Penn Medicine

ACC Events Bulletin

the cure is within
ABRAMSON CANCER CENTER

June 4, 2018

Upcoming Events

- Philadelphia Pride Parade and Festival—Sunday, June 10
- For ACC event information, go to https://cancer.pennmedicine.org/about/events

Inside this issue:

New Approach Could Limit Toxicity of CAR T Cell Therapy in AML

A new approach pioneered at the University of Pennsylvania's Abramson Cancer Center may provide a new path towards treating Acute Myeloid Leukemia (AML) with CAR T cells. To treat AML, investigators have to target a specific protein – CD33 – that's also expressed on healthy cells, meaning the therapy cannot attack the cancer without causing other serious damage to the residual normal bone marrow. The new method uses the gene editing tool CRISPR/Cas9 to remove CD33 from healthy blood-forming stem cells, leaving the cancerous cells as the only targets left for the CD33 hunter cells to attack. Penn researchers and their collaborators at the National Institutes of Health published their proof-of-concept findings in *Cell* last week.

AML is the second most common type of leukemia, and the American Cancer Society estimates there will be almost 20,000 new cases in the United States this year. Many of these patients will undergo a bone marrow transplant. To treat a related leukemia called acute lymphoid leukemia (ALL), investigators at Penn previously developed CAR T cell therapy, which involves collecting patients' own immune T cells, reprogramming them to kill cancer, and then infusing them back into patients' bodies. Currently, both CAR T cell therapys approved for use by the U.S. Food and Drug Administration target cells that express a protein called CD19, for ALL and non-Hodgkin's lymphoma. However, this is not an effective target for AML, since AML does not express CD19. Researchers have therefore been looking for other potential cellular targets.

One promising example is a protein known as CD33, but previous attempts to target CD33 have proven damaging to healthy cells. While damage to healthy cells could be prevented by making the CART cells short-lasting, this would defeat the purpose of one of CAR T's greatest strengths – their ability to last for years, circulate in the body, and protect the patient from relapse.

"This therapy is meant to be a true living drug, and we know that CAR T cells can live on in patients' bodies for years after infusion, so turning them off would be self-defeating," said the study's co-senior author Saar I. Gill, MD, PhD, an assistant professor of Hematology-Oncology at Penn and member of the ACC's Hematologic Malignancies research program. Cynthia E. Dunbar, MD, a senior investigator at the National Heart, Lung, and Blood Institute, is a co-senior author. The co-first authors are Miriam Yunhee Kim, MD, then a post-doctoral researcher in Gill's lab, and Kyung-Rok Yu PhD, a post-doctoral fellow under Dunbar.

"This study represents a significant advance toward effective and safe targeting of leukemia cells using CAR T cells," Dunbar said. "A key to this advance is the use of next-generation gene-editing technology to achieve this type of antigen-specific immunotherapy, even when the target is also present on normal bone marrow cells."

Since the hunter cells are unable to distinguish between normal and malignant cells, the researchers developed an innovative approach to genetically engineer the normal stem cells so they no longer resemble the leukemia. They used the CRISPR/Cas9 gene editing tool to remove CD33 from healthy cells. To their surprise, healthy stem cells lacking CD33 functioned normally. This resulted in the CD33 protein now being unique to the leukemia cells, leaving the CAR T cells free to attack.

"None of the existing CAR T approaches target a cancer-specific antigen – other than EGFRvIII in brain cancer – but with this approach, we can create a cancer-specific antigen, which allows us to unleash CAR T cells to their maximal capacity," Gill said.

Gill and his team have already put this concept into practice and have shown it to be effective in mouse and monkey models. They've also demonstrated its effect on human cells in a laboratory setting.

