ACC Researchers Receive 2 Grants, $2.7 Million from V Foundation

Cancer researchers from the Perelman School of Medicine at the University of Pennsylvania and the Basser Center for BRCA in the Abramson Cancer Center of the University of Pennsylvania, have received two major grants from the V Foundation for Cancer Research. Funded projects will work to better understand and treat cancers in patients with inherited mutations of the BRCA1 and BRCA2 genes, which produce tumor-suppressor proteins. These mutations significantly increase the risk for breast and ovarian cancer as well as other types of cancer in women and men.

The first grant, a three-year, $2.1 M Team Science Convergence Award, will be led by Roger A. Greenberg, MD, PHD, professor of Cancer Biology and co-leader of the ACC’s Breast Cancer Research Program, and Katherine L. Nathanson, MD, professor of Medicine and Genetics and the ACC’s Deputy Director. Comprising scientists and physicians from a number of schools, departments, and divisions at Penn, the team will seek to ultimately enhance the effectiveness of drugs called PARP inhibitors. PARP (poly-ADP ribose polymerase) is a protein that helps damaged cells repair themselves. In patients with cancer, PARP inhibitors stop PARP from repairing cancer cells, effectively killing them. These oral medications are effective and generally have fewer side effects than chemotherapy; however, they don’t work in all patients and resistance often develops.

Using sophisticated sequencing techniques, the Penn team will analyze primary tumors in patients with BRCA1/2 mutations, to identify small groups of cancer cells called “subclones” that resist PARP inhibitors and medications such as platinum-based chemotherapeutics. They aim to pinpoint the mechanisms behind this resistance.

Subclones are genetically distinct cancer cells that have varying genetic makeups that allow a subset of them to become resistant to targeted therapies, driving tumor formation and growth. The result is the major limitation to the clinical effectiveness of PARP inhibitors and platinum therapies in treating BRCA-related cancers.

Depending on the specific genetic characteristics of a particular subclone group of cells, many possibilities exist for targeted resistance at the single-cell level in complex tumors. Under the grant, the investigators will test their hypothesis that DNA repair-deficiency in PARP-sensitive cells can direct immune cells against resistant subclones in tumors. The hypothesis is based on proof of concept studies from Greenberg’s lab, published recently in the journal Nature, which described mechanisms of communication between DNA damage and immune responses that can promote anti-tumor immunity.

The second study, a three-year, $600,000 award, will be conducted by ACC members Fiona Simpkins, MD, assistant professor of Obstetrics and Gynecology at the Hospital of the University of Pennsylvania, Eric J. Brown, PhD, associate professor of Cancer Biology, and Payal Shah, MD, assistant professor of Medicine (Hematology-Oncology). Like the Team Science Award, this project centers on resistance to PARP inhibitors, but focuses specifically on designing and optimizing a combination treatment strategy to improve patient outcomes.

Laboratory data from Simpkins and Brown show that a protein called ATR kinase is a promising key to overcoming PARP inhibitor resistance. The group found that combining PARP and ATR inhibition causes complete tumor regression in BRCA-associated ovarian cancer animal models, an effect that is superior to that observed with PARP alone.

To translate these novel findings into better treatment outcomes, Simpkins and Shah are leading a clinical trial that studies the PARP inhibitor olaparib combined with an ATR inhibitor in patients with advanced ovarian cancer, in whom other treatments have failed. Since the genetic makeup of ovarian cancer differs from one patient’s cancer to the next potentially impacting treatment responses, the team will use sophisticated genomic and protein-based techniques to analyze tumors for markers that best predict benefit from treatment.

(Continued on page 2)
Telomere Dyfunction in Therapy-Resistant Melanoma

A study conducted at The Wistar Institute in collaboration with The University of Texas Southwestern Medical Center, along with researchers at the Abramson Cancer Center, has demonstrated the efficacy of targeting aberrantly active telomerase to treat therapy-resistant melanoma. The research was published in the journal Clinical Cancer Research.

The introduction of targeted therapies and immune checkpoint blockade therapies has revolutionized the therapeutic options for patients with advanced melanoma. However, the long-term therapeutic benefit of these new approaches is still hindered by the onset of therapy resistance, which can develop through different mechanisms.

A hallmark of several cancer types, including melanoma, is the aberrant regulation of telomerase activity due to mutations in the regulatory element of the telomerase gene, which results in increased production of the protein. Telomerase is an enzyme responsible for protecting the integrity of chromosome ends during replication. While it is absent in most normal adult cells that don’t actively proliferate, telomerase is reactivated in cancer cells, allowing continuous cell divisions and making them immortal.

“Our work presents pre-clinical evidence that targeting the aberrant telomerase activity may provide a universal strategy to overcome therapy resistance and achieve long-term melanoma control,” said lead researcher Meenhard Herlyn, D.V.M., D.Sc., Caspar Wistar Professor in Melanoma Research and director of The Wistar Institute Melanoma Research Center.

Herlyn and his collaborators used a modified telomerase substrate they had previously described, called 6-thio-dG, to impair telomerase activity by inducing telomere dysfunction. They showed that 6-thio-dG induced cell death in melanoma cells carrying mutations in the BRAF gene without affecting the viability of normal skin cells, and it impaired the growth of several BRAF-mutant melanoma cell lines transplanted in mice. The BRAF gene is mutated in approximately half of all cases of melanoma.

The team also studied the ability of 6-thio-dG treatment to stop proliferation and tumor growth of therapy-resistant melanoma cells. They created a large panel of human melanoma cell lines with acquired resistance to targeted therapy and immunotherapy and showed a general sensitivity of these cells to 6-thio-dG both in vitro and in vivo in mouse models.

