**CPRIT grant fuels progress of pH-sensitive nanoparticles**

With a multimillion-dollar grant to their start-up biotech company, Drs. Baran Sumer and Jinming Gao hope the pH-sensitive nanoparticles they are developing can become an essential tool in surgery for head and neck, and other, cancers.

The nanoparticles are self-assembling balls, or micelles, composed of thousands of polymers that each have a hydrophilic component (which ends up on the outside of the micelle) and a hydrophobic one (on the inside, joined to a dye molecule). While tightly packed inside the micelles, the dye molecules suppress each other’s glow. But when the micelles, which are delivered intravenously, encounter the acidic environment close to a tumor, they fall apart, and the dye lights up—a potential beacon to guide surgeons in removing every bit of a patient’s cancer.

The pH-sensitive design is an elegant solution to the challenges of precisely targeting tumors and delineating them using fluorescence, Dr. Sumer says. “Once the pH-sensitive polymer was invented, you could put any normal dye in there and it would work.”

In head and neck cancers, finely distinguishing malignant from normal tissue during surgery is critical: A significant proportion of side effects from the operation involve removal of normal tissue and structures, says Dr. Sumer, a surgeon and Associate Professor of Otolaryngology. “The mechanisms for swallowing, breathing, and speaking are all very sensitive, and when you go in and do a big surgery, you want to minimize removal of nerves and muscle that will compromise normal function. You can remove a tiny amount of tissue and really interfere with someone’s swallowing or speech.”

The ability to more precisely identify cancerous tissue intraoperatively could also dramatically reduce time spent in surgery, when the patient is still anesthetized, awaiting results from biopsy after biopsy to ensure optimal tumor removal. And the technology could reduce the need for repeat surgeries when the initial surgery didn’t remove all the cancer.

The researchers continue to optimize the chemistry of the polymers and the fluorescent dye so they work effectively with cameras used in the operating room. “We can fine-tune the pH transition threshold, dye payload, and ligand functionalization to further increase the illumination if necessary,” says Dr. Gao, Professor in the Simmons Cancer Center.

So far in mice, the nanoparticles’ use in surgery is linked to survival benefits in head and neck cancers and breast cancers. In all, the technology has successfully illuminated about

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**EVENTS**

**Two-day Small Molecule Development Symposium scheduled in November**

Students, scientists, pharmacologists, toxicologists, physicians, and regulatory personnel on campus are invited to the UT Southwestern/Clinical and Translational Science Award/Simmons Comprehensive Cancer Center Small Molecule Development Symposium. The two-day symposium will be held Thursday and Friday Nov. 19-20 in the T. Boone Pickens Medical Education & Conference Center, NG3.112.

Through mutual education, brainstorming, and building new collaborations, the event aims to accelerate development of new treatments for disease. Day 1 will focus on preclinical drug development, and Day 2 will highlight steps leading to and including clinical trials. The symposium, which is free of charge, is also open to staff, faculty, and students from partner institutions, including Parkland Health & Hospital System, Children’s Health, Texas Tech, Rice, UT Dallas, UT Arlington, and Southern Methodist University.

Registration deadline is Friday, Nov. 13, but early registration is encouraged. To register or for more information, visit www.utsouthwestern.edu/research/translational-medicine/education/course-descriptions/symposiums.html

**Agenda (roster of speakers not finalized)**

**Thursday, Nov. 19**

7-8 a.m. — Breakfast (provided)

8-9:30 a.m. — Target and Lead Compound Identification

- RNAi screen for target identification
  (Dr. Michael White, Professor of Cell Biology, UT Southwestern)

Continued on Page 4

Continued on Page 3
**RESEARCH SPOTLIGHT**

**PanCAN grants help put beta-lapachone to test against pancreas cancer**

Collaborative research on multiple fronts promises to shed new light on the potential of a natural substance, in drug form, to treat pancreatic cancer.