"Think of this as bone marrow transplant 2.0; the next generation of transplants," Gill said. "It gives you a super powerful anti-leukemia effect thanks

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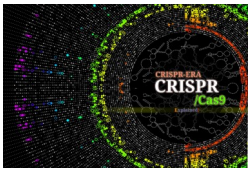

Limiting Toxicity of CAR T Cell Therapy in AML

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to the CAR T cells, but at the same time it has the potential to get rid of the main toxicity."

Their next step is to move this approach into human trials at Penn.

Journal Article: Kim MY et al. Genetic Inactivation of CD33 in Hematopoietic Stem Cells to Enable CAR T Cell Immunotherapy for Acute Myeloid Leukemia. Cell. 2018 May 31; 173(6) p1439–1453.e19

Source: Penn Medicine Communications

Fraietta and Melenhorst

CLL Patient Goes Into Remission Thanks to Single CAR T Cell

The doctors who have spent years studying the case call it "a series of fortunate events." What began as a remarkable response to chimeric antigen receptor (CAR) T cell therapy is now providing evidence about the human genome and immune response that could help turn gene therapy non-responders into responders. Researchers at the University of Pennsylvania's Abramson Cancer Center say a patient treated for chronic lymphocytic leukemia (CLL) in 2013 went into remission because of a single CAR T cell and the cells it produced as it multiplied, and has stayed cancer free in the five years since, with CAR T cells still present in his immune system. The findings, published last week in Nature, show the response is tied to where the CAR gene inserted itself into the patient's T cell DNA, a key factor that may help improve response rates to the therapy.

CLL is a type of cancer that starts in cells that become certain white blood cells in the bone marrow, and then move into the blood and lymph nodes. These cancer cells reproduce too quickly and crowd out other cells in the bone marrow. They also don't mature properly and thus don't fight off infection as well as they should. The American Cancer Society estimates there will be about 21,000 new CLL cases in 2018 and around 4,500 deaths from the disease.

Many of these patients will undergo a bone marrow transplant, but a potential additional treatment is CAR T cell therapy, which involves collecting patients' own immune T cells, reprogramming them to recognize and kill cancer, and then infusing them back into patients' bodies. The approach is approved by the U.S. Food and Drug Administration for certain acute lymphoblastic leukemia patients as well as some non-Hodgkin's lymphoma patients, but is not currently approved for treatment of CLL.

Patients typically receive three consecutive infusions with increasing doses – 10 percent, 30 percent, and 60 percent – to control for cytokine release syndrome (CRS). CRS is a common toxicity associated with CAR T therapy and includes varying degrees of flu-like symptoms, with fevers, nausea, and muscle pain, and can require ICU-level care. The patient in this report received the first two infusions of 10 and 30 percent, but did not initially respond.

"It wasn't until day 50 that the patient experienced CRS, which indicated the CAR T cells were active and may be having an anti-tumor effect," said the study's senior author J. Joseph Melenhorst, PhD, an associate professor of Pathology and Laboratory Medicine in Penn's Perelman School of Medicine and a member of Penn's Center for Cellular Immunotherapies.

Imaging showed the tumor had gotten smaller, so doctors decided to infuse the patient with the final 60 percent. The patient went into remission and has stayed there for five years and counting.

"It's the outcome we're always hoping for, but we know we can learn so much from every single patient no matter what. We brought this from the bedside back to the bench to understand as much as we could about what happened and why," said study co-senior author Carl June, MD, the Richard W. Vague Professor in Immunotherapy, a professor of Pathology and Laboratory Medicine, and director of the Center for Cellular Immunotherapies, and member of the ACC's Immunobiology research program.

"The first thing we found was that we could trace the lineage of the patient's CAR T cells back to a single, original cell," said the study's lead author Joseph A. Fraietta, PhD, an assistant professor of Pathology and Laboratory Medicine and a member of the Center for Cellular Immunotherapies. "It's a truly remarkable finding, and essentially tells us the minimum dose needed for CAR T cells to do their job is one."

This patient's CAR T cells were engineered to seek out a protein on leukemia cells known as CD19. In this strategy, the genetic code for the CAR that recognizes CD19 protein is randomly inserted into the patient's DNA by a genetically-modified virus.

