The “Immuno Revolution”: Turning Up the Heat on Resistant Tumors

A promising class of drugs known as CD40 monoclonal antibodies could be the spark needed to light the fire in the immune system of patients who don’t respond to the newer cancer immunotherapies.

Robert H. Vonderheide, MD, DPhil, director of the Abramson Cancer Center at the University of Pennsylvania and an internationally renowned cancer immunotherapy expert, makes the case for the drugs in a new perspective piece published last week in Cancer Cell, as part of a series in the issue focusing on the next phase of the evolving field of cancer immunotherapy.

“The ‘immuno revolution’ is upon us: We’re battling cancers like never before by tapping into the power of the immune system with checkpoint inhibitors and personalized cellular therapies that have elicited stellar responses in patients,” Vonderheide said. “But there is a bittersweet quality to these successes: many patients do not respond or quickly relapse after an initial response.”

The PD-1 antibody pembrolizumab, for example, is approved for use as a first-line therapy for patients with metastatic non-small cell lung cancer that overexpresses PD-L1, which cancer cells use to hide from the immune system, yet more than 50% of patients have tumor progression at one year.

“Think of the body’s immune response like an assembly line, with points A, B, C, D, and E, that kill the tumor at the end, Vonderheide said. For example, a T cell starts, it expands, it gets exhausted, and stops because of the PD-L1 pathways. Checkpoint inhibitors take that brake off toward the end, so the T cells can then attack the tumor.

“We’ve been drugging the very last step,” said Vonderheide, who serves as a principal investigator on several CD40 combination trials at Penn, including a national trial through the Parker Institute of Cancer Immunotherapy. “In many patients, however, that won’t work because points A through E hasn’t happened. You can give them a checkpoint inhibitor, but there are no T cells to take the brakes off.”

With the CD40 drugs, we’re back at point A to prime the T cells in the body to continue on in the immune response,” he added. “Once you get A going, you can potentially treat more patients.”

CD40 agonists have moved successfully from preclinical studies, many of which have been conducted by Penn researchers, where they have demonstrated anti-tumor activity, especially in combination with checkpoint inhibitors and chemotherapy, into human trials in recent years.

There are currently four clinical trials being conducted at Penn, including:

- A Phase I study, led by Vonderheide, to learn if adding the investigational anti-CD40 drug RO7009789 to nab-paclitaxel and gemcitabine both before surgery and after surgery is safe, feasible, and beneficial to patients with pancreatic cancer.

- A Phase 1b/2 study to evaluate the efficacy of the combinations of APX005M, Nivolumab, Gemcitabine, and Pembrolizumab.

(Continued on page 2)
Impact of Gut Microbiome on Cancer Immunotherapy?

The composition of bacteria in the gastrointestinal tract may hold clues to help predict which cancer patients are most apt to benefit from the personalized cellular therapies that have shown unprecedented promise in the fight against hard-to-treat cancers, according to new research from the Perelman School of Medicine at the University of Pennsylvania.

Reporting in JCI Insight, a team led by senior author Andrea Facciabene, PhD, a research assistant professor of Radiation Oncology and Obstetrics/Gynecology and member of the ACC’s Radiobiology and Imaging research program, found that the effectiveness of adoptive T cell therapy (ACT) in mice with cancer is significantly affected by differences in the natural makeup of gut bacteria and treatment with antibiotics. The team also found that the use of fecal transplants — which are increasingly used for treating recurrent C. difficile colitis — affected the efficacy of ACT between different strains of lab rodents.

ACT enlists a patient’s own immune system to fight diseases, such as cancer and certain infections. T cells are collected from a patient and grown in the lab to increase the number of tumor-killing T cells. The pumped-up cells are then given back to the patient as reinforcements to the body’s natural anti-tumor immune response.

Experiments performed by coauthor Mireia Uribe-Herranz, PhD, a research associate in Facciabene’s lab, demonstrate that when ACT was performed on genetically identical animals obtained from different vendors (Jackson Laboratory or Harlan Laboratories), which carry different microbiota, impact of the therapy was not identical. Animals obtained from Harlan showed a much stronger anti-tumor effect compared to animals from Jackson.

Depletion of gram-positive bacteria within the gut, using an antibiotic called vancomycin, also increased the efficacy of the therapy, improving the anti-tumor response and overall remission rate in less-responsive mice. The beneficial responses were associated with an increase in systemic dendritic cells, which in turn increased the expression of interleukin 12 (IL-12), which sustained expansion and anti-tumor effects of transferred T cells.

To define a relationship between gut bacteria and the efficacy of ACT, the researchers transplanted fecal microbiota from Jackson mice to Harlan mice. They found that Harlan mice transplanted with Jackson microbiota copied the anti-tumor response and tumor growth of Jackson mice.

