In the Spotlight

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Scientist Looks for Better Chemotherapy Management for Pancreatic Cancer
By Sheila Roberson

Pancreatic cancer is currently the fourth leading cause of cancer death in the United States and is anticipated to become the second by 2020, according to the American Cancer Society. In 2014 it is estimated that more than 46,400 people will be diagnosed with pancreatic cancer and about 85 percent will die within one year of diagnosis. The disease has a five-year relative survival rate of just 6 percent. Moreover the highly aggressive malignancy is resistant to most chemotherapeutic agents.

Rajgopal Govindarajan, an associate professor at the University of Georgia College of Pharmacy, hopes to improve pancreatic cancer chemotherapy with a $309,521 RO1 research grant he recently received from the National Institutes of Health. The study will evaluate the therapeutic potential of epigenetic reprogramming of cancer cells for improved effectiveness of current chemotherapeutic drugs in pancreatic cancer. The funding is projected for five years for a total grant of $1,554,521.

The poor prognosis of pancreatic cancer, he said, can be largely attributed to the innate drug resistance of the cancer cells, the spread of the cancer to distant sites of the body at the time of diagnosis, and a special cell population within the tumor that continually drives drug resistance and cell renewal. Large scale cancer DNA sequencing studies identify that these events occur not only as a result of changes in DNA sequence per se but other chemical modifications in the cancer cell DNA or DNA packaging elements called histones, together referred as epigenetic changes, he added.

A long-standing interest of Govindarajan’s lab is to understand the cellular transport pathways of nucleosides, the building units of DNA, and how this transport mechanism can be better exploited for uptake of anticancer nucleoside analog drugs.

“Nucleoside analogs, such as gemcitabine, are the most commonly used drugs to treat pancreatic cancer and work by entering into the DNA of cancer cells and stopping replication. Many pancreatic tumor cells, however, are resistant to nucleoside analogs, which makes the disease very difficult to treat,” said
Govindarajan, whose focus has recently turned to the regulatory activity of tiny RNA molecules, known as micro RNAs or miRs, as a means of reverting drug resistance and increasing tumor response to chemotherapy.

“We hypothesize that certain miRNAs have been silenced due to epigenetic activity in pancreatic cancer,” said Govindarajan, noting that the miRNA alterations in contributing to cancer chemoresistance are profound in pancreatic cancer cells.

The strategy, he said, is to use epigenetic reversal agents along with conventional chemotherapy agents to improve treatment criteria. In a previous NIH-funded project, his group demonstrated the potential of synthetic histone methylation inhibitors in attenuating the determinants of nucleoside analog chemoresistance, reducing pancreatic cancer cell growth and improving chemotherapeutic response to nucleoside analogs.

“These data support the use of epigenetic reversal agents as a promising group of ‘priming’ (or presensitization) agents in pancreatic cancer,” he said. “However, accompanying evidence also identifies challenges in transitioning such broad pharmacological agents to clinics because of their global effects on normal cellular epigenetic processes and related ‘off-target’ toxicities.”

“The new grant will specifically study mechanisms of action of synthetic epigenetic reversal agents that tease out the beneficial effects from the adverse effects. The overarching goal is to develop better understanding for desirably altering chemosensitization outcomes in pancreatic cancer with minimal or no adverse effect,” he said. “We have found epigenetic renewal agents to reprogram the cancer cell miRNA pool and open up new venue of research.”

So far Govindarajan has looked at close to 2,000 miRs to identify critical miRNA candidates that were predicted to directly target key determinants of tumor progression and drug resistance. Specific miR candidates, he noted, particularly show the potential to inhibit cancer cell growth, metastasis and chemoresistance when combined with synthetic epigenetic agents and these combinations will be tested in a mouse pancreatic tumor model, he added.

Another important part of his research involves collaboration with Dr. Shanta Dhar in UGA’s chemistry department to find ways to deliver miRNA into tumor cells.

“The challenge of the delivery of miRs to the tumor site will be addressed using novel miR-gold nanoparticle formulations as delivery agents,” he said. “We hope to find this technique as an alternative and improved miRNA targeting strategy to overcome existing drug delivery challenges and better handle the most aggressive human pancreatic cancers.”

“Our approach is innovative since we are utilizing new epigenetic avenues to target the crucial determinants of cancer chemoresistance in order to devise an improved and targeted approach for treating aggressive pancreatic cancer,” he added. “The importance of this novel approach is that it may advance the knowledge and principles for the successful development of future epigenetic-chemotherapeutic combination therapies for pancreatic cancer.”