One major, multi-part project, funded by a grant of $1 million for three years, will pursue laboratory studies and a clinical trial involving chemotherapy plus ARQ761 (a formulation of beta-lapachone). The Pancreatic Cancer Action Network, or PanCAN, jointly with the Rising Tide Foundation for Clinical Cancer Research and Gateway for Cancer Research, awarded the grant last year to Dr. David A. Boothman, Co-Leader of the Simmons Cancer Center’s Experimental Therapeutics Scientific Program and Associate Director for Translational Research. Another project, newly funded with a $300,000 American Association for Cancer Research/PanCAN Translational Research Grant, will explore the potential of combining ARQ761 with PARP inhibitors to treat pancreatic cancer.

Dr. Boothman and colleagues across the Cancer Center are investigating the therapeutic effect of a one-two punch: ARQ761, developed by the biotechnology company ArQule, plus drugs that cause DNA lesions preferentially in tumor cells and simultaneously block DNA repair pathways. Beta-lapachone synergizes with almost all DNA-damaging agents, Dr. Boothman says, including radiation, as well as gemcitabine plus nab-paclitaxel—the current standard of care for pancreatic cancer.

The 2014 grant has three aims. For Aim 1, collaborators including Dr. Boothman and Drs. Ralph DeBerardinis (Development and Cancer Program); Matthew Merritt, Associate Professor in the Advanced Imaging Research Center; and Dean Sherry and Rolf Brekken (both Experimental Therapeutics) are noninvasively imaging pancreatic cancers in animals using hyperpolarized glucose or pyruvate to better understand ARQ761’s impact on tumor metabolism. The work further explores a previous finding in mice that the drug simultaneously shuts down glycolysis and the Krebs cycle in tumors.

“The prospects for real-time metabolic imaging of pancreatic cancer appear excellent, as these tumors show strong uptake and subsequent metabolism of our agents,” Dr. Merritt says.

Aim 2 supports a phase IB clinical trial testing ARQ761 plus chemotherapy for pancreatic cancer. The multi-institution trial, expected to begin this winter and include 20 patients, will administer ARQ761 intravenously every other week, along with gemcitabine and nab-paclitaxel on a three-weeks-on, one-week-off schedule, says Dr. Muhammad Shaalan Beg, co-leader of the Cancer Center’s gastrointestinal disease-oriented team (DOT), who is principal investigator for the trial at UT Southwestern. Dr. Daniel Laheru will lead the trial at Johns Hopkins. The phase IB trial represents the first time patients will be given ARQ761 in conjunction with chemotherapy, Dr. Beg notes.

One novel feature of the trial is that the first dose of ARQ761 will precede the chemotherapy, so researchers can see the effects of the drug alone, Dr. Boothman says. Then, after chemo impairs pancreatic adenocarcinoma cells’ ability to repair DNA damage, subsequent gemcitabine and nab-paclitaxel plus ARQ761 treatment is expected to be a “kiss of death” that destroys tumor cells but spares normal cells.

In previous tests—published in Clinical Cancer Research and Cancer Research and involving pancreatic tumor orthotopic xenografts in mice—after one series of ARQ761 as the only active treatment, “we were able to see pretty dramatic changes,” Dr. Boothman says. All 10 mice given ARQ761 were alive 11 weeks later and appeared cured, while none survived among the 10 that did not receive the drug. Tests of ARQ761 in combination with gemcitabine, and in combination with nab-paclitaxel, were also promising.

The clinical trial is built on foundational safety testing spearheaded by Dr. David Gerber, Experimental Therapeutics Co-Leader. That testing, in advanced solid tumors, is ongoing, and has demonstrated that only patients with tumors testing positive for NQO1 expression—more than 80 percent of pancreatic tumors—appeared to benefit from ARQ761. “The ability to identify a potential biomarker after testing only a small number of patients is unusual in clinical trials,” Dr. Gerber says. “Currently we are restricting enrollment to patients with NQO1-positive tumors.”

