

Cancer Center BULLETIN

A PUBLICATION OF THE HAROLD C. SIMMONS COMPREHENSIVE CANCER CENTER

AMERICAN CANCER SOCIETY INSTITUTIONAL RESEARCH GRANT FUNDS RESEARCH PROJECTS

Six UT Southwestern Medical Center faculty members were recently awarded Harold C. Simmons Cancer Center new investigator awards, including one award for cancer disparities research.

The new investigator awards are funded by an American Cancer Society Institutional Research Grant and the Simmons Cancer Center and are designed to encourage new UT Southwestern faculty to develop cancer-related research projects.

The awards provide assistant professors who are in the first six years of their appointments at UT Southwestern with seed funding to initiate cancer research. Since 2003, \$1.79 million has been awarded to 59 new investigators at UT Southwestern.

The new investigator grant program encourages participation from across the campus in the cancer center's research and training programs.

The special interest award in cancer disparities research was awarded to



Dr. Heidi Hamann, assistant professor of psychiatry and clinical sciences and a member of the cancer center.

Dr. Hamann will study the racial, ethnic and economic disparities in genetic counseling, testing and risk management for women with

mutations in the *BRACA1* and *BRACA2* genes. Mutations in these genes are linked to hereditary breast and ovarian cancer.

For her pilot study, Dr. Hamann will use a retrospective medical record audit to characterize the population, examine genetic testing uptake and investigate cancer risk-management practices among women seen for breast/ovarian cancer genetic counseling at Parkland Memorial Hospital. Results from the study can help identify underserved, high-risk women who would benefit from interventions.

Other faculty members who received awards are:



Dr. Larry Anderson, assistant professor of internal medicine, will use his grant to study multiple myeloma – a

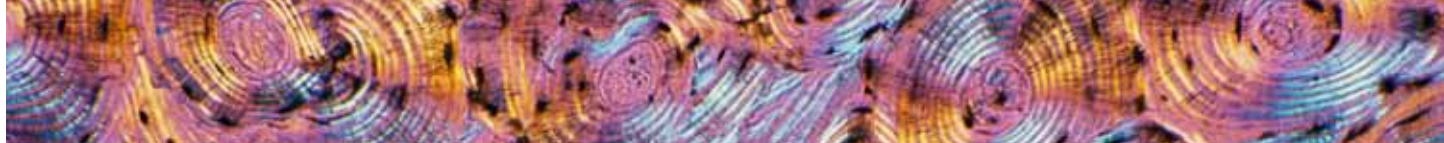
bone marrow plasma cell malignancy that is incurable with standard therapies, including autologous stem cell transplantation (SCT). Myeloma is susceptible to the graft-versus-myeloma (GVM) immune effect of allogeneic SCT, which could cure a subset of patients; however, attempts to separate GVM from the

GRAND ROUNDS

The speaker for the upcoming Simmons Cancer Center Grand Rounds is Dr. Kwok-Kin Wong, associate professor in the Department of Medicine at Harvard Medical School and instructor of adult oncology at the Dana-Farber Cancer Institute.

The lecture, which will address the development of a new lung cancer model, will be held Feb. 5 from 11:30 a.m. to 12:30 p.m. in the Medical Education and Conference Center in the T. Boone Pickens Biomedical Building (NG 3.112).

A physician-scientist, Dr. Wong's lab is building on the unique attributes of the telomerase-deficient mouse to develop a lung-cancer model that is driven by mechanisms underlying the genesis of human lung cancer. A physiologic mouse model of lung cancer may be developed by exposing the telomerase-deficient mice with shortened telomeres to chronic tobacco smoke, which will accelerate lung epithelial cell turnover and promote genome-wide mutagenesis. Once validated, this model will be used to examine the role of telomerase activation during cancer development and as a tool for novel lung-cancer gene discovery.



GRANTS AWARDED continued from page 1

excessive morbidity and mortality of graft-versus-host disease have been unsuccessful. The short-term goal of Dr. Anderson's project is to discover antigenic epitopes expressed by myeloma cells that can be recognized by T-cells from myeloma patients. The long-term goal is to utilize these antigens as targets for vaccination or T-cell therapy.



Dr. Gray Pearson, assistant professor in the Simmons Cancer Center and of pharmacology, studies the molecular underpinnings of breast cancer progression. His aim is to determine

how ligands secreted by mammary fibroblasts promote invasion. To do that, he will identify fibroblast-secreted ligands that promote the EMT-independent motility of breast cancer cells in organotypic culture models of early-stage breast cancer. Dr. Pearson also will investigate how the remodeling of the microenvironment by mammary fibroblasts promotes invasion. Understanding these processes could also help identify new targets of therapeutic intervention and improve the diagnosis of pre-invasive breast-cancer lesions.



Dr. Benjamin Tu, assistant professor of biochemistry, is investigating how the initiation of cell growth and proliferation is coordinated with metabolism, as well as how metabolic

disfunctions contribute to cancer. Dr. Tu has observed that the metabolic behavior of yeast cells undergoing a yeast metabolic cycle under glucose-poor conditions is highly reminiscent of cancer cells. He also has found that of all the amino acids, leucine is the most potent inducer of growth, a response that is mediated by the Target of Rapamycin (TOR) pathway. He will use the yeast metabolic cycle system to investigate the mechanism by which leucine activates the TOR signaling pathway and entry into growth. Dr. Tu is a W.W. Caruth Jr. Scholar in Biomedical Research.