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CAR T Cells for CLL

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In this particular case, researchers found the CAR sequence inserted into a gene called TET2 that normally regulates blood cell formation and keeps growth of these cells in check. Once the TET2 gene was disrupted, the single CAR T cell expanded massively and wiped out this patient's leukemia.

"Killer T cells that normally fight off infection generally can't beat cancer alone because they're older, past their prime, and often outnumbered," Fraietta said. "However, younger cells make the difference because of their ability to expand massively into an army of effectors. In this case, they got a chance to do their work because TET2 was inhibited which affected epigenetic pathways to drive this response."

"This analysis required a huge collaboration between immunologists, cell biologists, T cell experts, cancer biologists, and clinicians," Melenhorst said. "Fortunately, we have all of that expertise here, and it proved invaluable."

Other co-authors of the study include Frederic Bushman, PhD, the William Maul Measey Professor and chair of Microbiology, Shelley Berger, PhD, the Daniel S. Och University Professor and a Penn Integrates Knowledge Professor with appointments in the Perelman School of Medicine's department of Cell and Developmental Biology and the School of Arts and Sciences department of Biology, and David Porter, MD, the Jodi Fisher Horowitz Professor in Leukemia Care Excellence and director of Blood and Marrow Transplantation in the Abramson Cancer Center.

In 2012, Penn and Novartis entered into a global collaboration to further research, develop and commercialize Kymriah, formerly known as CTL019, and other CAR T cell therapies for the treatment of cancers. In August 2017, the U.S. Food and Drug Administration approved Kymriah for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or relapsed. In May of 2018, the approval was expanded to include the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) – the most common form of non-Hodgkin's lymphoma – as well as high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Journal Article: Fraietta JA et al. Disruption of TET2 promotes the therapeutic efficacy of CD19-targeted T cells. Nature. 30 May 2018.

Source: Penn Medicine Communications

In Helping Smokers Quit, Cash is King, E-cigarettes Strike Out

Free smoking cessation aids, such as nicotine patches and chewing gum, are a staple of many corporate wellness programs aimed at encouraging employees to kick the habit. But, new research shows that merely offering such aids for free does not help employees quit, whereas supplementing them with financial incentives is three times more effective. The study, led by researchers at the Perelman School of Medicine at the University of Pennsylvania, also provides the first large-scale evidence that offering e-cigarettes to known smokers is not effective at helping smokers stay smoke-free. The results were published in May in the New England Journal of Medicine and may hold significant policy implications as the U.S. Food and Drug Administration continues to weigh e-cigarette regulation.

"Smoking remains the leading cause of preventable deaths in the United States, and nearly all large employers offer wellness programs aimed at getting people to quit. But, these programs vary considerably, and to date, there has been little evidence to suggest which designs and strategies are most effective," said lead author Scott D. Halpern, MD, PhD, an associate professor of Medicine, Epidemiology, and Medical Ethics and Health Policy, and a member of the Steering Committee of the Penn Center for Health Incentives and Behavioral Economics (CHIBE), and member of the ACC's Cancer Control research program. "The new study drives forward previous research by showing that even among smokers who are not cherry picked on the basis of their motivation to quit, financial incentives still triple quit rates, whereas offering free conventional cessation aids or free e-cigarettes accomplishes nothing at all."

The study enrolled more than 6,000 participants from across 54 U.S.-based companies. Participants were assigned to one of four smoking cessation intervention groups or usual care (consisting of access to information regarding the benefits of quitting smoking and a motivational text-messaging service). Smoking cessation interventions included usual care plus one of the following: free e-cigarettes, in flavors of participants' choosing; free cessation aids (nicotine

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Cash Incentives Win Out Over E-cigarettes for Smoking Cessation

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patches, gum, and other medications, with free e-cigarettes only available for participants who've tried standard therapies previously); free cessation aids plus $600 in rewards for sustained abstinence from smoking; or free cessation aids plus $600 in redeemable funds, which were deposited in an account for each participant and removed if smoking cessation milestones were not met.

