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SAVE THE DATE

Advances in Thoracic Oncology

Friday, September 28, 2018
Weill Cornell Medicine
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For More Information

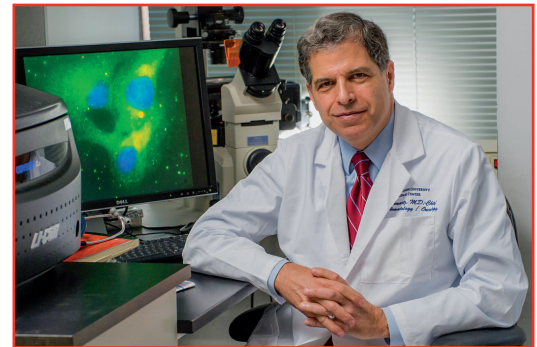
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2018 Young Investigator Awards: Recognizing Up and Coming Scientists

Five fellows in the Hematology/Oncology Fellowship Program at NewYork-Presbyterian/Columbia University Irving Medical Center have received 2018 Young Investigator Awards from the Conquer Cancer Foundation. “This is a record number of awards for our program, or for any cancer center, and it recognizes the outstanding teaching program we offer in medical oncology,” says Gary K. Schwartz, MD, Chief of Hematology and Oncology, and Deputy Director, Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian/Columbia. “These highly prestigious and competitive awards will encourage and support the best young physician-scientists in pursuing research aimed at improving the practice of cancer medicine.”

The Conquer Cancer Foundation was founded by the foremost cancer doctors of the American Society of Clinical Oncology (ASCO) to seek dramatic advances in the prevention, treatment, and cures of



Dr. Gary K. Schwartz

all types of cancer. The Young Investigator Award provides funding to promising investigators to inspire and promote quality research in clinical oncology during their transition from a fellowship program to a faculty appointment. The one-year grant of \$50,000 is based on individual merit.

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Confronting Solid Tumors: Vitamin C Takes on the KRAS Gene

In a study published in the December 11, 2015 issue of *Science*, Lewis C. Cantley, PhD, Director of the Sandra and Edward Meyer Cancer Center, Weill Cornell Medicine, and his team reported that high doses of vitamin C impaired the growth of KRAS mutant and BRAF mutant colorectal tumors.



Dr. Lewis C. Cantley

Now with a multimillion dollar grant from Stand Up to Cancer (SU2C)/American Association for Cancer Research, the investigators have moved to human trials to confirm their earlier findings.

KRAS-mutated cells make unusually large amounts of GLUT1, a protein that transports glucose across the cell membrane, supplying cancer cells with the high levels of the nutrient they need to survive. GLUT1 also transports the oxidized form of vitamin C, dehydroascorbic acid (DHA), into the cell. Normally, only a small fraction of vitamin C in the blood stream is converted to DHA, but in the microenvironment of KRAS mutant tumors, reactive oxygen generated by the tumor converts much of the vitamin C to DHA, which can enter the tumor rapidly. Once inside, the DHA acts like a Trojan horse. Natural antioxidants inside the cancer cell attempt to convert the DHA

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2018 Young Investigator Awards: Recognizing Up and Coming Scientists (continued from page 1)



(Seated) Dr. Mark L. Heaney, Director of the Hematology/Oncology Fellowship Program, and Anthony Rainone, Fellowship Program Coordinator
(Standing) 2018 Young Investigator Award recipients: Dr. Ruth A. White, Dr. David H. Aggen, Dr. Daniel S. O'Neil, Dr. Shawn M. Sarkaria, and Dr. Jessica Yang

Columbia's three-year Hematology/Oncology Fellowship provides 18 months of clinical training and 18 months of protected research time. At the end of their first year, fellows identify a research mentor and project to develop into what forms the foundation of an investigative career. "One of our priorities has been to augment research training by affording additional protected time and to expand the grant writing program," says **Mark L. Heaney, MD, PhD**, Director of the Hematology/Oncology Fellowship Program. "We are also very proud of providing opportunities for our fellows to work with great clinical and translational investigators who serve as outstanding mentors – it's very much an apprenticeship."

"We are extraordinarily fortunate to receive five Young Investigator Awards. It is a testament to the caliber of fellows that we are able to attract, the commitment of our faculty as mentors, and the preparation that fellows receive in writing the grants."

