Penn Immunologist Awarded SU2C “Convergence 2.0” Funding

E. John Wherry, PhD, co-leader of the Abramson Cancer Center’s Immunobiology Program and director of Penn’s Institute for Immunology, and one of the most highly cited investigators in his field, has been awarded a “Convergence 2.0” research grant by Stand Up to Cancer (SU2C) to investigate immune system response to cancers. Wherry, the Richard and Barbara Schiffrin President’s Distinguished Professor of Microbiology and director of the Institute for Immunology at Penn, will co-lead an 11-member, multidisciplinary team effort called Connecting Immune Health and Tumor Biology in Gynecologic Cancers.

The initiative is one of seven broad-based research teams drawn from the nation’s top academic research centers that will receive a total of $11 million over a three-year period. Each team will include experts in the life sciences, physical sciences, mathematics, and engineering and will partner with machine-learning experts from Microsoft to identify critical aspects of the interaction between cancer and the immune system, with a goal of identifying successful current treatments and developing new ones.

Using de-identified patient data, the teams will examine how individuals vary in their immune responses to different anti-cancer therapies. As part of this process, the researchers will scrutinize terabytes of data, including information on patients’ genomes, imaging studies, and medical and medication records, among other data. (A terabyte is a measure of computer storage capacity comprising one trillion bytes—about 1,000 gigabytes.)

The teams will work to pinpoint factors that could contribute to a patient’s response (positive or negative) to specific anti-cancer regimens, such as DNA repair and natural killer cells (white blood cells that fight infection and can destroy certain cancer cells). The researchers will work to determine and catalogue when and under what circumstances these therapies are effective and when they are not, supplying valuable information to physicians who treat cancer patients.

Wherry’s team will home in on DNA mismatch repair. In mismatch repair, certain genes correct mistakes made when DNA is copied in a cell. On the other hand, mismatch-repair deficiency is the inability to fix these problems, often resulting in weakened DNA structure, leading to an accumulation of mutations that may set cancer in motion.

Cabozantinib Shows Promise for Thyroid Cancer Treatment

A kinase inhibitor called cabozantinib could be a viable therapy option for patients with metastatic, radioactive iodine-resistant thyroid cancer. In a trial initiated and led by the Abramson Cancer Center and the Perelman School of Medicine at the University of Pennsylvania, tumors shrunk in 34 out of 35 patients who took the drug, and more than half of those patients saw the tumor size decrease by more than 30 percent. Researchers will present their findings at the 2018 Multidisciplinary Head and Neck Cancers Symposium in Scottsdale, Arizona earlier this month.

Most cases of differentiated thyroid cancer are treated with radioactive iodine therapy. Since the thyroid absorbs nearly all of the iodine in the human body, radioactive iodine given to a patient will concentrate in thyroid cancer cells, killing them with little effect on the rest of the body. The treatment can be curative, but about 15 percent of these patients have cancers that are resistant to the therapy. There are currently two approved treatments in these cases, both of which are kinase inhibitors – drugs that block enzymes that are crucial to a cancer cell’s ability to function. However, responses to these treatments are not durable. Once patients progress, they need additional therapeutic options.

“Our trial shows that cabozantinib is an active agent for patients with RAI-refractory thyroid cancer and may be able to significantly improve..."
SU2C “Convergence 2.0”

(Continued from page 1)

Certain mismatch-repair-deficient cancers, including gynecologic cancers, are often responsive to drugs called immune checkpoint inhibitors. But this varied response means that some patients are not helped by these medications. This lack of consistent treatment-success may be due to the number of mutations carried by each tumor cell (mutational burden). The Wherry team hypothesizes that tumors with a high mutational burden fail to respond to checkpoint inhibition because of an immune dysfunction that is based on the mechanism for the mismatch-repair deficiency. The researchers will conduct two clinical trials to test whether: a) factors inherent to the tumors affect the response to checkpoint inhibition; b) immune function and quality affect response to checkpoint inhibition; and c) blood markers may reflect the tumor-immune system interaction. (Blood markers are proteins found in the blood that can be elevated by the presence of one or more types of cancer.)

