UT SOUTHWESTERN MEDICAL CENTER NEWS

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UT Southwestern research advances fight against kidney cancer

DALLAS – March 31, 2011 – Researchers at UT Southwestern Medical Center have discovered genetic pathways to starve selectively kidney cancer cells.

Two separate studies indicate that both rare and common cases of kidney cancer may be susceptible to a new class of drugs that inhibits cancer cells from generating the energy needed to survive. In one study, available online and scheduled for the May 5 issue of the journal *Oncogene,* researchers found that inactivating the gene *von Hippel-Lindau (VHL)* in mice blocked cells from using oxygen to provide energy to the cell, forcing them to use another method of energy generation, such as glycolysis – the conversion of glucose to lactic acid.

Because the *VHL* gene is inactive in about 90 percent of clear-cell renal cell carcinomas, the most common type of kidney cancer in humans, the study provides a rationale for the evaluation of glycolytic inhibitors in fighting kidney cancer, said Dr. James Brugarolas, assistant professor of internal medicine and developmental biology and the study's senior author.

"It would be expected to kill cancer cells preferentially and spare most normal cells that would still have mitochondrial respiration to rely on," said Dr. Brugarolas.

An estimated 58,000 new cases of kidney cancer were reported in the U.S. in 2010, and 13,040 died of the disease. Based on incidence of this cancer from 2005 to 2007, 1 in 67 people will be diagnosed with cancer of the kidney or renal pelvis during his or her lifetime.

The study also revealed that the effect of *VHL* loss was mediated by hypoxia-inducible factors (HIF), a family of proteins that binds to specific DNA sequences and responds to decreases in oxygen, known as hypoxia.

"We discovered that simultaneous inactivation of HIF rescued the mice from the effects of *VHL* inactivation," Dr. Brugarolas said. "To our knowledge, this is the first demonstration in a living organism that simply activating HIF is sufficient to block cells from using oxygen. It also indicates that there are no other pathways that can allow the use of available oxygen when HIF is active."

In a related study, Dr. Brugarolas examined the effectiveness of a specific glycolytic inhibitor, 2-deoxy-D-glucose (2DG), in treating a rare form of kidney cancer. The case study, available in the

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March 1 issue of *Nature Reviews Urology*, details efforts to develop a personalized treatment plan for a patient who presented with an uncommon kidney cancer type when she was 24. Without any familial predisposition for kidney or other cancers, the patient was found to have a mutation in a gene called *fumarate hydratase*, which has been found to be mutated in approximately 100 families worldwide and which confers a strong predisposition to kidney cancer. The mutation was a novel mutation, and the patient is likely to have been the founder, Dr. Brugarolas said.

The gene encodes an enzyme which is important for cells to be able to use oxygen and generate energy, and studies showed that the enzyme was completely inactive in the tumor. The patient, who had an advanced case of cancer, underwent surgery and then standard treatment with mTORC1 inhibitors. After five months, however, her tumor progressed and there were no other proven treatments available. Given this situation, Dr. Brugarolas looked for options to exploit what was known about the tumor. After a discussion with the UT Southwestern Institutional Review Board, the Food and Drug Administration and the drug manufacturer, Dr. Brugarolas managed to secure for his patient a drug in development, 2DG, which previously had been used only in clinical trials.

Because the tumor was deficient in *fumarate hydratase*, researchers speculated that 2DG would block glycolysis and kill tumor cells, as it had in the laboratory. The drug, however, failed to produce the same results for the patient, who later died. The patient had given permission to have her tumor studied and research continues; the tumor DNA has been sequenced and tumor samples have been implanted in mice.

"We have the tumor growing so that we can test new drugs that may emerge and hopefully help other patients with this rare cancer type," Dr. Brugarolas said. In addition, through analysis of all the mutated genes in the patient's tumor, "we may identify other mutations, which may give us clues about other approaches against this aggressive cancer type."

Efforts of the care team in the National Cancer Institute-designated Harold C. Simmons Cancer Center, "illustrate the type of discovery-based personalized cancer care we strive to provide at UT Southwestern," Dr. Brugarolas said.

Other UT Southwestern researchers involved in the *Oncogene* study included lead author Dr. Blanka Kucejova, a postdoctoral fellow in Dr. Brugarolas' lab who is now a research associate in the Advanced Imaging Research Center (AIRC); Dr. Nishanth Sunny, assistant instructor in the AIRC;

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Dr. A.D. Nguyen, graduate student in molecular genetics; R. Hallac, graduate student in radiology; Xiaorong Fu, senior research associate in the AIRC; Samuel Peña-Llopis, assistant instructor of developmental biology; Dr. Ralph Mason, professor of radiology; Dr. Ralph DeBerardinis, assistant professor of pediatrics and in the Eugene McDermott Center for Human Growth and Development; Dr. Xian-Jin Xie, associate professor of clinical sciences; Dr. Russell Debose-Boyd, associate professor of molecular genetics; Dr. Vikram Kodibagkar, assistant professor of radiology; and Dr. Shawn Burgess, assistant professor in the AIRC.

UT Southwestern researchers involved in the *Nature Reviews Urology* case study were lead author Dr. Toshinari Yamasaki and Dr. Tram Anh T. Tran, both postdoctoral fellows in developmental biology; Dr. Orhan Oz, associate professor of radiology; Dr. Garnesh V. Raj, assistant professor of urology; Dr. Roderich Schwarz, professor of surgery; Dr. DeBerardinis; and Dr. Xuewu Zhang, assistant professor of pharmacology.

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