– Dr. Mark L. Heaney

"For decades, seminal discoveries in cancer biology have been made by investigators here at Columbia," continues Dr. Heaney. "What's new in the last five years has been the complementary development of a clinical research program, where we go from the bench to the bedside and back to the bench. Having a full-service research program has been tremendously attractive to potential hematology/oncology fellows."

2018 Young Investigators in Action

David H. Aggen, MD, PhD

Mentor: Charles G. Drake, MD, PhD

Targeting Myeloid-Derived Suppressor Cells in Renal Cell Cancer with Combination IL-1 Beta and PD-1 Blockade

Dr. David Aggen earned his PhD and MD in the Medical Scholars Program at the University of Illinois, graduating in 2013. His thesis work focused on developing a platform for *in vitro* screening of human T-cell receptors to enhance affinity to tumor-associated antigens. These high-affinity receptors were applied in adoptive transfer experiments in murine tumor models, demonstrating both efficacy and safety of receptors with 1,000-fold affinity for self-derived tumor antigens.

As a resident at Wayne State University, Dr. Aggen pursued his interest in immunology working closely with the bone marrow transplant service at Karmanos Cancer Center. Under the mentorship of Dr. Joseph Uberti, he reviewed early outcomes from HLA-mismatched haploidentical allogeneic stem cell transplants, presenting his findings at the 2015 American Society of Hematology Annual Meeting.

In 2016, Dr. Aggen joined the Hematology/Oncology Fellowship Program at Columbia. "I wanted to pursue a fellowship at a center where I could perform translational, high-impact research; I found a home at Columbia," says Dr. Aggen, who is now focused on defining mechanisms of tumor immunosuppression in human genitourinary cancer and exploring the mechanisms of resistance to immune escape in cancer. "While I think it is challenging for a CAR T-cell approach to work in solid tumors, in acute leukemia there has been a lot of early success and recent FDA approval of CAR T-cell-type strategies."

Working with Dr. Charles Drake, Director of Genitourinary Oncology and a nationally recognized expert in immunotherapy, Dr. Aggen is dedicating the next phase of his career to developing novel immunosuppressive combination therapies for patients with kidney, bladder, and prostate cancer.

“Dr. Drake and I share a common interest in trying to move immunotherapy forward in genitourinary malignancy,” says Dr. Aggen. “We know that kidney cancer and bladder cancer respond well to immunotherapy in some patients, but the question is how we can improve results in the remainder of those who don’t respond. The broad goal of my Young Investigator proposal is to try and target Interleukin 1, a cytokine that we think drives the cancer cell and causes tumor immunosuppression, in combination with PD-1. We’re working very rapidly to develop a robust clinical trial portfolio with novel immunotherapy combinations. Columbia is building a human immune monitoring core that is second to none. Eventually, we’ll be able to treat patients with immunotherapy, obtain treatment biopsies, and be able to tailor their treatment based on what we see.”

For More Information

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Daniel S. O’Neil, MD, MPH

Mentors: Alfred I. Neugut, MD, PhD, and Paul Ruff, MBBCh
Quality of Breast Cancer Care in Five Public Hospitals in South Africa and Effects on Survival

While at Albert Einstein College of Medicine, Dr. Daniel O’Neil served for a year as Program Coordinator for the Doctors for Global Health NGO in Uganda, giving him his first exposure to worldwide health issues. The experience prompted him to pursue a master’s in public health with a focus on epidemiology at the Harvard T.H. Chan School of Public Health. While there he also completed a residency in internal medicine and global health at Brigham and Women’s Hospital in 2016.

“There is still a lot of infectious disease in the developing world, but we’re also beginning to see chronic diseases in a big way, for example, heart disease, diabetes, and, increasingly, cancer,” says Dr. O’Neil, who during his residency also spent six months at a cancer referral hospital in rural Rwanda, completing a research project that applied quality standards adapted from the U.S. and Europe to the breast cancer care provided at the hospital.

“Resource-constrained populations and health systems face specific challenges in the delivery of effective, high quality cancer care,” says Dr. O’Neil. “As the global incidence of cancer increases, tools and techniques for addressing those barriers must be developed and tested.”