“This means that the microbiota-dependent response to ACT was successfully transferred between mice, and that modulation with specific antibiotics can be used to increase ACT efficacy,” Facciabene said, confirming that this technique could be applied to control gut microbiome populations and improve ACT. Collectively, the findings demonstrate an important role played by the gut microbiota in the antitumor effectiveness of ACT.

Contact: John Infanti, PhD, senior vice president of Communications and Public Affairs, Penn Medicine. Contact: Karen Kreeger, associate vice president of Communications. Contact: joh.infanti@uphs.upenn.edu. karen.kreeger@uphs.upenn.edu
NCI Unveils “NCTN Navigator” for Cancer Clinical Trials

The National Cancer Institute (NCI) has introduced a new research resource for the scientific community, called NCTN Navigator. Navigator is a publicly searchable database of specimens from completed National Clinical Trials Network (NCTN) Phase 3 adult cancer trials: https://navigator.ctsu.org. Investigators can search Navigator’s inventory of high-quality specimens that are linked to clinical trials outcomes data, which is a unique aspect of this resource.

The Navigator inventory currently has:

- 95+ trials
- 60,000+ patients
- 850,000+ specimens

To request specimens and data through Navigator, investigators must submit a research proposal which will be peer-reviewed by an external scientific committee. The review process is rigorous due to the quality and value of this non-renewable resource. Successful Navigator proposals will generally utilize the unique clinical data and trial design to test a question with potential clinical implications, rather than proposing exploratory studies.

Some additional tips for investigators:

- Investigators should review the primary trial publications to evaluate available data and develop their research question.
- Researchers are not required to have funding in advance to submit a proposal, but will need to obtain funding to cover processing and distribution costs for approved proposals within a certain time period.
- The review process will take several months, and applicants can follow the status of their proposal’s review on the Navigator website.
- Final specimen and data availability will not be confirmed until after a proposal is approved.

This unique resource that could facilitate innovative science developing ways to confirm how drugs work, selecting patients who are likely to benefit from a given treatment, and assessing new methods to monitor the effectiveness of treatments. For additional information regarding Navigator, visit https://navigator.ctsu.org.

Cancer Risk Rises As Patients Wait for Diagnostic Testing

The longer a patient with a positive screening result waits for diagnostic testing, the worse their cancer outcomes may become, according to a literature review of breast, cervical, colorectal, and lung studies in the journal CA led by researchers at the Perelman School of Medicine at the University of Pennsylvania.

After a patient receives a positive cancer screening result, the next recommended step is a follow-up evaluation with diagnostic testing, a CT scan for example, which is key to confirm the absence or presence of cancer(s) and the severity of any that may be present.

The authors, an interdisciplinary team of cancer experts from the Population-Based Research Optimizing Screening Through Personalized Regimens Consortium (PROSPR), urge patients who receive a positive screening to schedule a diagnostic test as soon as feasible. Articles considered were published between January 1998 and December 2017, conducted in an average-risk population, except in lung cancer, and used study designs that provided empirical evidence and evaluated the key question.

Although the findings of this research follow the longstanding conventional wisdom, this literature review backs up this message with patient outcome data. The authors make clear that each patient’s cancer trajectory is different and there is no established timeframe that is OK to wait before a diagnostic test without risk of cancer progression.

“To ignore these findings is not patient-centered,” said lead author Chyke Doubeni, MD, chair of Family Medicine and Community Health and a member of the ACC’s Cancer Control Research Program. “The longer a patient waits, the less likely they are to get the diagnostic testing done. There is also the risk that precancerous or early tumors will become more advanced cancers that are more difficult or impossible to cure.”

The paper offers suggested targets for each of the four cancers within which diagnostic testing should be performed. The targets range from 60-90 days, but were not able to ascribe a certain number of risk points based on exactly how long a patient waits. For example, on average, cervical cancer takes longer to progress than lung cancer does, but the authors caution against ascribing a safe period to wait or saying it’s safe to wait a little longer if you have cervical cancer vs another.

(Continued on page 4)
E. John Wherry Receives SU2C Innovation in Collaboration Award

E. John Wherry, PhD, co-leader of the Abramson Cancer Center’s Immunobiology Program and director of the Institute for Immunology at the University of Pennsylvania, has received a Phillip A. Sharp Innovation in Collaboration Award from Stand Up To Cancer (SU2C), the non-profit organization established by film and media leaders to support collaborative cancer research and increase awareness about cancer prevention.

