

# Cancer Center BULLETIN

A PUBLICATION OF THE HAROLD C. SIMMONS COMPREHENSIVE CANCER CENTER

Dr. Michael Roth | *Professor of Biochemistry*



## GRAND OPPORTUNITIES GRANTS AWARDED TO SIMMONS CANCER CENTER MEMBERS

UT Southwestern Medical Center has been awarded more than \$42 million to date for basic and patient-oriented research from the American Recovery and Reinvestment Act of 2009, the \$787 billion stimulus package President Barack Obama signed into law in February.

Two members of the Harold C. Simmons Comprehensive Cancer Center received Grand Opportunities grants through the National Institutes of Health, which was allotted \$10 billion to distribute through the Recovery Act. The Grand Opportunities grants support high-impact ideas that lend themselves to short-term funding and that might lay the foundation for new fields of investigation.

### ROTH: FOCUS ON LUNG CANCER

Dr. Michael Roth, professor of biochemistry, received \$3.75 million from the National Cancer Institute for a project that ultimately will produce a large database researchers can use to design patient-specific, individualized therapies for lung cancer.

The project will test the hypothesis that cell lines derived from human lung cancers can be used to identify therapeutic targets, as well as leads for therapeutic drugs, that are shared by tumors that have similar gene-expression signatures.

“It’s clear that there are multiple oncogenotypes that cause lung cancer and that these different genotypes respond differently to currently approved therapeutics,” Dr. Roth

## GRAND ROUNDS

The speaker for the upcoming Simmons Cancer Center Grand Rounds is Dr. Edward Chu, deputy director and chief of the section of medical oncology at Yale Cancer Center.

Dr. Chu is internationally known for his expertise in colorectal cancer and, along with his research team, is actively developing novel medications and strategies for the treatment of colorectal cancer and other malignancies.

The lecture will be held Dec. 18 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).

Among the many national posts he has held, Dr. Chu served a three-year term as chairman of the National Institute of Health’s Experimental Therapeutics I Study Section, which determines which potential new approaches to cancer treatment merit federal funding.

He is the founding editor-in-chief of “Clinical Colorectal Cancer” and is a current member of several editorial boards of cancer journals focusing on basic science and clinical research.

Dr. Chu is the author of the “Physicians’ Cancer Chemotherapy Drug Manual,” which provides a comprehensive review of all major cancer drugs and drug treatment regimens currently used in daily clinical practice by medical oncologists and health care professionals.



said. “However, the molecular bases of these differences are not completely understood.”

Dr. Roth and his team plan to use a systematic approach to identify most of the functional differences in cells derived from tumors having different oncogenotypes. The aim is to study how different oncogenic mutations affect the sensitivities of cells, ultimately revealing pathways that could contain novel drug targets.

The study will be conducted on a scale large enough to distinguish genetic differences that are specific for a single cell line from potential therapeutic targets that are present in all cells sharing the same set of oncogenic genetic changes.

In parallel, Dr. Roth will use high-throughput screening to determine if any of a set of 200,000 compounds, including a subset currently approved for use in humans, has therapeutic benefit in one or more subsets of genetically distinct lung cancer. Compounds that have such activity will be tested against human tumors in tissue culture.

“This will provide a potential fast-track for novel therapies as well as a method for detecting tumor-specific vulnerabilities that are resistant to detection by other methods, such as RNAi strategies,” Dr. Roth said.

A database of the combined functional genomic and compound screening results will be made available to researchers via caGrid, a platform that enables secure data sharing and analysis among institutions. The compound structures and linked biological data will be uploaded to the PubChem Web site.

This Grand Opportunities grant builds on the collaboration between

researchers across multiple disciplines at UT Southwestern and capitalizes on their collective expertise to advance cancer care.

“There is a lot of teamwork involved in this project,” Dr.

Roth said.

Over several decades, Dr. John Minna, director of the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research and the W.A. “Tex” and Deborah Moncrief Jr. Center for Cancer Genetics, and Dr. Adi Gazdar, professor of pathology in the Hamon Center, collected and characterized a large panel of lung-cancer tumor specimens from which they established lines of cells that grow in the laboratory.

Researchers from the Hamon Center and the Biostatistics and Bioinformatics Shared Resource at UT Southwestern used archived data and statistical techniques to group these cell lines according to similarities in gene expression.

At the same time, Dr. Roth and Dr. Michael White, professor of cell biology and associate director for basic science at the Simmons Cancer Center, were conducting genomic siRNA screening of a few of these lung-cancer cell lines and noticed that they differed in which genes were necessary for survival.

“These cell lines happen to be in different groups according to the gene expression data,” said Dr. Roth, who also was screening cancer cell lines against the compound libraries in the High Throughput Screening Shared Resource.

Once again, researchers saw differences in the compounds that killed different cell lines, suggesting that tumor cells in these different

groups might have different therapeutic targets.

“This raised the question of whether these differences are ‘private’ and important only for a single cell line or tumor, or whether they are vulnerabilities that are shared with other genetically related tumors,” Dr. Roth added. “It’s a question to be answered by the Grand Opportunities project.”

### VITETTA: HCV AND LIVER CANCER

Dr. Ellen Vitetta, director of the Cancer Immunobiology Center, was awarded \$1.3 million for research to develop a new vaccine for the hepatitis C virus (HCV), a major cause of liver cancer.