As a fellow with NewYork-Presbyterian/Columbia, Dr. O’Neil not only benefits from the clinical training provided in an NCI-sponsored comprehensive cancer center, but also from the research support of the Mailman School of Public Health and a well-established collaboration with the University of Witwatersrand in Johannesburg. “Columbia and the University of Witwatersrand have one of the largest, most comprehensive databases of breast cancer patients in sub-Saharan Africa who are seen at the five public hospitals there,” says Dr. O’Neil. “It’s very unusual to have a reliable set of easily accessible and analyzable information on cancer patients from sub-Saharan Africa.”

Dr. O’Neil’s Young Investigator Award will support his goal to develop quality metrics appropriate for cancer centers in Africa and

other low- and middle-income countries. He will be working with mentors Dr. Alfred Neugut, who has devoted his career to treating patients with cancer and conducting rigorous epidemiologic and health services research, and Dr. Paul Ruff, who leads the oncology program at the University of Witwatersrand. “The scope of our project, which calls on the extensive clinical and socioeconomic data available on thousands of patients, will provide the opportunity for me to further develop my skills with large databases, including conception and design, data cleaning and organization, primary and correlative analysis, preparing manuscripts, and presenting at international meetings,” says Dr. O’Neil. “Importantly, I want to lend my skills as a global oncology epidemiologist researcher to think about developing ways to deliver care more effectively in these low-resource settings.”

For More Information

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Shawn M. Sarkaria, MD

Mentors: Gary K. Schwartz, MD, and Lei Ding, PhD

Targeting PDGFR α -Expressing Stromal Cells in Primary Myelofibrosis

As an undergraduate in electrical engineering at the University of California, Los Angeles, Dr. Shawn Sarkaria worked in a cancer biology lab, and it was there that he says his “gravitation to oncology began.”

Dr. Sarkaria went on to earn his medical degree at Weill Cornell Medicine, followed by an internal medicine residency at the University of Washington. Throughout his education, Dr. Sarkaria’s interests have stayed firmly rooted in cancer research, having held positions as a staff research associate in brain tumors at UCLA and being named a Doris Duke Clinical Research Fellow in leukemia research at Washington University in St. Louis.

With the support and guidance of his mentors, Dr. Gary Schwartz, whose lab focuses on identifying new targeted agents for cancer therapy, and Dr. Lei Ding, Assistant Professor of Rehabilitation and Regenerative Medicine and a member of the Columbia Stem Cell Initiative, Dr. Sarkaria is applying his Young Investigator Award to study primary myelofibrosis, a clonal stem cell-derived hematologic malignancy characterized by chronic myeloproliferation, atypical megakaryocytic hyperplasia, and bone marrow fibrosis.

“For myelofibrosis, which is the subtype of myeloproliferative neoplasm [MPN] that I’m focusing on, there is only one FDA-approved drug, ruxolitinib, developed to specifically target the JAK2 mutation that we commonly see in myeloproliferative neoplasms,” says Dr. Sarkaria. “It has turned out that all three subtypes of MPN have activation of the JAK/STAT pathway, the central molecular pathway that drives cell growth in this disease. Ruxolitinib is actually effective whether or not you have the JAK2 mutation because it targets this common pathway. Clinical trials show that the drug mainly reduces spleen size and symptom burden, but it doesn’t change the fundamental biology. Side effects improve, so patients feel better, but as myelofibrosis progresses, the bone marrow is replaced by fibrotic tissue, eventually leading to bone marrow failure. The central goal of my research is to slow down that progression by targeting components of the tumor microenvironment. If we can slow down the process of fibrosis, it would help preserve normal bone marrow function and, potentially, enhance the efficacy of other drugs such as ruxolitinib.”

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“Though it is sometimes hard to maintain a footing in both arenas,” adds Dr. Sarkaria, “I want to establish my own translational research laboratory as well as maintain a footing in clinical medicine. The connection to patients not only informs my research, it motivates me to keep at it.”

For More Information

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Ruth A. White, MD, PhD

Mentor: Timothy C. Wang, MD

Cholinergic Regulation of the Neural Microenvironment in Pancreatic Cancer

“Both of my parents were researchers and so I was exposed very early to basic science,” says Dr. Ruth White. “I actually spent a lot of my childhood saying that I was absolutely not going to do research!”

Dr. White’s views changed the summer after graduating from Scripps College while working in a laboratory in Germany. “I loved the atmosphere,” she recalls. “I like thinking of why a disease works in a particular way, finding ways to harness that understanding, and then trying to find new therapies. That really struck a chord in me.”

