Penn Researchers Identify New Treatment Target for Melanoma

Researchers in the Perelman School of Medicine at the University of Pennsylvania have identified a new therapeutic target for the treatment of melanoma. For decades, research has associated female sex and a history of previous pregnancy with better outcomes after a melanoma diagnosis. Now, a research team from Perelman School of Medicine at the University of Pennsylvania says it may have determined the reason for the melanoma-protective effect. The mechanism is related to a cellular protein called the G protein-coupled estrogen receptor (GPER). When GPER was activated and combined with anti PD-1-inhibitor drugs in mouse cancer models, the therapy dramatically extended survival in all animals and completely eliminated the tumor in 50 percent of the mice. Researchers published their findings in the journal eLife in January.

Melanoma is the deadliest form of skin cancer, despite accounting for only about one percent of skin cancers overall. Rates of melanoma have been rising for 30 years, and the American Cancer Society estimates there were more than 87,000 new cases in the United States in 2017. Even with recent advances in immunotherapy, the majority of patients with metastatic forms of melanoma will die from their disease.

“In melanoma and many other types of cancer, women have a better prognosis than men, and women with a history of pregnancy seem to have a better prognosis than those women that have never been pregnant” said the study’s senior author Todd W. Ridky, MD, PhD, an assistant professor of Dermatology at Penn. “Decades of research certainly suggests that there is something about female sex and pregnancy hormones that helps protect against melanoma, but no one really understood how that might work.”

Researchers say the key is GPER, a receptor found on melanocytes, which are pigment-producing cells in the skin. The receptor is normally activated by estrogen, which is higher in females, especially during pregnancy. Activation of GPER likely explains why many women notice that many areas of their skin gets darker during pregnancy. Previous research from the Ridky lab has shown the effects of GPER activation are totally different than the effects of classical estrogen receptor signaling, which is important in breast cancer. The team discovered that melanocytes do not even express the classical estrogen receptor, and that all estrogen effects were the result of GPER.

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ACSO Annual Report Recognizes Penn Research Achievements

Research led by ACC members was selected by the American Society of Clinical Oncology for inclusion in Clinical Cancer Advances 2018: ASCO’s Annual Report on Progress Against Cancer. Developed under the guidance of an expert editorial board, Clinical Cancer Advances is an independent annual review of the year’s major achievements and emerging trends in clinical cancer research and care.

Stephen J. Schuster’s study, “Global pivotal phase 2 trial of the CD19-targeted therapy CTLO19 in adult patients with relapsed or refractory (r/r) diffuse large b-cell lymphoma (DLCBL)—an interim analysis” and Corey Langer’s “Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study” were both featured in the report.

In addition, ASCO named adoptive cell immunotherapy as the Clinical Cancer Advance of the Year. Cited, among other important work, was the FDA approval of Kymriah™ in August 2016, and additional research by Steven Schuster, Stephan Grupp, Susan Rheingold, and others at Penn.

The report is available at asco.org/CCA, and is also published online in the Journal of Clinical Oncology at ascopubs.org/journal/jco.
New Treatment Target for Melanoma

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In melanoma specifically, once GPER is activated, the cancer cell becomes more differentiated. This means it divides less frequently, makes more pigment, and becomes more visible and vulnerable to the natural immune system. This makes it harder for the cancer to become resistant to immunotherapies.

No drugs specifically target GPER, but Ridky and his team used a lab compound called G-1, originally developed by Eric Prossnitz, PhD, at the University of New Mexico Comprehensive Cancer Center, to stimulate GPER in mice, and then used anti-PD-1 inhibitors to treat the melanoma. The approach eliminated the tumors in half of all mice. The authors note that anti-PD-1 inhibitors, when used alone in mice with melanoma, extend survival modestly, but do not completely eliminate tumors, and no animals survive long-term.

“We hope this work inspires other researchers to revisit old ideas of differentiation-based cancer therapies now that immune therapies are available,” said the study’s lead author Christopher A. Natale, a researcher in Ridky’s lab. “It is clear that the future of cancer therapy lies in combination treatments, and differentiation drivers may be a very useful component in future cancer therapy regimens.”

As Ridky points out, this represents a unique approach to immunotherapy and cancer therapy in general.

“So much of the cancer field is focused on inhibitors, but in this new treatment approach, we’re actually activating something rather than blocking it,” Ridky said. “We used a synthetic compound to mimic part of what happens naturally during pregnancy, and as a result, the GPER activator is very well tolerated without any obvious toxic side effects that are common with most cancer drugs.”

Ridky also said this approach could be promising beyond melanoma.

