FDA Approves Penn/CHOP CAR-T Cell Therapy for ALL

In a landmark decision for the field of cancer immunotherapy, the U.S. Food and Drug Administration (FDA) on August 30 approved a personalized cellular therapy developed by the University of Pennsylvania and Children’s Hospital of Philadelphia (CHOP) for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. The approval was granted to Novartis for the chimeric antigen receptor (CAR) T-cell therapy, Kymriah™ (tisagenlecleucel, formerly CTL019). In 2012, Penn and Novartis entered into a global collaboration to further research, develop and commercialize Kymriah and other CAR-T cell therapies for the treatment of cancers. Kymriah is the first therapy based on gene transfer approved by the FDA.

On the day of approval, physicians, patients, and friends of the Abramson Cancer Center and Children’s Hospital of Philadelphia converged in a “flash mob” at the Perelman Center for Advanced Medicine to celebrate this historic milestone in the fight against cancer by Penn Medicine’s own Carl June, MD, the Richard W. Vague Professor in Immunotherapy in the department of Pathology and Laboratory Medicine in Penn’s Perelman School of Medicine and director of the Center for Cellular Immunotherapies in the Abramson Cancer Center. From an improvised stage atop a coffee stand, Abramson Cancer Center Director Robert H. Vonderheide, MD, DPhil addressed the crowd, “There’s one thing I want to tell you: the Abramson Cancer Center is on fire.” Dr. June added, “The world of cancer is forever changed today. This is a day I will always remember.”

“This is a turning point in the fight against B-cell ALL that opens up opportunities for patients across the world who desperately need new options,” June says. “We’re excited and proud to have moved this CAR therapy, in collaboration with Novartis and CHOP, through all phases of development and clinical trials, established its efficacy, and now extended its reach to children across the country under this FDA approval,” he added. “We hope the momentum behind the technology builds as we continue to investigate the abilities of personalized cellular therapeutics in blood cancers and solid tumors to help patients with many other types of cancer.”

Kymriah is expected to be available through a network of certified treatment centers throughout the United States.

“We delivered engineered T-cell therapy at CHOP for the first pediatric patient in the world, Emily Whitehead, who was only six years old when her leukemia stopped responding to conventional treatments. Emily’s cancer remains in remission, and in larger trials, we’re seeing overall remission rates over 80 percent, which is a remarkable improvement upon previous treatment success rates,” said lead investigator of the CHOP and global trials of the therapy, Stephan Grupp, MD, PhD, the Yetta Deitch Novotny Professor of Pediatrics at Penn and director of the Cancer Immunotherapy Frontier Program and chief of the section of Cell Therapy and Transplant at CHOP.

The new treatment modifies patients’ own immune T cells, which are collected and reprogrammed at the Novartis manufacturing facility to potentially seek and destroy the patients’ leukemia cells. After being infused back into patients’ bodies, these newly built “hunter” cells both multiply and attack, targeting cells that express a protein called CD19. Tests reveal that the army of hunter cells can grow to more than 10,000 new cells for each single engineered cell patients receive, producing high remission rates in completely refractory leukemia – and can survive in the body for years.

CTL019 was first tested at Penn in 2010, in adult patients with advanced chronic lymphocytic leukemia (CLL). In 2012, CHOP became the first institution to investigate Kymriah in pediatric patients with ALL, the most common childhood cancer. About 20 percent of the 3,500 pediatric and young adult patients diagnosed every year with ALL in the United States relapse or do not respond to conventional treatment.

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Katherine L. Nathanson, MD, New ACC Deputy Director

The ACC is pleased to announce the appointment of Katherine L. Nathanson, MD, as Deputy Director of the Abramson Cancer Center. Dr. Nathanson is a distinguished physician-scientist and has long been a valued colleague and member of the ACC. Her clinical and research portfolio incorporates an impressive array of diseases. She has played a critical role in many of ACC’s most recent advancements, and is well-known as an international expert in somatic and germline genetics.

As Deputy Director, Dr. Nathanson will oversee multiple aspects of the scientific and clinical missions of the ACC, including strategic planning, program development and evaluation, faculty recruitment, leadership appointments, and resource allocation.