"Our results add to the mounting evidence supporting the existence of an important relationship between telomeres and telomerase and cancer," said Gao Zhang, Ph.D., a staff scientist in the Herlyn Lab and first author of the study. "Our data suggest that 6-thio-dG may be used either as monotherapy following first- and second-line therapies to prolong disease control after onset of resistance, or in combination with first-line therapies to overcome intrinsic resistance."

ACC contributors to the study included Giorgos C. Karakousis, Lynn M. Schuchter, Tara C. Gagdhar, Ravi K. Amaravadi, Katherine Nathanson, and Xiaowei Xu.


Source: The Wistar Institute
Seminars and So Forth

Monday 4/2/18 12:00 pm
CDB Distinguished Seminar
“Nuclear organization and its role in lymphocyte development and cancer.” Jane Skok, PhD, Sandra and Edward H. Meyer Professor of Pathology, New York University School of Medicine
BRB II/III Glen Gaulton Auditorium

Tuesday 4/3/18 12:00 pm
Distinguished Lecture in Cancer Research
“New Mechanisms of Vertebrate DNA Repair.” Johannes Walter, PhD, Investigator, Howard Hughes Medical Institute; Professor of Biological Chemistry and Molecular Pharmacology, Harvard Medical School
BRB II/III Glen Gaulton Auditorium

Thursday 4/5/18 12:00 pm
Gastroenterology Seminar Series
“Immunotherapy in Pancreatic Cancer.” Christina Twyman-Saint Victor MD, MTR, Assistant Professor of Medicine (Gastroenterology), PSOM
SCTR 8-146AB

Friday 4/6/18 5:00 pm
Department of Radiation Oncology—17th Annual Morton M. Kligerman Lecture
“Radiation Oncology at a Crossroads: Harmonizing Biology with Technology.” Paul M. Harari, MD, FASCO, Chair, Department of Human Oncology, University of Wisconsin School of Medicine and Public Health
JMEC Law Auditorium, 5 PCAM South

Monday 4/9/18 1:00 pm
CHOP Normal and Malignant Hematopoiesis
RAG Seminar Series
“Modeling myeloid leukemia with patient-derived iPSCs.” Eirini Papapetrou, MD, PhD, Associate Professor, Icahn School of Medicine, Mount Sinai
CTR 1100B (CHOP)

Monday 4/9/18 2:00 pm
PMI Seminar Series
“Mechanisms of chromosome segregation and how they are disrupted in breast tumors.” P. Todd Stukenberg, PhD, Professor, Biochemistry and Molecular Genetics, University of Virginia School of Medicine
CRB Austrian Auditorium

Tuesday 4/10/18 12:00 pm
Distinguished Lecture in Cancer Research
“How Nuclear Architecture Regulates Transcription.” Rafael Casellas, PhD, Senior Investigator and Branch Chief, NIAMS, NIH
Caplan Auditorium, 37th & Spruce Sts. (Wistar)

Tuesday 4/10/18 4:00 pm
Immunology Colloquium
“Molecular Mapping of Lung Cancer Progression.” Tyler Jacks, PhD, Director and David H. Koch Professor of Biology, Koch Institute for Integrative Cancer Research, MIT
CRB Austrian Auditorium

Wednesday 4/11/18 8:00 am
Abramson Cancer Center Grand Rounds
Dean’s Distinguished Visiting Professorship
Bart C. De Jonghe, PhD, Associate Professor of Nursing; Associate Director, Nutrition Science Programs, Penn Nursing
SCTR 9-146AB

Thursday 4/12/18 12:00 pm
Special Lecture in Cancer Research
“Making sense of Myc in cancer.” Gerard I. Evan, PhD, FRS, FMedSci, Sir William Dunn Professor of Biochemistry and Head of Department of Biochemistry, University of Cambridge, United Kingdom
BRB II/III Glen Gaulton Auditorium

Thursday 4/12/18 12:00 pm
Radiation Oncology Seminar Series
Alexander Lin, MD, Associate Professor, Radiation Oncology, PSOM
SCTR 8-146AB

Thursday 4/12/18 4:00 pm
Penn Vet Cancer Center / Mari Lowe Comparative Oncology Seminar Series
“Interferon-gamma: The Rogue One.” M. Raza Zaidi, PhD, Assistant Professor, Fels Institute for Cancer Research and Molecular Biology; Assistant Professor, Medical Genetics and Molecular Biochemistry, Lewis Katz School of Medicine, Temple University
132 Hill Pavilion (School of Vet. Med.)
Up to 12 Harrington Scholar-Innovator awards will be made each year. The award includes:
- $100,000 guaranteed, opportunity to qualify for up to $700,000
- Drug development expertise and project management support through the Harrington Discovery Institute Innovation Support Center

The Harrington Discovery Institute and its Innovation Support Center team will work closely with the awardee and their affiliated institution to maximize the clinical and commercial potential of selected projects.

Details available here.

**Children’s Leukemia Research Association Research Grants**

**Deadline:** June 30, 2018

The [Children’s Leukemia Research Association](http://www.childrensleukemia.org), also known as the National Leukemia Research Association, was founded in 1965 to support research efforts toward finding the causes of and a cure for Leukemia. To that end, CLRA is seeking applications from investigators for promising research projects related to childhood leukemia. Grants of up to $30,000 will be awarded to promising projects focused on isolating the causes of and finding a cure for childhood leukemia. Funding from other sources is permissible, but CLRA funding objectives should not duplicate those of other sources.

Any doctor at the PhD or MD level involved in research on identifying the causes of and a cure for leukemia may apply.

Details [here](http://www.childrensleukemia.org/funding-opportunities/).