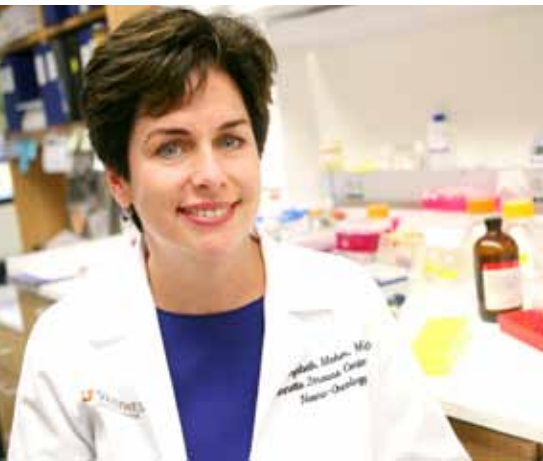
An estimated 170 million people worldwide and 20 million Americans are infected with the hepatitis C virus. Although some individuals clear the infection, there are many whose virus progresses into a chronic disease and, years later, into liver cancer.

“Since 85 percent of liver cancers are HCV-associated, if infection could be avoided by vaccination, this would have a major impact on the incidence of liver cancer,” Dr. Vitetta said.

Dr. Vitetta’s vaccine platform is based on synthetic structures called peptoids, which are selected by existing monoclonal antibodies already known to neutralize the virus. The peptoids will be screened with the antibodies, and those that react will be coupled to carrier proteins and used to immunize mice. The mice should make antibodies that then recognize both the peptoid and the virus, Dr. Vitetta said. ❖

## MAHER AWARDED CHALLENGE GRANT

Dr. Elizabeth Maher, associate professor of internal medicine and neurology at UT Southwestern and a member of the Simmons Cancer Center, received a National Institutes of Health Challenge Grant in Health and Science Research.



Dr. Elizabeth Maher

Dr. Maher's \$1 million grant was awarded as part of the American Recovery and Reinvestment Act of 2009. She is among 10 UT Southwestern researchers who received Challenge Grants.

The Challenge Grants fund specific knowledge gaps, scientific opportunities, new technologies, data generation or research methods that can benefit from an influx of funds to quickly advance disease-specific areas in significant ways.

A neuro-oncologist, Dr. Maher will study the genotype and metabolic phenotypes in glioblastoma, which is the most common primary brain tumor and one of the deadliest of human cancers. Although progress has been made over the past five years, Dr. Maher said, there is a clear need for new approaches to treatment.

Dr. Maher and her colleagues in the Annette G. Strauss Center in Neuro-Oncology and in the Advanced Imaging Research Center (AIRC) have focused on the metabolism of glioblastoma cells as a potential novel target. As is common in other cancers, glioblastoma cells use glucose at a much higher rate than normal cells, thus "fueling" the growth of the cancer cell, she said.

Physicians and scientists at UT Southwestern are collaborating in clinical and translational studies designed to identify the critical metabolic pathways that drive unregulated tumor cell growth in the brain.

"The overarching goal of our studies is to identify new therapeutic targets quickly for this devastating disease," Dr. Maher said. "Since altered metabolism is a key feature in cancer, we anticipate that the discoveries we make in glioblastoma metabolism will be applicable to other types of cancer as well."

The collaborating investigators in these studies are Dr. Craig Malloy, medical director of the AIRC; Dr. Robert Bachoo, assistant professor of neurology and internal medicine (hematology/oncology); Dr. Juan Pascual, assistant professor of neurology, pediatrics and physiology; Dr. Ralph DeBerardinis, assistant professor of pediatrics; Dr. Changho Choi, associate professor in the AIRC and of radiology; Dr. Hao Huang, assistant professor in the AIRC and of radiology; Dr. Bruce Mickey, vice chairman of neurological surgery and director of the Strauss Center; and Dr. Christopher Madden, associate professor of neurological surgery. ❖

## AIRC ADVANCES IMAGING TECHNIQUES TO GET CLEARER PICTURE OF CANCER

UT Southwestern's Advanced Imaging Research Center (AIRC) is collaborating with several Simmons Cancer Center members to develop new imaging agents to monitor physiologic parameters, such as pH in a tumor and its environs.



Dr. Dean Sherry

Located in the Bill and Rita Clements Advanced Medical Imaging Building, the AIRC provides imaging research expertise for cancer center investigators and offers UT Southwestern researchers magnetic resonance imaging (MRI) and proton spectroscopy (MRS) of mice and other small animals.

The services provided by AIRC are linked to other shared resources provided through the Simmons Cancer Center and the UT Southwestern Small Animal Imaging Resource. Services



provided to cancer center members at these facilities are subsidized in part by the Simmons Cancer Center.

The AIRC facility also includes a 7 Tesla human MRI scanner and various physiology monitoring capabilities.

At the AIRC laboratory, chemists also are building novel targeted nanoparticles for molecular imaging of cancer. The center is directed by Dr. Dean Sherry, professor of radiology at UT Southwestern who also holds a joint appointment as a professor of chemistry at UT Dallas.

Dr. Sherry and his research team recently discovered a class of magnetic resonance contrast agents called

PARACEST agents, which can be activated by specific radio-frequency pulses. The discovery has generated considerable enthusiasm in the MRI community, Dr. Sherry said, because this new class of agents offers the potential to image a broader spectrum of physiological and biochemical parameters, including cell oxidation status, enzyme activity and tissue hypoxia.

Dr. Sherry has a National Cancer Institute grant to study two specific targeting systems – a phosphatidyl serine antibody and adenovirus particles with modified knob domain proteins. The goal is to

create PARACEST systems that are completely “off” unless bound to their intended targets in vivo. Researchers also will develop a PARACEST agent that is trapped only in hypoxic tumor cells.

“Our goal is to develop a new paradigm of molecular imaging agents for anatomical MRI of cancer based upon high-sensitivity PARACEST agents,” Dr. Sherry said. For more information on how to access these and other state-of-the-art small animal imaging resources, visit the Simmons Cancer Center Web site: <http://www.utsouthwestern.edu/utsw/cda/dept24734/files/285156.html>. ❁