The study found that overall, only 1.3 percent of participants remained smoke-free for at least six months. However, the quit rates for redeemable deposits were significantly higher than with free cessation aids or with free e-cigarettes, and the quit rate for the rewards group was also higher than for cessation aids. By contrast, no differences were found in the quit rates among participants assigned to free e-cigarettes, free cessation aids, or usual care.

Of the more than 6,000 participants enrolled in the trial, 1,191 actively engaged with their assigned program. Those engaged in the trial were more motivated to quit, making them similar to smokers enrolled in prior studies that only enrolled participants who expressed an active interest in quitting. These motivated smokers were four to six times more likely to stay smoke-free for six months after the target quit date compared to those who did not actively engage. The authors say the quit rates observed among these engaged participants are consistent with those found in prior studies of incentives among motivated smokers. However, in the new study, even among these engaged participants, neither free e-cigarettes nor free cessation aids produced higher quit rates than usual care.

"Knowing that offering free e-cigarettes does not help smokers quit should inform the policies being deliberated at the FDA regarding whether or how to regulate e-cigarettes," Halpern said. "The result is concerning because it suggests that e-cigarettes may do more harm than good." A study by the National Academy of Science, Engineering, and Medicine concluded earlier this year that if e-cigarette use by adult smokers does not "lead to long-term abstinence from combustible tobacco cigarettes," then "e-cigarette use could cause considerable harm to public health in the short- and long-term."

Additional results of the study showed that the overall costs of the programs per participant who remained smoke-free for at least six months was lower in the financial incentives groups than in either the free e-cigarettes or cessation aids groups. "One of the key virtues of incentive programs is that they only cost money if people succeed in changing their behavior," said senior author Kevin Volpp, MD, PhD, director of CHIBE, and chief of the division of Health Policy in Penn's department of Medical Ethics and Health Policy, and also a member of the ACC Cancer Control program. "By contrast, employers that offer free cessation aids to their employees are paying money whether or not the aids help the smokers quit."

"It's estimated that it costs employers anywhere from $3,000 to 6,000 more per year to employ a smoker over a non-smoker, making the initial financial investment in smoking cessation programs well worth the cost," Volpp noted.

In addition to having a large sample size, the authors say having participants from 54 different companies suggests the results may be generalizable to most workplace settings. Additionally, because nearly everyone who was identified as a smoker at these companies was enrolled automatically, the results are more indicative of the real-world effects employers can expect when offering these programs to all employees who smoke, compared with prior studies that only enrolled people who were already motivated to quit.

Journal Article: Halpern SD et al. A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation. N Engl J Med. 2018 May 23

Source: Penn Medicine Communications

Penn Medicine Program for LGBT Health Celebrates Pride Month

June is Pride Month! Penn Medicine's Program for LGBT Health is celebrating by sponsoring the annual Philly Pride Parade and Festival.

Evidence suggests that the LGBT community is at higher risk for some cancers, particularly those related to oncogenic viruses such as HIV and HPV. In addition, they face health care disparities including discrimination and a lack of health-care provider research and training in LGBT-specific cancer risks and treatment. (Excellent information and further reading here.)

On Sunday, June 10, join the Penn Medicine community who identify as LGBTQ+ or allies to show our Penn Pride and commitment to the community. Sign up to join the Parade or staff the Table at the Pride Festival on Penn's Landing!

