UT SOUTHWESTERN MEDICAL CENTER NEWS

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Tracing agent, ultrasound combo helps test cancer therapy's effectiveness

DALLAS – Jan. 8, 2007 – An inexpensive tracing agent used in combination with ultrasound can pinpoint how effectively drugs targeting pancreatic cancer work, researchers at UT Southwestern Medical Center have demonstrated for the first time.

The study, involving human pancreatic tumor cells implanted in mice, opens a new avenue for real-time imaging of a patient's response to cancer therapies. It appears in the Jan. 1 issue of the journal *Clinical Cancer Research*.

The UT Southwestern research team focused on pancreatic cancer because it is one of the deadliest cancers, characterized by extensive local invasion and metastasis to the liver, said Dr. Rolf Brekken, assistant professor of surgery and pharmacology and the study's senior author. The five-year survival rate ranges from only 1 percent to 4 percent for patients diagnosed with the most severe form of cancer of the pancreas called pancreatic andenocarcinoma.

"The current best therapy – including surgery, radiation and chemotherapy – has done little to alter cancer-related deaths of these patients, emphasizing the need for more effective treatment," said Dr. Brekken, a researcher at the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research.

The research team examined how pancreatic tumor cells respond to an experimental anti-cancer agent that targets vascular endothelial growth factor (VEGF), a protein responsible for triggering the development of blood vessels that deliver nutrients and oxygen to tumors, enabling them to grow and spread. Drugs that target VEGF are in a class called anti-angiogenic agents that are designed to choke tumor growth by reducing the number of blood vessels feeding the cancer.

"In general, it has been difficult to assess whether anti-angiogenic drugs are having an impact on tumors in human patients," said Dr. Brekken. "The sooner we can measure the effectiveness of the treatment, the earlier we can intervene to change anti-cancer agents if a particular drug has no effect. This could be a lifesaving approach in patients with rapidly fatal disease."

To find the answer, the UT Southwestern team resorted to an inexpensive and commonly used contrast, or tracing agent, called microbubbles. Each tiny bubble measures about one to two microns in

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diameter – about a hundredth the width of a human hair – and consists of albumin, sugar and an inert gas. Microbubbles are used routinely in echocardiography, for example, allowing cardiologists to see how efficiently and how much blood the heart pumps.

UT Southwestern researchers linked the microbubbles to a targeting agent that delivered the imaging agent to proteins or protein complexes on the surface of tumor blood vessels. They found that the ultrasound signal from the microbubbles decreased in mice that received therapy. The harmless microbubbles remained in the bloodstream and allowed researchers to use ultrasound to get a crisp picture of what was occurring on blood vessels inside the tumor, Dr. Brekken said.

In one of the studies reported, the researchers observed that blocking VEGF activity achieved a 40-percent reduction in mean tumor size after four treatments over a two-week period, a significant controlling of tumor growth, Dr. Brekken said. Importantly, the reduction in tumor size was predicted by the decrease in signal observed non-invasively with the targeted microbubbles.

"Ultrasound is a safe technology and most physicians have an ultrasound machine in their office," Dr. Brekken said. "In addition, this monitoring technology would neither require radiation nor the injection of toxic substances for imaging purposes.

"We are the first group to show that this technique can be used to monitor the effectiveness of an anti-cancer agent," he said.

The monitoring method developed by Dr. Brekken and his colleagues would need to obtain approval from the U.S. Food and Drug Administration before it could be used in humans. Microbubbles will have to be engineered for human patients and these microbubbles will need to be linked to anti-cancer agents using chemicals acceptable to the FDA for use in humans.

The research was supported by a grant from Peregrine Pharmaceuticals Inc, a biopharmaceutical company that has an exclusive license from the University of Texas System for the anti-VEGF agent that Dr. Brekken and other UT Southwestern researchers developed and are testing in several preclinical studies. Dr. Brekken also is a consultant to and has equity interest in the company.

Other UT Southwestern researchers contributing to the study included Juliet Carbon, a senior research associate at the Hamon Center; lead author Dr. Grzegorz "Greg" Korpanty, formerly a researcher at the Hamon Center and now a resident in internal medicine at Mater Misericordiae University Hospital in Dublin, Ireland; and Dr. Jason Fleming, former associate professor of surgery at

(MORE)

Cancer tumor test – 3

UT Southwestern and now a surgical oncologist at the University of Texas M.D. Anderson Cancer Center. A researcher from Baylor University Medical Center in Dallas also participated.

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UT Southwestern Medical Center, one of the premier medical centers in the nation, integrates pioneering biomedical research with exceptional clinical care and education. Its more than 1,400 full-time faculty members – including four active Nobel Prize winners, more than any other medical school in the world – are responsible for groundbreaking medical advances and are committed to translating science-driven research quickly to new clinical treatments. UT Southwestern physicians provide medical care in 40 specialties to nearly 89,000 hospitalized patients and oversee 2.1 million outpatient visits a year.

The UT Southwestern Harold C. Simmons Comprehensive Cancer Center combines the highest standards of individual care with innovative programs for cancer diagnosis, treatment and prevention based on UT Southwestern's internationally recognized research coupled with the most sophisticated equipment and advanced technologies available. The expertise of the physicians in the Simmons Cancer Center extends to virtually every cancer in every age group, from breast, urologic, gynecologic, lung, gastrointestinal, head and neck, brain, and skin to lymphomas, leukemia, and bone marrow transplantation.

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