“This is a receptor that is expressed in many organs, so there’s a reasonable expectation that this may work in other tumor types too,” Ridky said.

Although researchers did not observe any toxicities from the compound in mice, though they say they plan further toxicity studies before hopefully moving on to human trials.

Publication: eLife
Source: Penn Medicine Communications

New ACC Members
Elizabeth A. White, PhD, Assistant Professor, Otorhinolaryngology (Tumor Virology)
Rong Zhou, PhD, Research Associate Professor, Radiology (Radiobiology and Imaging)
Ronald P. Matteo, MD, John Rhea Barton Professor and Chair, Surgery (Immunobiology)

Gifts and Grants
Naya Foundation / No More Kids with Cancer: CD33 CAR T cells – Richard Aplenc
V Foundation for Cancer Research: BRCA Convergence Team Award - Roger Greenberg, Katherine Nathanson, Andy Minn, Junwei Shi, Ronny Drapkin, and Susan Domchek; BRCA Translational Award – Fiona Simpkins, Eric Brown, Payal Shah.

Publications
Maude SL et al. Tsigeneneleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018 Feb 1;378(5):439-448. In this global study of CAR T-cell therapy, a single infusion of tsigeneneleucel (Kymriah™) provided durable remission with long-term persistence in pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects.


Waxman AJ et al. Carfilzomib-Associated Cardiovascular Adverse Events: A Systematic Review and Meta-analysis. JAMA Oncol. 2017 Dec 28:e174519. Carfilzomib was associated with a significant incidence of CVAE, with higher rates seen with higher doses of carfilzomib.

Palozola KC et al. Mitotic transcription and waves of gene reactivation during mitotic exit. Science. 2017 Oct 6;358(6359):119-122. We propose that the cell’s transcription pattern is largely retained at a low level through mitosis, whereas the amplitude of transcription observed in interphase is reestablished during mitotic exit.
Seminars and So Forth

**Tuesday 2/6/18** 12:00 pm
Distinguished Lecture in Cancer Research
"Biomaterials approaches to study ECM dynamics in the tumor microenvironment." Claudia Fischbach-Teschl, PhD, Associate Professor of Biomedical Engineering, Cornell University
BRB II/III Glen Gaulton Auditorium

**Monday 2/5/18** 12:00 pm
Distinguished Seminar Series | CDB Seminar
"On the biosynthetic mechanism coupling cell growth to division." Jan Skotheim, PhD, Associate Professor of Biology, Stanford University
BRB II/III Glen Gaulton Auditorium

**Tuesday 2/6/18** 12:00 pm
Penn Bioethics Seminar
"Humanism and Professionalism Training for Pediatric Trainees: A Play in 3 Acts." Jennifer Kesselheim, MD, M.Ed, MBE, Fellowship Program Co-Director & Senior Physician, Boston Children's/ Dana-Farber Cancer and Blood Disorders Center; Director, Master of Medical Sciences (MMSc) in Medical Education; Assistant Professor of Pediatrics, Harvard Medical School
1402 Blockley Hall

**Tuesday 2/6/18** 3:00 pm
Institute on Aging Vincent Cristofalo Lectureship
"The Surprising Role of Architecture in Aging." Tom Misteli, PhD, Director for the Center for Cancer Research, National Cancer Institute, NIH. Register here.
SCTR Rubenstein Auditorium

**Tuesday 2/6/18** 4:00 pm
CHOP CCCR Oncology Seminar Series
"Implementing Cancer Care in Low Resource Settings: Lessons from Rwanda." Lawrence Shulman, MD, FACP, Professor of Medicine, PSOM; Deputy Director for Clinical Services and Director, Center for Global Cancer, ACC
CTR 1200B (CHOP)

**Tuesday 2/6/18** 4:30 pm
Women of Color at Penn Social Media Launch/ Networking Reception (WOCAP)
This event will double as a fundraiser for Daughters of the Diaspora/DoD (a non-profit organization that teaches self-esteem and reproductive health to adolescent young women throughout the African Diaspora). Register here.
JMEC Auditorium

**Wednesday 2/7/18** 3:00 pm
PSOM Faculty Career Workshop
"Strategies for Success on the Research Track.”
David Margolis, MD, PhD, Professor of Dermatology, and Biostatistics & Epidemiology; and Chair, PSOM COAP. Register here.
1412 BRB II/III

**Wednesday 2/7/18** 12:00 pm
Microbiology Seminar Series
"Lessons learned from intracellular bacteria: How to rewire and remodel the host cell." Shaeri Mukherjee, PhD, Assistant Professor of Microbiology and Immunology, UCSF
CRB Austrian Auditorium