Dr. Nathanson is a Professor of Medicine in the Division of Translational Medicine and Human Genetics in the Perelman School of Medicine at the University of Pennsylvania. She is Associate Director for Population Sciences in the Abramson Cancer Center, co-Leader of the Cancer Control Program, and Chief Oncogenomics Physician. She also serves as Director of Genetics for the Basser Center for BRCA. Dr. Nathanson received her bachelor’s degree from Haverford College and her MD from the University of Pennsylvania. She completed residencies in Internal Medicine at Beth Israel Hospital in Boston, as well as in Clinical Genetics at the Children’s Hospital of Philadelphia and here at Penn. Dr. Nathanson joined the Penn faculty in 2001. Since then, Dr. Nathanson has published more than 250 peer-reviewed articles in journals such as Nature, JAMA, Cancer Cell, and the New England Journal of Medicine. She has an extensive record of national service for multiple organizations including the American College of Medical Genetics and Genomics, for which she serves as the Cancer Genetics editor for Genetics in Medicine, and the American Association for Cancer Research. Dr. Nathanson is the Chair of the Cancer Genetics study section for the National Institutes of Health and is an elected member of the American Society of Clinical Investigation and the American Association of Physicians.

The ACC looks forward to Dr. Nathanson’s leadership to advance the mission of the Abramson Cancer Center: to reduce the burden of cancer throughout our region, the nation, and the world by extending our integrated program of laboratory, clinical, and population-based research.

Penn Medicine Receives Two NIH T-32 Grants

Researchers from the Perelman School of Medicine at the University of Pennsylvania have received two highly competitive post-doctoral Institutional Training Grants for genomic science from the National Human Genome Research Institute of the National Institutes of Health. The awards, known as T32 grants, are distributed in a variety of biomedical categories by divisions of the NIH and help institutions support training of pre- and post-doctoral fellows in basic, clinical, and behavioral research.

The University of Pennsylvania is the first institution with more than one training grant from the National Human Genome Research Institute, now with three: These two new post-doctoral grants and an existing pre-doctoral training grant.

The first new award will support a post-doctoral training program in genomic medicine focused on translational medicine and informatics. It will be led by Jason Moore, PhD, Edward Rose Professor of Informatics, and director of the Penn Institute for Biomedical informatics; and Katherine Nathanson, MD, the deputy director of the Abramson Cancer Center.

“Genomics technology is making enormous advances in measuring DNA sequence variation and RNA expression in clinical samples,” said Moore. “However, the integration of genomic measurements into health care is outpacing the training of physicians and scientists to effectively use the information to improve the health of patients. “Our program will play a vital role in meeting this need by training the next generation of physician and scientist leaders in genomic medicine.”

The two-year program, which will serve MD and PhD fellows at Penn and Children’s Hospital of Philadelphia, will include courses, clinical and laboratories rotations, interactive learning experiences, and research training. Fellows will be exposed to the latest advances in genomics, focusing on alleviating disease, effective use of biomedical informatics and biostatistics, scientific writing, and ethical, legal, and social implications of genetics and genomics issues. Trainees will participate in clinical rotations on topics ranging from massively parallel sequencing – which uses technology to read the genomic sequences of...
Germline BRCA1/2 Mutations & Risk for Primary Treatment Resistance

Determining which cancer patients are likely to be resistant to initial treatment is a major research effort of oncologists and laboratory scientists. Now, ascertaining who might fall into that category may become a little easier for physicians taking care of people with BRCA1/2 mutations. Researchers in the Perelman School of Medicine at the University of Pennsylvania found a relationship between the genetics of tumors with germline BRCA1/2 mutations and whether the tumor retains the normal copy of the BRCA1/2 gene, and risk for primary resistance to a common chemotherapy that works by destroying cancer cells’ DNA. The team published their study in Nature Communications.

Researchers estimate that 5 percent of breast cancers and 20 percent of ovarian cancers are attributable to germline mutations in BRCA1 and BRCA2, the focus of the current study. Overall, 252,710 people will be diagnosed with breast cancer this year and 40,610 will die of the disease, according to the National Cancer Institute. For ovarian cancer, NCI projects 22,440 new cases and 14,080 deaths.

There are many reasons patients may be resistant to treatment — the immune system, the complex landscape of a tumor, or a patient’s own genes can all play a role. Without explicitly looking for it, the Penn team found another mechanism of resistance to a standard treatment for patients with BRCA-associated cancers. “Our primary question was not aimed at evaluating resistance to therapy, but we did end up there,” said senior author Katherine Nathanson, MD, deputy director of the Abramson Cancer Center, and director of Genetics at the Basser Center for BRCA.