Conflicted as to whether she should go to medical school or graduate school, she decided to do both, applying to the MD-PhD Medical Science Training Program at Oregon Health and Science University. When writing her PhD dissertation and studying mouse models of head and neck cancer, she knew she had found her specialty. After completing her residency at the University of Maryland Medical Center, Dr. White applied to the Hematology/Oncology Fellowship Program at Columbia. “In my first year, I thought I would focus on head and neck cancer, but I have spent a lot of time in GI clinical work and really enjoy it.”

Dr. Susan Bates, a clinical mentor for Dr. White, encouraged her to meet with Dr. Timothy Wang, Chief, Division of Digestive and Liver Disease at Columbia, and a renowned researcher in GI cancers. Dr. Wang’s lab, which is a member of the NCI-sponsored Tumor Microenvironment Network, is an international leader in models of Helicobacter-mediated gastric cancer and has also developed inflammatory models of colorectal, esophageal, and pancreatic neoplasia.

For her Young Investigator project, Dr. White will be exploring the cholinergic regulation of the neural microenvironment in pancreatic cancer. “There haven’t been any real breakthroughs in pancreatic cancer, but there have been some improvements recently, particularly in understanding biomarkers of the tumor microenvironment,” she says. “If patients have those markers, we can treat them with a targeted drug that will allow some of the chemotherapies to get to the cancer cells more easily.”

Dr. White notes that the range of research represented in her fellowship class demonstrates a depth and breadth of interests along the full continuum. “We are all passionate about research and continuing on as clinician-scientists,” she says. “Having support during our fellowship encourages and motivates us to maintain a research mindset going forward and to make real contributions.”

For More Information

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Jessica Yang, MD

Mentor: Richard D. Carvajal, MD

Efficacy of Bromodomain and Extra-Terminal (BET) Protein Inhibition in Advanced Uveal Melanoma

Prior to beginning her hematology/oncology fellowship at NewYork-Presbyterian/Columbia, Dr. Jessica Yang was clearly on a research track, spanning a variety of fields that included molecular biology, surgical outcomes, and ICU quality improvement. As an undergraduate at Harvard University, Dr. Yang worked in the laboratory of Dr. Leonard Zon at the Dana Farber Cancer Institute to help create a zebrafish model of adult hematopoietic stem cell niche development. While there she also conducted research with Dr. Nicole Francis in the Department of Molecular Biology on the mechanisms of histone methylation by Polycomb group proteins, culminating in her senior honors thesis.

As a medical student at Johns Hopkins University School of Medicine, she pursued research projects that included finding innovative ways to improve access to surgical care in resource-limited settings and assessing the methodology and outcomes of an ICU-wide study on the effects of multifaceted sleep promoting interventions on delirium and cognition.

“Through all of these endeavors I have gained invaluable experience in large data collection and analysis, as well as feasibility studies, all of which will be relevant to clinical trial implementation and results analysis,” says Dr. Yang, whose exposure to exciting advances in cancer therapeutics during her residency renewed her interest in molecular biology, leading her to come full circle in pursuing a career in oncology and epigenetics.

“The skills and knowledge I’ve acquired in basic science and outcomes research have given me the impetus to concentrate the next stage of my career on developing early phase clinical trials,” says Dr. Yang. “I want to focus on novel therapies for rare and understudied tumor types and treatment strategies directed against specific oncogenic pathways common to different malignancies.”

Dr. Yang will work with Dr. Richard Carvajal, Director of Experimental Therapeutics and Director of the Melanoma Service, on her Young Investigator project, which focuses on the development of clinical trials in advanced uveal melanoma. Her previous research in this area has included writing two review articles on the role of nivolumab in advanced melanoma and the clinical management of ocular melanoma, as well as a commentary on KIT inhibition in mucosal melanoma and a comprehensive book chapter on the evaluation and management of cutaneous melanoma. “Funding from the award will provide me with the tools and experience necessary to achieving my career goals as a translational clinical investigator,” says Dr. Yang.

For More Information

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Confronting Solid Tumors: Vitamin C Takes on the KRAS Gene (continued from page 1)



Dr. Manish A. Shah

back to ascorbic acid; in the process, these antioxidants are depleted, and the cell dies from oxidative stress.

