UT SOUTHWESTERN MEDICAL CENTER NEWS

Media Contact: Connie Piloto
214-648-3404
conniepiloto@utsouthwestern.edu

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Chemotherapy plus synthetic compound provides potent anti-tumor effect in pancreatic cancers, researchers at UT Southwestern report

DALLAS – March 23, 2010 – Human pancreatic cancer cells dramatically regress when treated with chemotherapy in combination with a synthetic compound that mimics the action of a naturally occurring "death-promoting" protein found in cells, researchers at UT Southwestern Medical Center have found.

The research, conducted in mice, appears in today's issue of *Cancer Research* and could lead to more effective therapies for pancreatic and possibly other cancers, the researchers said.

"This compound enhanced the efficacy of chemotherapy and improved survival in multiple animal models of pancreatic cancer," said Dr. Rolf Brekken, associate professor of surgery and pharmacology and the study's senior author. "We now have multiple lines of evidence in animals showing that this combination is having a potent effect on pancreatic cancer, which is a devastating disease."

In this study, Dr. Brekken and his team transplanted human pancreatic tumors into mice, then allowed the tumors to grow to a significant size. They then administered a synthetic compound called JP1201 in combination with gemcitabine, a chemotherapeutic drug that is considered the standard of care for patients with pancreatic cancer. They found that the drug combination caused regression of the tumors.

"There was a 50 percent regression in tumor size during a two-week treatment of the mice," Dr. Brekken said. "We also looked at survival groups of the animals, which is often depressing in human therapeutic studies for pancreatic cancer because virtually nothing works. We found not only significant decrease in tumor size, but meaningful prolongation of life with the drug combination."

The drug combination was also effective in an aggressive model of spontaneous pancreatic cancer in mice.

The compound JP1201 was created in 2004 by UT Southwestern researchers to mimic the action of a protein called Smac. The researchers discovered Smac in 2000 and found that this protein plays a key role in the normal self-destruction process present in every cell.

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Cell death, or apoptosis, is activated when a cell needs to be terminated, such as when a cell is defective or is no longer needed for normal growth and development. In cancer cells, this self-destruct mechanism is faulty and lead to breaks in the cell-death cascade of events. The synthetic Smac, or Smac mimetic, developed at UT Southwestern inhibits these breaks, allowing the cell to die.

"In essence, we're inhibiting an inhibitor," Dr. Brekken said. "And we're allowing the apoptotic cascade to kick off, resulting in the death of cancer cells."

UT Southwestern researchers are using Smac mimetics in breast and lung cancer research, as well. Dr. Brekken said the next step is to develop a compound based on JP1201 that can be tested in humans in clinical trials.

Other UT Southwestern researchers involved in the study included lead author Dr. Sean Dineen, surgery resident; Dr. Christina Roland, surgery resident; Rachel Greer, student research assistant in the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research; Juliet Carbon, senior research associate in surgery and in the Hamon Center; Jason Toombs, research assistant in surgery and in the Hamon Center; Dr. Puja Gupta, a pediatric hematology/oncology fellow; Dr. Noelle Williams, associate professor of biochemistry; and Dr. John Minna, director of the W.A. "Tex" and Deborah Moncrief Jr. Center for Cancer Genetics and of the Hamon Center.

The research was supported by Susan G. Komen for the Cure and Joyant Pharmaceuticals, a Dallas-based company and UT Southwestern spinoff that is developing medical applications of Smac-mimetic compounds.

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