Her group evaluated the genetic profiles of 160 breast and ovarian cancers associated with germline mutations in BRCA1 and BRCA2, in the largest study of these tumors to date. They were interested in determining what types of secondary, additional changes occur in primary BRCA1/2 germline mutation-associated cancers that might act in concert with mutant BRCA1 and BRCA2 to drive the cancers.

The team evaluated how frequently the non-mutated version of the gene lost its function in concert with the original BRCA1/2 germline mutation-associated cancers. In oncology terms, this double-hit status is called “loss of heterozygosity,” or LOH, to signify that both versions (one inherited from mother, one from father) of the normal BRCA gene have been hobbled.

Historically, it had been thought that all tumors associated with germline BRCA1/2 mutations lose the second version of the gene, or LOH. The investigators were surprised to find that was not the case in a surprisingly large percentage of patients. In addition, they found that other genetic and clinical features of patients whose tumors did not undergo LOH (LOH-negative) were significantly different from those that did undergo LOH (LOH-positive).

Notably, they evaluated the overall survival of patients with ovarian tumors with and without loss of heterozygosity. LOH-negative status was associated with worse overall survival in ovarian cancer patients treated with platinum chemotherapy, with a median of 39 months, compared to 71 months in the LOH-positive group who received the same treatment.

The researchers believe the patients with LOH-negative tumors (those with one working copy of BRCA1 or BRCA2 and the other copy carrying the germline mutation) had tumor cells that could still repair the chemotherapy-induced DNA damage in order to survive. In contrast, the investigators surmise that the LOH-positive group (with both gene copies disabled) responded better to the same therapy because their tumor cells died more readily.

“Identifying the LOH status of BRCA1/2 carriers may be useful to predict who might be at risk for primary resistance to DNA-damaging agents such as platinum, which has important implications for treatment of patients with these mutations,” said the study’s first author Kara N. Maxwell, MD, PhD, an instructor of Hematology/Oncology.

“We only need to determine the LOH at a specific gene’s location, which is more cost effective than sequencing a patient’s whole genome, for example, and compatible with standard testing.”

By looking at a person’s individual genetics and type of cancer, the Penn team hopes to be able to better tailor care soon after an initial diagnosis to improve survival. Nathanson surmises that knowing a person’s LOH status could guide treatment decisions. She suggests that certain drugs already in today’s cancer treatment arsenal will likely work for patients who are at risk for resistance due to their LOH genetics; however, it’s a matter of choosing the right one.

Other Penn coauthors include Susan Domchek, Michael Feldman, and Jennifer Morrissette.

Publication: Nature Communications
Source: Penn Medicine Communications
Contact: karen.kreeger@uphs.upenn.edu
FDA Approves CAR-T Cell Therapy for ALL

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Those early-stage clinical trials, in which more than 90 percent of patients achieved a complete remission one month after receiving the therapy, led to a global registration trial in 2015, involving 68 children and young adults with advanced ALL treated at 25 centers across the world. Eighty-three percent of the patients who received a single dose of their own engineered cells achieved a complete remission.

In July 2017, an FDA advisory panel unanimously recommended approval of the therapy, paving the way for today’s FDA approval. After presentation of trial data and testimony from families whose children have received the therapy, one expert on the panel said this was "the most exciting thing I’ve seen in my lifetime."

Many patients in the ALL trials experienced a side effect called cytokine release syndrome (CRS) including grade 3 or grade 4, which includes varying degrees of flu-like symptoms, with high fevers, nausea, and muscle pain, and temporary neurologic symptoms, including delirium, but also low blood pressure and breathing difficulties requiring ICU-level care in the most severe cases. Eighteen percent of patients experienced grade 3 or grade 4 neurologic events. Patients were treated with the immunosuppressant drug tocilizumab or short courses of steroids to combat the symptoms.

Other trials with CTL019 therapy are also underway in the Abramson Cancer Center for adult ALL patients and those with CLL and non-Hodgkin lymphoma. Penn and Novartis are also investigating the next generation of CAR therapies for multiple myeloma, and for solid tumors, through trials in glioblastoma, mesothelioma, and ovarian and pancreatic cancer. Other CAR trials at Penn are exploring the technique for prostate cancer, melanoma, and triple-negative breast cancer.