Wherry, the Richard and Barbara Schiffrin President’s Distinguished Professor of Microbiology in Penn’s Perelman School of Medicine, and Matthew Hellmann, MD, a medical oncologist at Memorial Sloan Kettering Cancer Center, comprise one of five teams to receive $1.25 million to cross institutional lines and collaborate on new research projects. The members of the five teams are all part of the SU2C research community. In selecting the winning projects, the organization placed an emphasis on projects that involved SU2C-funded researchers with different skill sets.

Under the award, Wherry and Hellmann will seek to improve reinvigoration of exhausted T cells, which are white blood cells that are part of the immune system. The “T” stands for “thymus” – the organ in which these cells mature, as opposed to B cells, which mature in the bone marrow. T cell exhaustion can arise during chronic infections and cancer; it prevents optimal control of infections and tumors. Durable reprogramming of exhausted T cells is a fundamental goal of cancer researchers.

Recently, Wherry demonstrated that exhausted T cells are epigenetically distinct compared to other T cell subtypes. Epigenetics refers to external modifications to DNA that turn genes “on” or “off.” Additionally, Wherry demonstrated that PD-1 blockade therapy, a highly promising anti-cancer treatment, is insufficient to reinvigorate exhausted T cells for any meaningful length of time. As a result, the T cells quickly revert to an exhausted, dysfunctional state. To try and address this problem, Wherry teamed up with Hellman, a lung cancer physician who has been leading combination immunotherapy studies in lung cancer patients, to test whether modifying epigenetic pathways in T cells in concert with PD-1 pathway blockade can help “reset” the exhausted cells. They hypothesize that the combined approach will improve exhausted T cell reinvigoration compared to PD-1 blockade therapy alone.

Source: Penn Medicine Communications
Contact: gregory.richter@uphs.upenn.edu

Impact of Delays In Diagnostic Testing on Cancer Progress

(Continued from page 3)

er type based on the limited body of knowledge to date.

The National Academy of Medicine has identified improving the timeliness and patient-centeredness of care as an important unmet health priority. Screening is proven to reduce the risk of death from some cancers and is currently recommended at grade A or B by the US Preventive Services Task Force in eligible persons for breast, cervical, colorectal, and lung cancers, which enables full coverage of those services under the Affordable Care Act.

Future research will aim to identify the appropriate data to identify time intervals during which it is potentially safe to wait before undergoing diagnostic testing.

Doubeni and his colleagues note that prompt diagnostic testing may also reduce mortality risk, and may also reduce worries about uncertainty about the procedure. Additionally, sooner is better, as provider or system delays in follow-up may increase the likelihood that diagnostic testing may not occur at all, such as changes in patient contact information or insurance coverage changes.

Based on the few direct studies cited, overall, there is evidence that if you wait longer than 60-90 days, generally cancer will progress. This is not surprising biologically, but the paper provides guidance on how to set metrics to measure improvement. Next steps for the research will seek out the most effective interventions to reduce the time to diagnosis for vulnerable and minority populations, and any patients who have barriers to timely follow up.


Source: Penn Medicine Communications
Contact: john.Infanti@uphs.upenn.edu
Seminars and So Forth

**Monday 4/16/18**  
12:00 pm  
**CDB Distinguished Seminar**  
“Contact-dependent cell-cell signaling essential for development and cancer.” Thomas Kornberg, PhD, Professor, Cardiovascular Research Institute, UCSF Medical School  
BRB II/III Glen Gaulton Auditorium

**Monday 4/16/18**  
12:00 pm  
**Pathology & Laboratory Medicine Grand Rounds**  
James E. Wheeler Distinguished Alum. Lecture  
“Pathology Data Refineries: Extracting Value from Digital Images and Laboratory Information Systems.” Douglas P Clark, MD, Frederick H. Harvey Chair and Professor, Department of Pathology, University of New Mexico  
CRB Austrian Auditorium

**Monday 4/16/18**  
1:00 pm  
**ACC Population Science Research Seminar**  
“Neural Predictors of Cancer Relevant Behavior Change.” Emily Falk, Associate Professor, Annenberg School for Communication, PENN  
1319 Blockley Hall

**Thursday 4/26/18**  
9:00 am  
**CCWB Weekly Seminar Series**  
“Funky Genomic Phenomena: A Landscape of Acquired Allelic Imbalance across the Cancer Continuum.” Paul Scheet, PhD, Associate Professor, Epidemiology, Cancer Prevention and Population Sciences, MD Anderson Cancer Center  
JMB Class of ‘62 Auditorium

