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FALL 2016 | Advancing Cancer Care

CINCINNATICHILDRENS.ORG/RESEARCH
Drug Reverses Lung Damage in Mice

Researchers here have developed a compound that appears to reverse life-threatening lung damage.

When mice lack the transcription factor FOXF1, the endothelial cells lining the blood vessels of their lungs no longer provided a protective barrier, which leads to edema, lung inflammation and fatal respiratory problems. However, a compound that simulates FOXF1 promotes recovery from lung injury, according to findings published May 10 in Science Signaling.

The study’s leading co-authors were Vladimir Kalinichenko, MD, PhD, of the Divisions of Pulmonary Biology and Developmental Biology, and Tanya Kalin, MD, PhD, Perinatal Institute.

“The small molecule compound we developed stabilizes the FOXF1 protein in cell cultures and mouse lungs, and shows promise in inhibiting lung inflammation and injury,” says Kalinichenko.

With further development, the compound could be used in children and adults to promote blood vessel formation in lungs, promote healing, and decrease breathing complications.

How Computers Can Become Recruiters

Finding families willing to participate in medical studies has been a constant challenge for the research community. Now, a computer algorithm may make the job easier.

Yizhao Ni, PhD, and colleagues in Biomedical Informatics have developed an algorithm that helps predict who is more likely to participate in a study, and why. Current recruitment rates hover around 60 percent of eligible patients, but this tool could boost participation rates to 72 percent or beyond, according to findings published online April 27 in the Journal of the American Medical Informatics Association.

How Computers Can Become Recruiters

Fouladi Joins Cancer Moonshot

Maryam Fouladi, MD, MSc, Medical Director, Brain Tumor Center, has been invited to participate in the National Cancer Moonshot initiative as a member of the Blue Ribbon Panel Working Group on Pediatric Cancer.

The Moonshot initiative, led by Vice President Joe Biden, aims to accelerate current cancer research efforts and break down barriers to progress, making more therapies available to more patients, while further improving early detection and cancer prevention efforts.

The National Cancer Institute (NCI) has assembled a blue ribbon panel and related working groups to provide expert advice on the vision, proposed scientific goals, and implementation of the National Cancer Moonshot. The panel will use input from the working groups to make recommendations to the NCI director on how to best advance the themes proposed for the Moonshot.

“This appointment recognizes Dr. Fouladi’s work as a national leader in brain cancer treatment and research,” says Margaret Hostetter, MD, Chair, Department of Pediatrics and Director, Cincinnati Children’s Research Foundation. “Her work is a prime example of the enormous potential impact of our new Proton Therapy Center and the genomics innovations occurring at Cincinnati Children’s.”

— Margaret Hostetter, MD

Read more about Fouladi’s brain tumor research.
An emerging biomarker for eosinophilic esophagitis (EoE) may someday allow a simple blood test to replace endoscopic procedures as the primary tool for monitoring children with the condition.

Elevated levels of eosinophil progenitor cells in blood samples appear to correlate with elevated eosinophil counts obtained through tissue biopsies, according to findings published online May 16 in the Journal of Allergy and Clinical Immunology by researchers at the Cincinnati Center for Eosinophilic Disorders.

Testing involving more patients across varying disease states will be needed to validate the latest findings. If the results hold, a viable blood test could reduce costs and transform the patient experience.

“Children with EoE can be on highly restricted diets of formula alone or only a few foods,” says Patricia Fulkerson, MD, PhD, senior study author. “One of the major obstacles to families participating in studies to introduce foods back into the child’s diet is the need for endoscopy after each food is tried to see whether or not it triggers disease activity.”

That cute, chubby baby could be headed for health problems.

A study conducted by Allison Smego, MD, Division of Endocrinology, is believed to be the first to show that a body mass index (BMI) above the 85th percentile as early as 6 months of age can predict later obesity. Her findings were presented in April at the national Endocrine Society meeting in Boston.