The Novartis-Penn Center for Advanced Cellular Therapeutics (CACT) opened in 2016 and hosted Vice President Joe Biden at the launch of his Cancer Moonshot initiative, cementing Penn’s role as an international innovator in the development and manufacturing of personalized cellular therapies.

Additional leaders of the research include Penn’s David Porter, MD, the Jodi Fisher Horowitz Professor in Leukemia Care Excellence and director of Blood and Marrow Transplantation in the ACC; Noelle Frey, MD, MSCE, an assistant professor of Hematology-Oncology; Bruce Levine, PhD, the Barbara and Edward Netter Professor in Cancer Gene Therapy in the department of Pathology and Laboratory Medicine; Michael Milone, MD, PhD, an associate professor of Pathology and Laboratory Medicine; and CHOP pediatric oncologist Shannon Maude, MD, PhD, an assistant professor of Pediatrics.

Adult patients who are interested in T cell therapies at Penn Medicine can call 215-316-5127 for more information. For information about the Cancer Immunotherapy Program at CHOP, please call 267-426-0762.

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

Celebrating a Cancer Milestone

On August 30, physicians, patients, and friends of the Abramson Cancer Center and Children’s Hospital of Philadelphia converged in a “flash mob” at the Perelman Center for Advanced Medicine to celebrate a historic milestone in the fight against cancer – the FDA approval of Kymriah™, the first personalized cellular therapy to treat cancer, developed by Penn Medicine’s own Carl June, MD.

Dr. June said it best, "What you have all done for patients is amazing. The world of cancer is forever changed today. This is a day I will always remember."

We are grateful that people were able to attend this truly unique event on such short notice, and for anyone who couldn't make it, t-shirts will be available on Thursday, September 7th at the Abramson Cancer Center, 12 South Tower. Please continue to wear your shirts with pride and snap photos or video and send them to pennmedphotos@gmail.com, and check out our "flash mob" photos on Facebook – tag yourselves and share with friends with #CARTcell.

If anyone is interested in making a philanthropic contribution, or if you know anyone who wants to show their support, click here or contact Tricia Bruning at tbruning@upenn.edu.
Seminars and So Forth

Tuesday 9/5/17  4:00 pm
CHOP CCCR Oncology Seminar Series
“Neuroblastoma: MYCN and MYC Commandeer Core Transcriptional Circuitry to Create Dependencies with Therapeutic Implications.” Thomas Look, MD, Professor, Pediatrics, Harvard Medical School; Vice-Chair for Research, Pediatric Oncology, Dana-Farber Cancer Institute
CTR1100B (CHOP)

Friday 9/8/17  12:00 pm
Basser Center for BRCA Monthly Seminar Series
“Pancreatic Cancer with HRD: A New Therapeutic Niche.” Kim Reiss-Binder, MD, Assistant Professor of Medicine (Hem-Onc), PSOM
Room 252 BRB II/III

Tuesday 9/12/17  12:00 pm
Distinguished Lectures in Cancer Research
“Gene regulation in normal and malignant hematopoiesis.” Vikram R. Paralkar, MD, Assistant Professor of Medicine, PSOM
BRB II/III Glen Gaulton Auditorium

Wednesday 9/13/17  5:00 pm
5th Annual David K. Ginsberg, MD Lectureship
“Current and Emerging Developments in Molecular Biology Pertaining to the Diagnosis and Treatment of Pancreatic Adenocarcinoma.” Gregory L. Beatty, MD, PhD, Assistant Professor of Medicine (Hem-Onc), PSOM and Anil K. Rustgi, MD, T. Grier Miller Professor of Medicine & Chief, Division of Gastroenterology, PSOM. Reception to follow.
BRB II/III Gaulton Auditorium

Thursday 9/14/17  12:00 pm
ACC Radiobiology and Imaging Program Seminar
Special Session: Review of K-Award Application of Junior Investigators. Title of Grant: Disparities in Initial Presentation between Black and White children with Cancer. Lena Winestone, Instructor at CHOP, Pediatric Oncology
1319 Blockley Hall

COMING SOON
Friday 9/29/2017  7:30am-2:35pm
9th Annual Focus On Lung Cancer Conference
This conference is for those who are at risk, newly diagnosed, currently in treatment or survivors of non-small cell and small-cell lung cancer, as well as family members, caregivers, and health care professionals. To register, click here.

Penn Medicine Receives Two NIH T-32 Grants

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millions of fragments of DNA – to reporting the results back to patients. Mghdfghfsfoore and Nathanson plan to enroll two trainees per year for the first two years, and three in the three years after that.