**Thursday 2/8/18** 12:00 pm
Radiobiology & Imaging Program Seminar Series
"Synthesis of Natural and Unnatural Products." Jeffrey D. Winkler, PhD, Merriam Professor of Chemistry, UPenn SAS
SCTR 8-146AB

**Monday 2/12/18** 1:00 pm
CHOP Normal and Malignant Hematopoiesis
RAG Seminar Series
"APOBEC3 Enzymes: From Anti-Viral Defenses to Anti-Cancer Therapy." Abby Green, MD, Attending Physician, Divisions of Infectious Diseases and Oncology; Instructor, Oncology, PSOM
CTRB 1100B (CHOP)

**Tuesday 2/13/18** 12:00 pm
Distinguished Lecture in Cancer Research
"Cancer Cell Migration in 3D.” Denis Wirtz, PhD, Theophilus H. Smoot Professor of Chemical and Biomolecular Engineering, Vice Provost for Research, Johns Hopkins University
Caplan Auditorium, 37th & Spruce Sts. (Wistar)

**Thursday 2/15/18** 12:00 pm
Gastroenterology Seminar Series
"The origins of metastasis in pancreatic cancer: a colorful tale.” Ravikanth Maddipati, MD, Instructor in Medicine, PSOM
901 BRB III/III

**COMING SOON**

February 16-18, 2018
2nd Annual American College of Cardiology Course in Cardio-Oncology
This educational opportunity offers contemporary care strategies for healthcare providers involved in cardiovascular care of cancer patients and cancer survivors. Join emerging pioneers in the field of cardio-oncology as they present, evidence-based treatment strategies that address pre, during and post-cancer treatment heart health. Register here.
Ritz-Carlton, Washington DC
Funding Opportunities


Application Deadline: June 27, 2018; October 24, 2018, etc.

The purpose of this FOA is to support studies on electronic nicotine delivery systems (ENDS) that examine population-based, clinical and applied prevention of disease, including etiology of use, epidemiology of use, potential risks, benefits and impacts on other tobacco use behavior among different populations.


**PAR-18-605/PAR-18-606 Leveraging Cognitive Neuroscience to Improve Assessment of Cancer Treatment-Related Cognitive Impairment (R01 Clinical Trial Optional (R01/R21)**

Application Deadline: April 11, 2018; October 10, 2018, etc.

This FOA encourages transdisciplinary research that will leverage cognitive neuroscience to improve traditional measurement of cognitive impairment following cancer treatment, often referred to as “chemobrain.” A better understanding of the acute- and late-term cognitive changes following exposure to adjuvant chemotherapy and molecularly-targeted treatments, including hormonal therapy, for non-central nervous system tumors can inform clinical assessment protocols with downstream implications for survivorship care plans.


**When Everyone Survives—2018 Leukemia Research Grant**

Application Deadline: April 1, 2018

This request for proposals (RFP) is offered by the When Everyone Survives Foundation (WES Leukemia Research Foundation) to solicit innovative research in leukemia. Grants of $50,000 for one year are offered to new and established investigators who are requesting support for laboratory, translational, or clinical research related to acute leukemia. Renewal of initial research support may be considered for one or more additional years based upon productivity.

[http://www.wheneveryonesurvives.org/grant_application](http://www.wheneveryonesurvives.org/grant_application)

**B*CURED - Brain Cancer Research Investigator Grant**

Application Deadline: April 1, 2018

B*CURED’s primary goal is to fund innovative brain cancer research that helps end brain cancer. To that end, the foundation is accepting applications for its 2018 Brain Cancer Research Investigator Grant, which is presented annually to a clinical doctor or research scientist whose primary focus is brain cancer research. Grants of up to $50,000 will be awarded over twelve months to support clinical and translational research projects directly related to the field of brain cancer. Projects for adult and pediatric brain cancer research will be considered. To be eligible, applicants must be a faculty member at a research institution in North America who is undertaking clinical or translational research with the intention of applying for R01 NIH funding or the equivalent within five years; or undertaking innovative research to bridge from bench to animal research or to acquire preclinical data from animal models.

[http://bcured.org/grants/](http://bcured.org/grants/)

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Funding Opportunities

**Philanthropy & Development Corner**

Are you looking for ideas for a meaningful Valentine’s Day gift? Show your Valentine’s Day love by making a gift to the Abramson Cancer Center in honor of a special loved one! They will be notified of your thoughtful gift. A special gift like this is not only meaningful to them, but also to the ACC’s patients and their families and loved ones.