A majority of solid tumors overexpress NQO1, Dr. Boothman says, including breast and non–small cell lung cancers.

Other contributors to the clinical trial include Department of Surgery Chair Dr. Michael Choti (Experimental Therapeutics), who has consulted in the trial setup and linked UT Southwestern investigators to Dr. Laheru at Hopkins, and Dr. Art Frankel (Experimental Therapeutics), leader of the Phase I Clinical Trials Unit.

Additional research, under Aim 3 of the grant, will examine biomarkers associated with pancreatic tumors that may be signposts of ARQ761’s impact. Those include inherited NQO1 mutations that render specific patients incapable of expressing NQO1, as well as pre-treatment tumor expression levels of NQO1 and catalase, an enzyme that is lower in pancreatic cancer than normal tissue. Testing for specific predictive or responsive protein biomarkers, performed by Dr. Venetia Sarode, Professor of Pathology, and Associate Professor of Pathology Dr. Agnes Witkiewicz (Development and Cancer), respectively, will be correlated with drug levels in the blood, as measured by Drs. Richard Leff and Claudia Meek of Texas Tech University Health Sciences Center School of Pharmacy.

The newest PanCAN grant also supports research that takes a double-barreled approach against pancreatic cancer—in this case, combining ARQ761 with drugs called PARP1 (poly[ADP-ribose] polymerase 1) inhibitors. Previous work funded by PanCAN showed that genetic damage caused by ARQ761 hyperactivates PARP1 to cause a catastrophic metabolic cascade that kills cancer cells. The new combination treatment—with both types of drugs used at relatively low doses, to minimize side effects—has proved effective against pancreatic cancer cells and non-small cell lung cancer in mouse xenografts.

Researchers including Dr. Boothman, Dr. Beg, and Dr. Ganesh Raj (Experimental Therapeutics) hope in new preclinical work to develop an optimal approach

Continued on Page 4
New Cancer Targets & Nanomedicine seminar series begins Thursday, Sept. 10

A new seminar series, Cancer Targets & Nanomedicine (CTN), kicks off in September and will be presented the second Thursday of each month through May, except in October (fourth Thursday) and March (no session). The seminars, in ND3.218 beginning at noon, aim to synergize chemistry and engineering science with cancer biology and clinical oncology.

On Thursday, Sept. 10, Professor of Cell Biology Dr. Michael White will discuss “Targeting Mechanistic Subtypes of Neoplastic Disease.” Dr. Jiming Gao, Professor in the Simmons Cancer Center, will host the session.

Other speakers in the 2015-16 series are:

- Oct. 22: Dr. Justin Hanes, Lewis J. Ort Professor of Ophthalmology, Departments of Biomedical Engineering, Chemical & Biomolecular Engineering, Environmental Health Sciences, Neurosurgery, and Oncology at Johns Hopkins. Topic: Nanoscopic drug-filled particles targeting cancer. Host: Dr. Dan Siegwart, Assistant Professor in the Cancer Center.
- Nov. 12: Dr. Estela Jacinto, Associate Professor of Biochemistry and Molecular Biology at Rutgers University’s Robert Wood Johnson Medical School. Topic: TOR pathway and cancer. Host: Dr. Angelique Whitehurst, Assistant Professor in the Cancer Center.
- Dec. 10: Dr. Tanya Paull, Professor in Molecular Genetics and Microbiology and Howard Hughes Medical Institute investigator at the University of Texas Austin. Topic: Biochemical analysis of cell stress and genome-based cancer therapy. Host: CTN Student Committee.
- Jan. 14: Dr. Shuming Nie, Wallace H. Coulter Distinguished Chair Professor in Biomedical Engineering at Emory University and the Georgia Institute of Technology. Topic: Biomolecular engineering and nanotechnology for cancer imaging, molecular profiling, and targeted therapy. Host: Dr. Gao.
- Feb. 11: Dr. Darrell Irvine, Professor of Materials Science & Engineering and Biological Engineering, and HHMI investigator, at MIT’s Koch Institute for Integrative Cancer Research. Topic: Materials for enhanced vaccines and immune response modulation. Host: Dr. Siegwart.
- April 14: Dr. Shelley Berger, Daniel S. Och University Professor, Cell and Developmental Biology, of the University of Pennsylvania. Topic: Epigenetics, oncogenes, and tumor suppressors. Host: Dr. Cheng-Ming Chiang, Professor in the Cancer Center.
- May 12: Dr. Alissa Weaver, Professor of Cancer Biology at Vanderbilt Medical Center. Topic: Deregulated signaling and invasive, metastatic phenotypes. Host: Dr. Whitehurst.
NANOPARTICLES