The Wherry team, co-lead by Claire Friedman from the Memorial Sloan Kettering Cancer Center, comprises Robert Burger, MD; Daniel Powell, PhD; Shelley Berger, PhD; and Erica Carpenter, MBA, PhD, all from Penn, as well as researchers from the Icahn School of Medicine at Mount Sinai, Massachusetts General Hospital/ Harvard Medical School, and the Massachusetts Institute of Technology (MIT).

Wherry will also be a collaborator on a team led by Ernest Fraenkel, MIT, which will use artificial intelligence to determine which patients are most likely to benefit from a particular cancer immunotherapy. They will use machine learning and natural language processing to integrate diverse types of data, such as lab values and observational data recorded in electronic medical records.

Additionally, Carl H. June, MD; Pablo G. Câmara, PhD; and J. Joseph (“Jos”) Melenhorst, PhD; all from the Abramson Cancer Center, are members of a team led by Rong Fan, Yale University, that will determine key mechanisms of CAR T therapy, including identifying molecular characteristics underlying therapeutic efficacy and toxicity. CAR T therapy is a pathbreaking cancer treatment in which a patient’s T cells are altered in the laboratory to attack and destroy cancer cells.

Source: Penn Medicine Communications
Contact: karen.kreeger@uphs.upenn.edu

Cabozantinib Shows Promise for Thyroid Cancer

(Continued from page 1)

the care of patients who are at this advanced stage of their disease,” said the study’s lead author Marcia S. Brose, MD PhD, an associate professor of Otorhinolaryngology: Head and Neck Surgery and director of the Center for Rare Cancers and Personalized Therapy at Penn.

As part of a phase II trial, Brose and her team gave the drug as a first line therapy to 35 patients with metastatic, radioactive iodine-resistant thyroid cancer starting in March of 2014. Thirty-four experienced tumor shrinkage, and 19 of the 35 (54 percent) achieved a partial response – defined as a shrinkage greater than 30 percent. The median time on the study was 35 weeks (range 3-197), and 16 patients are currently still enrolled.

“These results indicate cabozantinib may offer an additional treatment option to these patients that will shrink tumors and provide an additional progression-free period for our patients,” Brose said.

Twenty-three of the 35 patients (66 percent) required dose interruptions and dose adjustments during the trial. The most common toxicities attributable to cabozantinib included hyperglycemia, which presented in 28 patients (80 percent). Twenty-seven patients experienced diarrhea (77 percent), 26 had fatigue (74 percent), and 25 had weight loss (71 percent). Five patients experienced grade 3-5 hypertension (14 percent), 3 had grade 3-5 increase lipase (9 percent), 2 had grade 3-5 weight loss (6 percent), 2 had grade 3-5 pulmonary embolism (6 percent), and 2 had hyponatremia (6 percent).

Brose says the data show the need for a larger, multi-center study, plans for which are already underway.