“These children have a high lifetime risk for persistent obesity and metabolic disease and should be monitored closely at a very young age,” says Smego.

The researchers studied 783 lean and 480 severely obese children ages 2 to 6. At around 4 months of age, the trajectories of BMI in the children who became obese by age 6 began to differ from those who maintained healthy weight.

Smego says BMI is not typically measured before age 2, but should be to identify children at risk and provide counseling to families about healthier lifestyles.

Obesity Can Be Predicted At 6 Months

Our scientists joined researchers around the world in a study that could transform the treatment of children with life-altering birth defects.

The study, published Feb. 20 in Nature Neuroscience, focuses on CHARGE syndrome, a genetic condition that causes craniofacial malformations, neurological dysfunction and growth delay. The researchers discovered that a gene associated with CHARGE, CHD7, serves as a control point in the production of myelin, which forms a protective sheath around nerves. Defects in CHD7 disrupt molecular pathways that help form the myelin sheath in nerves and make bones and other organs.

Qing Richard Lu, PhD, scientific director of the Brain Tumor Center in our Division of Experimental Hematology and Cancer Biology and a study co-author, says the findings could identify “signaling pathways and molecules as therapeutic targets for myelin regeneration in patients with CHARGE and other demyelinating diseases.”

New Model Offers Insights to AML

Scientists are gaining insight into a virulent form of acute myeloid leukemia (AML) thanks to a new mouse model reported in the journal Cancer Discovery.

“Our goal was to create a model that was faithful to the human form of the disease,” says senior author H. Leighton Grimes, PhD, Division of Immunobiology. “We hope it will open the way for other researchers to join us in attacking this particularly lethal AML subtype.”

The team used single-cell RNA sequencing to produce a model that reflects AML patients with mutations in the genes Dnmt3a and Flt3, who face a more aggressive form of the disease. “Comparing Flt3-mutant AML with and without Dnmt3a mutation allowed us to more finely identify patterns specific to the Dnmt3a mutation,” says postdoctoral fellow Sara Meyer, PhD.

The researchers confirmed that low level Dnmt3a activity is cancer-causing, allowing genes normally expressed only in early blood cell formation to continue expression, leading to the development of AML.

More research is warranted to determine if rescuing normal Dnmt3a function would be a viable therapy for treating human AML.
Chemogenetic agents that can silence signaling transmissions from newly formed interneurons may emerge as a new approach to treating the often deadly infections that can follow spinal cord injury. Study results from a team of scientists from Cincinnati Children’s and The Ohio State University (OSU) Wexner Center were posted online April 18 in *Nature Neuroscience*. The researchers found that as the body reacts to spinal cord damage, abnormal nervous system circuitry starts to form, resulting in an immune suppressive reflex.

“This abnormal spinal cord circuitry likely causes chronic immune suppression and increases the chance of complications from common infections, such as pneumonia,” says study co-author Phillip Popovich, PhD, Department of Neuroscience at OSU.

“In mice with spinal cord injury, the team reports success at targeting the abnormal reflex circuitry for chemogenetic silencing using the compound hM4Di-DREADD. This halted immune suppression, reversed spleen atrophy and increased white blood cell counts. As the team continues evaluating the potential treatment, human clinical trials likely remain several years away.

Drugs that target the protein calpain 14 may someday help treat the inflammation and scarring that can occur in people with eosinophilic esophagitis (EoE), according to new research from the Cincinnati Center for Eosinophilic Disorders.

Previous research led by Marc Rothenberg, MD, PhD, has established a powerful link between EoE and the CAPN14 gene, which codes for calpain 14. In the latest findings, posted online April 7 in *JCI Insight*, Rothenberg and colleagues detail the biochemical and functional properties of CAPN14 and the disruptions in esophageal cells that occur when the expression of CAPN14 is experimentally regulated.

“The new information suggests that controlling the activity of calpain 14 may prevent the development of EoE, thus making the protein an important target for further drug research.