15 different types of cancer and different cell lines. Preliminary toxicity tests in mice have indicated that the micelles are safe at 1,000 times the effective dose of 0.5 mg/kg.

“The goal is to try and get this to the clinic in two years,” Dr. Sumer says, “and we’d like to do that in as many types of cancer as possible.”

The $6 million commercialization grant from the Cancer Prevention and Research Institute of Texas, awarded last year to the biotech startup OncoNano Medicine, will help bridge the mouse research to human applications. The award will also fund development of good manufacturing and good laboratory practice (GMP, GLP) standards for production of the micelles. “We need to produce these particles in GMP grade (scale up), and perform preclinical toxicity studies,” Dr. Gao says. “Depending on the outcome, we may need to tweak the chemistry and composition a bit.”

An earlier scientific grant from CPRIT provided support for Drs. Gao and Sumer to develop and produce the pH-sensitive polymers. “That’s the secret sauce in all this,” Dr. Sumer says of the polymers. “That grant allowed us to come up with a design that was exquisitely sensitive to pH—and then study this in mice and show it can detect tumors with fluorescence.” The investigators, both members of the Cancer Center’s Experimental Therapeutics Scientific Program, have applied to renew the scientific grant, with the goal of demonstrating the technology’s utility during surgery for various cancers, including head and neck.

The pH-sensitive micelles also have cancer research applications, Dr. Gao notes. “The nanoprobes can also be used to monitor tumor acidosis for drug discovery,” he says. “We are also using them as a imaging tool to screen for compounds that control lysosome functions, which is also important for cancer.”

Other projects the team is working on include using a nanowire for early detection of cancer (in collaboration with UT Dallas); novel composition and configuration of nanoparticles designed to extend a drug’s time in the circulatory system; and photodynamic therapy using nanoparticles to kill microscopic residual cancer cells.

Dr. Sumer says his interest in nanotechnology and nanoparticles, nurtured during his fellowship and residency at Washington University, was pivotal in his choice to come to UT Southwestern. He interviewed with Dr. Gao, “and from that moment, we decided this is a good collaboration—I can discuss the clinical problems that need to be solved, and his lab has the nanotech expertise to come up with solutions.”

PANCREAS

for deploying ARQ761 with PARP inhibitors (in particular, the ovarian cancer drug olaparib and the investigational treatment rucaparib) against pancreatic cancer. The work will also examine which factors best predict efficacy of the treatment combination, and search for biomarkers that indicate response.

As a framework for discovery and collaboration, the Cancer Center has been “essential in the initial development of ARQ761 and the push for the very first clinical trials,” notes Dr. Boothman. The new pancreatic cancer trial will be the third study of the drug in patients, along with the current trial in all solid cancers that started in 2012, and a new bladder cancer trial, whose accrual is set to begin shortly.

“The Experimental Therapeutics Program and the Simmons Cancer Center have provided key support and infrastructure for this and other multi-investigator projects,” says Dr. Gerber. “These efforts are advancing UT Southwestern science to the clinic and will hopefully improve outcomes for patients with pancreatic cancer and other malignancies.”