medicine have modified a toxin from honeybees to be used as a tool to study the inner workings of ion channels that control heart rate and the recycling of salt in kidneys. Ion channels selectively allow the passage of small ions such as sodium, potassium, or calcium into and out of the cell.

The study, published in the *Proceedings of the National Academy of Sciences*, is the work of Zhe Lu, MD, PhD, professor of physiology and a Howard Hughes Medical Institute investigator. Dr. Lu looked at the action of a natural bee toxin on inward-rectifier potassium channels (Kir Channels), to identify new approaches to treat cardiovascular disease.

The honeybee venom toxin, called tertiapin (TPN), stops the flow of potassium ions across cell membranes by plugging up the opening of Kir channels on the outside of cells. Kir channels in kidneys are potential new targets for treating hypertension. “The clue comes from patients with genetic defects in these channels who lose a lot of sodium because it cannot be effectively reabsorbed and thus have low blood pressure,” said Lu.

Developing a specific inhibitor for one type of Kir channel has been challenging because the target site is very similar among different types of Kir channels. For example, while TPN inhibits Kir type 1 channels in kidney cells, it also inhibits other types of Kir channels in heart cells. After more than a decade, Lu and his colleagues succeeded in bioengineering a TPN that selectively inhibits Kir channels important for salt recycling in kidneys.

By introducing two mutations into TPN, they engineered a variant, called TPN<sub>LQ</sub>, which stems the flow of potassium ions in renal Kir type 1 channels at low concentrations, and with a 250-fold sensitivity over six other types of Kir channels.

The development of TPN<sub>LQ</sub> demonstrates that a highly specific inhibitor of potassium channels can be engineered. TPN<sub>LQ</sub> can now be used as a tool to prove the concept, in animal studies, that reducing salt reabsorption by plugging up renal Kir type 1 potassium channels is a potential new way to treat hypertension.

*Yajamana Ramu and Yanping Xu of Penn conducted this study with Dr. Lu. The research was supported by the National Institutes of General Medical Sciences and the University of Pennsylvania Research Foundation.*

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