Source: Penn Medicine Communications
Contact: john.infanti@uphs.upenn.edu

E. John Wherry, PhD

Marcia Brose, MD PhD
### Seminars and So Forth

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Event</th>
<th>Speaker(s)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday 2/19/18</td>
<td>10:00 am</td>
<td>CHOP Faculty Candidate Seminar</td>
<td>&quot;How Stem Cells of the Immune System Resist Damage and Regulate Homeostasis.&quot; Mary Mohrin, PhD, Scientist, Calico Labs, San Francisco</td>
<td>CRB Austrian Auditorium</td>
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<tr>
<td>Monday 2/19/18</td>
<td>12:00 pm</td>
<td>Pathology &amp; Laboratory Medicine Grand Rounds</td>
<td>&quot;Targeting Chromatin in Leukemia.&quot; Kathrin M Bernt, MD, Attending Physician, CHOP; Assistant Professor of Pediatrics, PSOM</td>
<td>CRB Austrian Auditorium</td>
</tr>
<tr>
<td>Monday 2/19/18</td>
<td>12:00 pm</td>
<td>SPATT Seminar Series</td>
<td>&quot;Treatment-induced Phenotypic Reprogramming in Prostate Cancer: Significance in Overcoming Therapeutic Resistance.&quot; Natasha Kyrianou, PhD, James F. Hardymon Chair in Urologic Research, University of Kentucky Medical Center</td>
<td>SCTR 10-146 AB</td>
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<tr>
<td>Tuesday 2/20/18</td>
<td>12:00 pm</td>
<td>Distinguished Lecture in Cancer Research</td>
<td>&quot;Drugging RAS for cancer treatment: Know your enemy.&quot; Channing Der, PhD, Sarah Graham Keenan Distinguished Professor, Department of Pharmacology, UNC Lineberger Comprehensive Cancer Center</td>
<td>BRB II/III Glen Gaulton Auditorium</td>
</tr>
<tr>
<td>Tuesday 2/20/18</td>
<td>4:00 pm</td>
<td>CHOP CCCR Oncology Seminar Series</td>
<td>&quot;Internal transcriptional initiation sites generate defective Rag 1 proteins: Implications for an alternative proteome.&quot; Edward M. Behrens, MD, Chief, Division of Rheumatology, Joseph Lee Hollander Chair in Pediatric Rheumatology, CHOP</td>
<td>CTRB 1200B (CHOP)</td>
</tr>
<tr>
<td>Wednesday 2/21/18</td>
<td>12:00 pm</td>
<td>CDB Faculty Recruitment Seminar</td>
<td>&quot;Cellular Sensing of Mechanical Environment: Lessons from Directed Cell Migration.&quot; Vinay Swaminathan, PhD, Research Fellow, National Institutes of Health</td>
<td>SCTR 10-146 AB</td>
</tr>
<tr>
<td>Thursday 2/22/18</td>
<td>12:00 pm</td>
<td>Gastroenterology Seminar Series</td>
<td>&quot;Intercellular signaling at the nexus of diabetes, chronic pancreatitis and pancreatic cancer: the legacy of our hungry ancestors.&quot; Seung K. Kim MD, PhD, Professor, Developmental Biology; Director, Stanford Diabetes Research Center</td>
<td>901 BRB III/III</td>
</tr>
<tr>
<td>Thursday 2/22/18</td>
<td>3:00 pm</td>
<td>Cancer Biology Special Seminar</td>
<td>&quot;Mechanisms of Cellular Decision Making in Chemotaxis and the Cell Cycle.&quot; Hee Won Yang, PhD, Postdoc, Stanford University School of Medicine</td>
<td>CRB Austrian Auditorium</td>
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<tr>
<td>Thursday 2/22/18</td>
<td>12:00 pm</td>
<td>Radiobiology &amp; Imaging Program Seminar Series</td>
<td>&quot;Predicting outcomes in radiation oncology using treatment planning, imaging, and genomic data.&quot; Joseph Deasy, PhD, Chair, Department of Medical Physics; Enid A. Haupt Chair in Medical Physics, Memorial Sloan Kettering Cancer Center</td>
<td>SCTR 8-146AB</td>
</tr>
<tr>
<td>Tuesday 2/27/18</td>
<td>12:00 pm</td>
<td>Distinguished Lecture in Cancer Research</td>
<td>&quot;Pancreatic Cancer Biology and Medicine.&quot; David Tuveson, MD, PhD, Professor and Director, Cold Spring Harbor Cancer Center</td>
<td>Caplan Auditorium, 37th &amp; Spruce Sts. (Wistar)</td>
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<tr>
<td>Tuesday 2/27/18</td>
<td>4:00 pm</td>
<td>Immunology Colloquium</td>
<td>&quot;Aire Expand: Central Tolerance in Autoimmunity and Cancer.&quot; Associate Professor, Department of Pediatrics and Microbiology/Immunology, University of North Carolina, Chapel Hill</td>
<td>CRB Austrian Auditorium</td>
</tr>
<tr>
<td>Tuesday 2/27/18</td>
<td>4:00 pm</td>
<td>CHOP CCCR Oncology Seminar Series</td>
<td>&quot;Advanced Pediatric Endocrine Cancers: Current Management and Hope for the Future.&quot; Steven G. Waguespack, MD, FACE, Professor, Endocrine Neoplasia &amp; Hormonal Disorders and Pediatrics Patient Care, MD Anderson Cancer Center</td>
<td>ARC 123ABC (CHOP)</td>
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<tr>
<td>Friday 3/2/18</td>
<td>10:30 am</td>
<td>Gastroenterology Chalk Talk</td>
<td>&quot;Mechanisms Underlying Clonal Evolution and Heterogeneity in Pancreatic Cancer.&quot; Ravikanth Madipati, MD, Physician, HUP; Instructor in Medicine, PSOM</td>
<td>901 BRB III/III</td>
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Funding Opportunities