Seminars and So Forth

Monday 6/4/18 **12:00 pm**
Distinguished Seminar Series/CDB Seminar
"Identication and dissection of long noncoding RNA Machines." John Rinn, PhD, Leslie Orgel Professor of RNA Science, University of Colorado
BRB II/III Glen Gaulton Auditorium

Tuesday 6/5/18 **12:00 pm**
Distinguished Lecture in Cancer Research
"Disorders of Histone Methylation in Hematological Malignancy." Jonathan D. Licht, MD, Director, University of Florida Health Cancer Center, The Marshall E. Rinker, Sr. Foundation and David B. and Leighan R. Rinker Chair
CRB Austrian Auditorium—note location!

Wednesday 6/6/18 **8:00 am**
Abramson Cancer Center Grand Rounds
"Are young rectal cancer patients like everyone else? A genomic exploration." Joshua E. Meyer, MD, Associate Professor, Radiation Oncology and Vice Chair, Translational Research, Dept. of Radiation Oncology, Fox Chase Cancer Center
SCTR Rubenstein Auditorium

Thursday 6/7/18 **7:00 am**
Department of Otorhinolaryngology
David Myers Distinguished Lectureship
"The Era of Immunotherapy for Head and Neck Cancer." Robert L. Ferris, MD, PhD, Hillman Professor of Oncology; Director, UPMC Hillman Cancer Center, University of Pittsburgh
CRB Austrian Auditorium

Thursday 6/7/18 **9:00 am**
CCEB Seminar Series
"The Health System as a Laboratory: Using EHR Data to Study Drug Effects in Hospitalized Patients." Todd Miano, PharmD, MSCE, Fellow, Biostatistics and Epidemiology, PSOM
JMB Class of '62 Auditorium

Friday 6/8/18 **7:00 am– 3:15 pm**
Neuro-Oncology Symposium Brain Tumors 2018
CME/CNE-certified activity featuring keynote presentations by Roger Stupp, MD and Ezekiel Emanuel, MD. Presented by the ACC and The Penn Brain Tumor Center. Details and registration here.
JMEC Law Auditorium

Monday 6/11/18 **12:00 pm**
Path & Lab Medicine Grand Rounds
Martha S Jordan, PhD, Research Assistant Professor and Matthew B Palmer, MD, PhD, Assistant Professor, Pathology and Laboratory Medicine
CRB Austrian Auditorium

Monday 6/11/18 **12:00 pm**
CHOP Normal and Malignant Hematopoiesis
RAG Seminar Series
"Targeting Signaling Pathways to Reprogram Epigenetic Regulation of Gene Expression in High-risk Leukemia." Sinisa Dovat, MD, PhD, Professor of Pediatrics, Biochemistry and Molecular Biology and Pharmacology, and Four Diamond Endowed Chair, Department of Pediatrics, Pennsylvania State University College of Medicine
CTRB 1200B (CHOP)

Thursday 6/14/18 **12:00 pm**
ACC Radiobiology and Imaging Program/
Penn Radiation Oncology Invited Speaker
Timothy Zhu, PhD, Professor, Radiation Oncology, PSOM
SCTR 8-146AB

Thursday 6/14/18 **9:00 am – 2:30 pm**
Symposium on High-throughput Screening Technologies at Penn
The symposium will be an exciting day filled with engaging speakers, including: a keynote lecture by Anthony G. Letai MD, PhD from the Dana-Farber Cancer Center; expert Penn faculty highlighting technologies and results of screens done by users of the Penn HTSC; and a workshop on basic principles of turning your laboratory assay into an optimized, miniaturized assay ready for HTS. Details and registration (required): https://micro.med.upenn.edu/htc_symposium/
SCTR 10-146AB

Friday 6/15/18 **2:00 pm**
Inaugural Wachs Weingarten Family Lecture in Cancer and Women's Health
"Targeting the Unexpected Origins of Ovarian Cancer." Ronny Drapkin, MD, PhD, Director, Penn Ovarian Cancer Research Center; Director, Gynecologic Cancer Research, Basser Center for BRCA; Franklin Payne Associate Professor of Pathology in Obstetrics & Gynecology. Lunch will be provided at 1:00 pm.
SCTR 8-146AB

COMING SOON

Tuesday 6/26/18 **9:00 am – 4:30 pm**
Wistar Institute Melanoma Symposium
"*Noreen O'Neill Melanoma Research Symposium – Host Response in Melanoma*." Details and registration (required) at https://wistar.org/melanoma2018
The Wistar Institute, 3601 Spruce St.