**Friday 4/20/18**  
12:00 pm  
**IFI-ACC Research in Progress Seminar**  
Robert Vonderheide, MD, DPhil, John H. Glick Abramson Cancer Center Professor of Medicine and Director, Abramson Cancer Center, PENN, with Mark Diamond, MD, PhD: “Mechanisms of Tumor Immune Escape when Antigen is Replete,” and Nune Markosyan PhD: “Tumor Cell COX-2 Contributes to Immune Escape in Pancreatic Cancer”  
BRB II/III Glen Gaulton Auditorium

**Monday 4/23/18**  
12:00 pm  
**Pathology & Laboratory Medicine Grand Rounds**  
“Deregulating the Hippo pathway resets the clock in sarcoma.” Tzipora Sarah Karin Eisinger, PhD, Ann B. Young Assistant Professor in Cancer Research, Pathology & Laboratory Medicine, PSOM  
CRB Austrian Auditorium

**Monday 4/23/18**  
1:00 pm  
**CHOP Normal and Malignant Hematopoiesis RAG Seminar Series**  
“ASCT2-mediated amino acid metabolism in normal hematopoiesis & leukemogenesis.” Cheng-Kui Qu, MD, PhD, Professor of Pediatrics, Children’s Healthcare of Atlanta, Emory University School of Medicine  
CTRB 1100B (CHOP)

**Tuesday 4/24/18**  
12:00 pm  
**Agilent Technologies OMICS Seminar Series**  
Focusing on the latest innovations for various – OMICS topics. For more information, and to register, visit: [https://agilent.cvent.com/omics-upenn](https://agilent.cvent.com/omics-upenn)  
SCTR 8-146AB

**Tuesday 4/24/18**  
12:00 pm  
**Distinguished Lecture in Cancer Research**  
“Tumor suppressor inactivation by human papillomaviruses.” Elizabeth A. White, PhD, Assistant Professor of Otorhinolaryngology: Head and Neck Surgery, PSOM.  
BRB II/III Glen Gaulton Auditorium

**Wednesday 4/25/18**  
8:00 am  
**Abrahamson Cancer Center Grand Rounds**  
David Gaffney, MD, Vice-Chair and Professor, Radiation Oncology, Senior Director for Clinical Research, Huntsman Cancer Institute  
SCTR Rubenstein Auditorium
Perelman School of Medicine Deans’ Distinguished Visiting Professorship

Bart C. De Jonghe, PhD, Associate Professor of Nursing, Associate Director, Nutrition Science Programs, Penn Nursing, and member of the ACC’s Cancer Control Program presented the PSOM Deans’ Distinguished Visiting Professorship on April 11, 2018.

Dr. De Jonghe described his groundbreaking findings on the neurological molecular mechanisms of cisplatin-induced nausea during the lecture, which was sponsored in conjunction with ACC Grand Rounds.

Funding Opportunities

American Cancer Society Institutional Research Grant (ACS IRG) Pilot Project Program 2018

Application Deadline: 5/1/2018

The Abramson Cancer Center of the University of Pennsylvania will provide research project grants to initiate promising new cancer research projects. Support for these pilot grants comes from an American Cancer Society Institutional Research Grant (ACS IRG). Projects that have relevance across multiple types of cancer are encouraged. Proposals that span basic, translational, clinical, or population science research are welcome. The objective of these grants is to facilitate the collection of preliminary data, which will enable the successful competition for national, peer-reviewed research grants.

Three ACS IRG pilots will be awarded in the amount of $30,000 each to junior faculty members (within six years of their initial faculty appointment) who do not currently have nationally peer-reviewed research project funding. For further information and application instructions, please contact Cecilia Scavelli, ACC Associate Director for Research Administration, at cecilia2@upenn.edu.

Breast Cancer Research Foundation Androgen Receptor Translational Biology Program (ARP)

LOI Deadline: 5/15/2018
Proposal Deadline: 9/15/2018

The Breast Cancer Research Foundation is pleased to announce the launch of an open request for proposals for the Androgen Receptor Translational Biology Program (ARP).

The goal of the ARP is to evaluate the role of androgens and androgen receptors in driving breast tumor biology. A new mechanism now offers the opportunity for this community of researchers to focus on a specific scientific issue: how can the androgen receptor be most effectively utilized as a target for therapy in breast cancer?


PAR-18-740 Lasker Clinical Research Scholars Program (Si2/R00)

Application Deadline: 8/31/2018

The Lasker Clinical Research Scholars Program supports research activities during the early stage careers of independent clinical researchers.

The program offers the opportunity for a unique bridge between the NIH intramural and extramural research communities and contains two phases. In the first phase, Lasker scholars will receive appointments for up to 5-7 years as tenure-track investigators within the NIH Intramural Research Program with independent research budgets. In the second phase, successful scholars will receive up to 3 years of NIH support for their research at an extramural research facility; or, the scholar can be considered to remain as an investigator within the intramural program.