Basser Center for BRCA 2018 Grants Program (Internal funding, Penn investigators)

LOI Deadline: 3/12/2018
Application Deadline: 4/3/2018

The Basser Center for BRCA has the unique opportunity to catalyze research to change the paradigm of discovery, innovation, and care for issues related to BRCA1 and BRCA2 mutations. Germline mutations in BRCA1 and BRCA2 significantly increase the risk of breast and ovarian cancer and also are associated with prostate cancer and pancreatic cancer. Awards are $50,000-$150,000 yearly for 2 years.

Details: https://www.basser.org/investigators/grants-program

ACC RFP: Emerson Collective Cancer Research Fund (ECCRF)

Application Deadline: 3/16/2018

The University of Pennsylvania’s Abramson Cancer Center (ACC) is seeking proposals from the University of Pennsylvania research community for funding by The Emerson Collective Cancer Research Fund. The goal of this program is to fund innovative research that has the potential to substantially increase our basic understanding of cancer and/or to significantly impact the prevention, diagnosis, or treatment of this disease.

Funding levels range from $50,000-$85,000 per year, for up to 2 years (total grant $100,000-$170,000). We expect to award 10 grants in the inaugural year of this program. Review criteria will include innovation, impact, translational potential, experimental approaches, and applicant’s need.

For a copy of the RFP and the budget template, contact Leslie Medley at lmedley@upenn.edu.

PAR-18-658 Administrative Supplement for Research on Sex/Gender Influences

Application Deadline: 3/26/2018

The NIH Office of Research on Women’s Health (ORWH) announces the availability of administrative supplements to support research highlighting the impact of sex/gender influences in human health and illness, including basic, preclinical, clinical, translational, and behavioral studies. Of special interest are studies relevant to understanding the significance of biological sex on cells and tissue explants; comparative studies of male and female tissues, organ systems and physiological systems; sex-based comparisons of pathophysiology, biomarkers, gene expression, clinical presentation, and prevention and treatment of diseases.


PAR-18-654/PAR-18-655 Basic Research in Cancer Health Disparities (R01/R21)

Application Dates: 6/19/2018; 11/19/2018, more

These FOAs encourage grant applications from investigators interested in conducting basic research studies into the biological/genetic causes and mechanisms of cancer health disparities. The awards will support pilot and feasibility studies designed to investigate biological/genetic bases of cancer disparities, such as (1) mechanistic studies of biological factors associated with cancer disparities, (2) the development and testing of new methodologies and models, and (3) secondary data analyses. These FOAs are also designed to aid and facilitate the growth of a nationwide cohort of scientists with a high level of basic research expertise in cancer health disparities research who can expand available resources and tools to conduct basic research in cancer health disparities.


PAR-18-646 Opportunities for Collaborative Research at the NIH Clinical Center (U01)

Application Deadline: 4/11/2018

The goal of this program is to support collaborative translational research projects aligned with NIH efforts to enhance the translation of basic biological discoveries into clinical applications that improve health. It encourages high quality science demonstrating the potential to result in understanding an important disease process or lead to new therapeutic interventions, diagnostics, or prevention strategies within the research interests and priorities of the participating NIH Institutes/Centers (ICs).