“The program will draw upon the extraordinary strengths of Penn and CHOP in the areas of genomics, translational medicine, and bioinformatics,” said Nathanson. “It will prepare trainees for impactful careers applying genomic medicine to improve health care through advances in diagnosis, therapeutics, and prevention.”

The second award, led by Steven Joffe, MD, MPH, Emanuel & Robert Hart Professor of Medical Ethics & Health Policy and Chief of the Division of Medical Ethics at the Perelman School, will support the Penn Postdoctoral Training Program in the Ethical, Legal and Social Implications of Genetics and Genomics. “Rapid advances in genomic technology offer unprecedented promise for treating individuals with or at risk of disease, and even to alter the identities or futures of individuals not yet born,” said Joffe. “Such knowledge and power require us to use them in ways that promote individual and collective welfare, expand social justice, protect the vulnerable, and respect the autonomy of persons and the interests of communities. Our new program aims to train scholars who will help ensure that the field of genomics meets these important obligations.”

The program will feature two core components. The first is didactic training in conceptual bioethics, empirical methods, and genetic science. The second is mentored original research leading to empirical and conceptual scholarly publications. Training will be provided by faculty members from departments at the Perelman School of Medicine, School of Arts and Sciences, and the University of Pennsylvania Law School.

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

**RFA-CA-17-049 Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium (U54)**

LOI DUE: 30 days prior to application due date
APPLICATION DUE: 11/15/2017

This FOA is associated with the Beau Biden Cancer MoonshotSM Initiative that is intended to accelerate cancer research. Its purpose is to promote research on fusion oncproteins in childhood cancers; the goal is establishment of a consortium of collaborating research teams to advance our understanding of the biology and mechanisms of action of fusion oncproteins in pediatric cancers, and to apply this knowledge towards developing targeted therapeutic approaches. Increased attention to this important but under studied field can help overcome existing barriers to progress and pave the way to novel therapeutic approaches with increased efficacy and fewer side effects than current options. The research teams comprising the Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium will take a comprehensive approach to understanding the biology of fusion oncproteins in childhood cancers and will use this information to inform strategies for therapeutic targeting.


**PA-17-440/PA-17-449 The Interplay of Cell Death Pathways in Cancer Cell Survival and Resistance to Therapy (R01/R21)**

DEADLINES: Standard dates apply

The purpose of these FOAs is to stimulate research in the interplay between cell death pathways in naive and drug resistant cancers. Regularized cell death, especially apoptosis and necroptosis, are natural barriers that restrict malignant cells from surviving and disseminating. Evasion of cell death mechanisms is one of the hallmarks of cancer contributing to tumor progression, metastases and resistance to therapy. Recent studies show that the machinery to activate different forms of cell death coexists in cells but the crosstalk of cell death pathways in cancer has not been systematically studied.


**PA-17-459/PA-17-460 Biology of Lung, and Head and Neck Preneoplasias (R01/R21 - Clinical Trial Not Allowed)**

DEADLINES: Standard dates apply

These FOAs seek applications investigating mechanistic and biological aspects of preneoplasia leading to lung, and head and neck (HN) cancers. Despite improved therapies and a deeper molecular understanding of lung and HN cancers, these tumors remain a major health problem in the United States and globally. While molecular markers of early injury to the aerodigestive epithelial field have been found, relatively little is known about the molecular mechanisms that initiate these preneoplasia and drive their progression to invasive cancer.


**IBI Bioinformatics Core Support for ACC Investigators**

ACC has been collaborating with the IBI Bioinformatics Core ("BIC") to build a team to meet the growing need for bioinformatics support among ACC members in the areas of massively parallel sequencing data analysis, bioinformatics application development, and multi-omics data management and integration.

To provide this service, the ACC supports IBI’s Taehyong Kim, PhD to assist in data analysis for pilot projects or analysis of preliminary data for grant applications. Dr. Kim can also assist investigators in the analysis of discrete data sets for manuscript publication. This service will provide support for multiple individuals and thus Dr. Kim will only take on one project per investigator.

Downstream statistical analyses of informatics data will continue to be provided by the ACC Biostatistics Core, which is committed to working closely with the IBI BIC.

Investigators interested in larger-scale bioinformatics support should contact Paul Wang, PhD, director of the IBI BIC. Dr. Kim is pleased to consult on an individual basis to scope project need and support.