UT SOUTHWESTERN MEDICAL CENTER NEWS

Media Contact: Toni Heinzl
214-648-3404
Toni.Heinzl@utsouthwestern.edu

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Analysis of breast-cancer gene role offers promising target for drugs to stop or slow progression of the disease

DALLAS – Oct. 30, 2006 – Researchers at UT Southwestern Medical Center have for the first time described how multiple copies of a gene are responsible for metastases in early-stage breast cancer and poor prognosis for patients.

In a study published in this week's issue of the *Proceedings of the National Academy of Sciences,* the gene, called *uPAR*, offers a promising target for therapeutic drugs to stop or slow the progression of the disease and could serve as a screening tool for assessing which types of drugs a patient will respond to.

The gene launches a biochemical process in which a molecule called plasmin perforates the membranes of tissues, causing the membranes to break down and allowing the cancer cells to escape into the bloodstream and to adjacent tissues. The result is metastasizing breast cancer. About 20 percent to 25 percent of breast-cancer patients were shown to have *uPAR* gene amplification, which means they carry too many copies of the gene.

"The *uPAR* system probably plays a role in metastases in many of the common solid tumors," said Dr. Jonathan Uhr, professor in the Cancer Immunobiology Center and of microbiology and the study's senior author.

While analyzing slides of individual tumor cells – either from the primary tumor or circulating tumor cells – of 72 patients with advanced recurrent breast carcinoma, the UT Southwestern research team discovered how *uPAR* may work in concert with another known breast cancer gene, *HER-2.*

The researchers suggest that *uPAR* may amplify the cancer-causing effects of *HER-2.*

"This gene, *uPAR*, is an important oncogene, and that is why we determined whether or not it is amplified," said Dr. Uhr. "Unexpectedly, it is usually amplified in the same tumor cell with *HER-2* gene amplification. This has significant implications for treatment with targeting agents. Moreover,

we stress the value of individual tumor cell analysis for providing information that cannot be obtained by conventional pathological examination."

Dr. Debu Tripathy, professor of internal medicine, director of the Komen/UT Southwestern Breast Cancer Research Program and a coauthor of the study, said the biochemical process triggered by *uPAR*, called the urokinase plasminogen activator system, is one of the breast-cancer prognostic factors that has the greatest level of evidence.

"All the work has been on the protein and enzymatic activity and not amplification of the gene, which is a very reliable and easy-to-use diagnostic test called FISH," said Dr. Tripathy. "The other important finding is that *HER-2* and *uPAR* gene amplification tend to co-exist, and this has implications in new strategies to address *HER-2*-positive breast cancer with drugs that block both *HER-2* and urokinase given together."

The study opens a promising avenue to increase the effectiveness of the drug trastuzumab (Herceptin) by adding a second drug seeking to neutralize the *uPAR* gene.

"One major avenue of investigation would be to develop an antibody that prevents *uPAR* from binding to a molecule called uPA that can activate *uPAR*," Dr. Uhr said.

Other UT Soutwestern researchers contributing to the study included: Dr. Songdong Meng, a postdoctoral researcher in the Cancer Immunobiology Center; Dr. Raheela Ashfaq, professor of pathology; Dr. Barbara Haley, professor of internal medicine; Dr. Eugene Frenkel, professor of internal medicine and radiology; Dr. David Euhus, associate professor of surgical oncology; Dr. Marilyn Leitch, professor of surgical oncology; and Nancy Lane, a research scientist, and Jianqiang Wang, research assistant, both in the Cancer Immunobiology Center. Additional research was contributed by the UT M.D. Anderson Cancer Center; Texas Oncology Group; Surgical Associates of Irving-Coppell; Dallas Surgical Group; Abbott Molecular Inc. the Wistar Institute; and Immunicon Corp.

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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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