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Philanthropy & Development Corner

Has a patient or family member ever asked you how to direct memorial gifts to the ACC?

Whether given in memory, in honor, or in celebration of anniversaries, birthdays, or other special occasions, a contribution in the name of a loved one plays an important role in the ACC's ongoing ability to explore new avenues of targeted research, effective cancer prevention and detection strategies, and compassionate approaches to patient care.

Below is information to share should anyone inquire about how to direct gifts:

Online:
https://www.pennmedicine.org/cancer/giving

By Mail: Penn Medicine's Abramson Cancer Center
Office of Development
3535 Market Street, Suite 750
Philadelphia, PA 19104

Make the check payable to Trustees of the University of Pennsylvania.

Please include the name and address of the person to be notified about the thoughtful donation. A notice of the generous gift will be sent to the individual honored or to the family of the person memorialized.

Create a personalized giving page to encourage friends and family to donate in honor of the loved one or an event at GivingPages.upenn.edu.

Contact ACC Development Office at 215.898.0578 or Abramson-Gifts@upenn.edu.

Funding Opportunities

RFA-RM-18-009 NIH Director's Transformative Research Award (R01)

Application Due Date: 9/21/2018

The NIH Director's Transformative Research Award supports individual scientists or groups of scientists proposing groundbreaking, exceptionally innovative, original, and/or unconventional research with the potential to create new scientific paradigms, establish entirely new and improved clinical approaches, or develop transformative technologies. Applications from individuals with diverse backgrounds and in any topic relevant to the broad mission of NIH are welcome. Little or no preliminary data are expected. Projects must clearly demonstrate the potential to produce a major impact in a broad area of biomedical or behavioral research.

https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-18-009.html

RFA-RM-18-008 NIH Director's New Innovator Award Program (DP2)

Application Due Date: 9/10/2018

The NIH Director's New Innovator Award supports early stage investigators of exceptional creativity who propose highly innovative new research approaches with the potential to produce a major impact on broad, important problems in biomedical or behavioral research. Applications from individuals with diverse backgrounds and in any topic relevant to the broad mission of NIH are welcome. The NIH Director's New Innovator Award complements ongoing efforts by NIH and its Institutes and Centers to fund early stage investigators through R01 grants, which continue to be the major sources of NIH support for early stage investigators.

https://grants.nih.gov/grants/guide/rfa-files/RFA-RM-18-008.html

PAR-18-787/PAR-18-788 Precision Imaging of Oral Lesions (R01/R21)

LOI Due Date: 30 days prior to application due date

Application Due Dates: Standard dates apply

The intent of these FOAs is to advance the development, adaptation, optimization, and validation of accurate, reproducible, specific, and sensitive imaging approaches to improve diagnosis, treatment, and treatment monitoring for diseases and conditions in the oral cavity and oropharynx.

R01: https://grants.nih.gov/grants/guide/pa-files/PAR-18-787.html

R21: https://grants.nih.gov/grants/guide/pa-files/PAR-18-788.html

PAR-18-789 Genetic analysis of non-human animal models to understand the genomic architecture of substance use disorders and addictive behaviors (U01)

Application Due Dates: 8/21/2018, 3/19/2019

The goals of this initiative are to discover allelic variants, genomic alterations, and functional changes associated with addictive behaviors in non-human animals through systems studies that employ genetic and genomics strategies. We also encourage applications that take genetic and/or genomics approaches to integrate data, delineate gene networks, and uncover the function of known or newly discovered genetic or epigenetic variants.

https://grants.nih.gov/grants/guide/pa-files/PAR-18-789.html

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