Dr. Cantley partnered with **Manish A. Shah, MD**, Director of the Gastrointestinal Oncology Program at Weill Cornell, to design a clinical trial to test the safety and efficacy of intravenous ascorbate as a treatment for KRAS mutant cancers, identify who is most likely to respond, learn more about the basic science mechanisms involved in

the responses, and collect some early evidence of clinical benefit. “We would expect and hope to see some tumor shrinkage among those with KRAS and BRAF mutations,” says Dr. Cantley. “Increased time to progression or quantified stable disease would also be considered a good response.”

The phase 2 pilot study evaluates high dose intravenous vitamin C in two cohorts. The first cohort is of patients with resectable solid tumor malignancies likely to harbor mutations in KRAS or BRAF – for example, colon, pancreatic, and lung cancers – about to undergo surgery. The second group would be previously treated patients known to have KRAS or BRAF mutations, whose tumors were non-responsive to traditional therapies, or whose diseases had metastasized. They would receive the same infusions, for up to six months, with six-week and three-month checks to see disease response.

“The clinical trial, which opened last summer, is an important translational study of men and women with resectable or metastatic solid tumor malignancies to look at the metabolism of these tumors before and after vitamin C,” says Dr. Shah. “We are also

looking at the RNA expression of the tumors to determine if what we saw in the lab is actually validated in patients. We’re quite excited about this.”

“KRAS mutations are prevalent in solid tumor cancers, and about 40 to 50 percent of colon cancers have a mutation in the RAS pathway, which includes the KRAS, NRAS, and BRAF genes. A mutation in this pathway makes the disease more aggressive and less likely to respond to current therapies,” adds Dr. Shah. “Historically, these tumors have been very challenging to treat. In fact, they’re used as a biomarker for exclusion of available EGFR inhibitor targeted therapy.”

Dr. Shah notes that dosing was an important consideration. The infusion treatment is given at 1.25 grams per kilogram every day for four days a week for two to four consecutive weeks prior to surgery in patients in Cohort A, and four days per week up to six months in Cohort B. “It’s a challenge to have patients come in every day, so we are working to find an alternative formulation that may be able to be given to patients orally,” says Dr. Shah.

In addition, tumor samples collected during surgery will undergo extensive genetic sequencing and molecular characterization, and include the development of organoid models. The organoids will be treated with vitamin C *ex vivo* to see if the response replicates the patient response. “More importantly, the organoids provide us with the ability to manipulate them so that we can see if they can overcome resistance as well,” says Dr. Shah.

“I think we’re going to learn, in clinical and translational population sets, how vitamin C works and if it can be used to treat this previously untreatable population.”

— Dr. Manish A. Shah

“At the end of this study, I think we’re going to learn, in clinical and translational population sets, how vitamin C works and if it can be used to treat this previously untreatable population,” says Dr. Shah. If there appears to be a clinical benefit, he adds, additional trials could be designed to determine optimal efficacy and dosage, and to compare therapeutic results against other treatments, such as current chemotherapy-based standard of care or combination therapy.

For More Information

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Clinical Trial

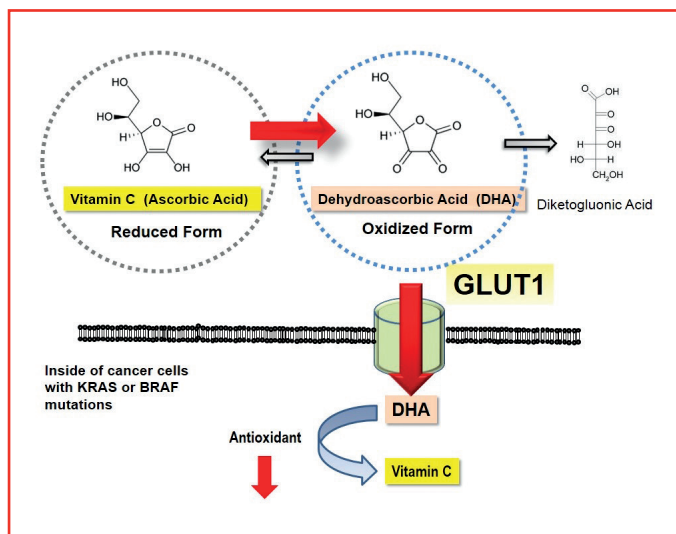
High Dose Vitamin C Intravenous Infusion in Patients with Resectable or Metastatic Solid Tumor Malignancies
<https://clinicaltrials.gov/ct2/show/NCT03146962>

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Vitamin C and DHA conversion and transport in KRAS and BRAF mutated cells

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