Dr. Yihong Wan, assistant professor of pharmacology, studies the nuclear receptor family of transcription factors, in

particular their role in breast cancer and bone health. She is investigating the role of PPAR-gamma (peroxisome proliferators-activated receptor gamma) signaling in breast-cancer development, research that is based on her postdoctoral findings that PPAR-gamma suppresses inflammation during lactation. For this study, she and her team will generate mouse models with inducible and titratable mammary tumorigenesis to determine the effect of altered PPAR-gamma signaling and aberrant lactation on breast-cancer development. Dr. Wan

will use mouse genetic and disease models, molecular and cellular biology, biochemistry, genomics, metabolomics, imaging and small molecules for the study. Dr. Wan is a Virginia Murchison Linthicum Scholar in Medical Research.

Dr. David Wang, assistant professor of internal medicine, studies developmental pathway signaling in upper gastrointestinal tract malignancies. He has discovered that Hedgehog pathway



activation, which is absent in the esophagus of normal adults, occurs in patients with Barrett's esophagus and esophageal adenocarcinoma. Using cultured cells and genetically engineered mice, Dr. Wang has shown that gene targets of the Hedgehog protein are able to induce esophageal squamous epithelial cells to acquire a columnar cell phenotype. He will use the grant to characterize the transcriptional regulation of Hedgehog ligands in esophageal epithelial cells and the role of each ligand in inducing a columnar phenotype. It is hoped that these insights might lead to a chemopreventative or targeted therapy for esophageal cancer. ❖

CPRIT NAMES FIRST SCHOLAR IN CANCER RESEARCH

The Cancer Prevention and Research Institute of Texas (CPRIT) recently awarded its initial grant for a first-time, tenure-track faculty member to UT Southwestern.



Dr. Ralf Kittler

The four-year, \$2 million grant was used to recruit to UT Southwestern Dr. Ralf Kittler, whose research focuses on developing whole-genome approaches to probe the biology of cancers. Dr. Kittler's goal is to discover new diagnostic and therapeutic targets that can be used for the detection, staging and treatment of cancer, especially prostate cancer.

In his new position as assistant professor in the Eugene McDermott Center for Human Growth and Development, Dr. Kittler will establish his own laboratory and serve as the first CPRIT Scholar in Cancer Research. Dr. Kittler's appointment began Feb. 1.

"Dr. Kittler brings important new skills, technical expertise and experimental approaches to UT Southwestern," said Dr. Helen Hobbs,

director of the McDermott Center and an investigator for the Howard Hughes Medical Institute. "He will bring to cancer research in general and UT Southwestern in particular an unusual combination of skills that extend from cell biology to human genetics and genomics."

The CPRIT award is designed to recruit promising early-career investigators to Texas universities or cancer research institutions in the state and provide them with scientific and programmatic support.

Before arriving in Dallas, Dr. Kittler was a postdoctoral fellow in the Department of Human Genetics and the Institute for Genomics and Systems Biology at the University of Chicago.

He received his doctoral degree from the Max Planck Institute for Molecular Cell Biology and Genetics in Dresden, Germany.

CPRIT was established in 2007 after Texas voters approved a constitutional amendment that authorized the state to issue \$3 billion over 10 years to fund cancer research and prevention programs. ❖

CANCER CENTER RESEARCHERS IDENTIFY POSSIBLE THERAPY TARGET FOR AGGRESSIVE CANCER

Dr. David Boothman, a professor of radiation oncology and pharmacology and associate director of translational research in the Simmons Cancer Center, recently published a study showing that transforming growth factor beta1 (TGF- β 1), which normally suppresses the growth of cancer cells, causes a rebound effect after a prolonged exposure. Cancer cells



Dr. David Boothman

go into overdrive and become more aggressive and likely to spread.

The mechanism for this reversal is unknown, but UT Southwestern researchers and their colleagues in Indiana suspect that cancerous cells activate a defense mechanism in response to the lethal protein. This mechanism turns on a cascade of cancer-promoting genes.

The study, published in the January edition of *The Journal of Clinical Investigation*, was conducted on cells from mice and in samples from women with metastatic breast cancer.

The researchers examined a cascade of biochemical reactions in cells exposed to TGF- β 1. They suspected that prolonged exposure would turn on a particular cancer-causing gene, which in turn activates other cancer-supporting reactions.

In tissue from women with metastatic breast cancer, 60 percent of the patients showed both TGF- β 1 action and high levels of the cancer-causing gene.

The team also looked at nutlin3, a protein that blocks the action of the cancer-causing gene. They found that nutlin3 blocks the cancer-boosting effects of long-term TGF- β 1 exposure, preventing metastasis and killing cancer cells. Further research will be needed to determine whether nutlin3 might be worth developing as an anti-cancer drug, Dr. Boothman said. ❖