Two recent studies from Cincinnati Children’s show the potentially transformative technology of induced pluripotent stem cells (iPSCs) is not quite ready to deliver on the promise of regenerative medicine.

Specialized iPSCs can be reprogrammed from adult skin or infant cord blood cells to become any cell type in the body—a condition called pluripotency that mimics the function of human embryonic stem cells (hESCs). Although not currently used to treat patients in the United States, researchers are working to ensure that iPSC technology is grounded in safe and sound science so it can safely advance to clinical use in the future.

A multi-institutional study appearing June 9 in *Stem Cell Reports*, and led by Cincinnati Children’s, found that about 30 percent of tested iPSCs were genetically unstable and otherwise not safe for clinical use. The study analyzed 518 different lines of iPSCs submitted by 10 different research institutions.

The study also announced an online web portal and database (hosted at https://www.synapse.org/) giving scientists open access to data from the study, including methods for generating safe and stable iPSCs lines that meet quality standards.

The research was led by Carolyn Lutzko, PhD, co-senior study author and director of translational development in the Translational Core Laboratories at Cincinnati Children’s, associate professor of pediatrics at the University of Cincinnati College of Medicine and division director of Regenerative Medicine and Cellular Therapies at Hoxworth Blood Center in Cincinnati.

A second study, published April 14 in *Cell Stem Cell*, reports iPSC lines intended for therapeutic use should be screened for age-dependent accumulation of mutations in the mitochondrial genome and DNA—which support energy production and other basic cell functions.

Researchers often just check the nuclear genome of cells when looking for mutations, but testing mitochondrial DNA is also vital, especially when reprogramming iPSCs from the adult cells of elderly people, according to co-corresponding author Taosheng Huang, MD, PhD, a medical geneticist and director of the Mitochondrial Disorders Program at Cincinnati Children’s.
In a world where advances in medical technology tend to be measured in microns and nanograms, the idea of cancer research leaping forward through the installation of equipment weighing more than 280 tons seems almost absurd. Yet that’s how much just one of the precision-guiding gantries at Cincinnati Children’s new Proton Therapy Center weighs. And once the facility reaches full-service capacity this fall, it will have three of these behemoths – including the world’s only proton treatment gantry dedicated exclusively to research and development.

This is big medicine intended to make a big difference. The Proton Therapy Center’s grand opening later this month caps off more than a decade of planning, an investment approaching $120 million, and a three-year construction project that involved 31,000 yards of concrete and more than 155 miles of wiring. The first patients will begin receiving treatments in September, soon to be followed by a swarm of research initiatives.

“Even with all the work that goes into making conventional radiotherapy as safe as possible, we know that as much as one-third of the radiation dose a patient receives can wind up deposited away from the targeted tumor,” Perentesis says. “Unfortunately for some children, this can lead to some immediate side effects and secondary cancers and other side effects developing as much as 25 to 30 years after treatment. We expect proton therapy to dramatically reduce these risks.”

Proton therapy reduces risk by sending particles into the body at relatively low levels of radiation, which then stop within the targeted tissue to release nearly all their energy in a spike of output known as a Bragg peak. The photon energy from conventional X-ray beams passes all the way through tissue, killing the targeted cancer cells but also damaging healthy tissue on the way in and out.

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TRANSFORMING RADIATION THERAPY

Across the U.S., about one-quarter of all children diagnosed with cancer receive radiotherapy as part of their care. These treatments have contributed to rapid improvements in cure rates. However, the price of progress has included children surviving brain tumors, but growing up with cognitive impairment; or beating Hodgkin lymphoma only to face heart disease caused by stray radiation.

Proton therapy already represents a significant step forward. However, much more research is needed to refine the technology.

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FINE TUNING AN EMERGING TOOL

Proton therapy is applicable for more than 80 percent of children in need of radiation therapy as part of their treatment regimen. For many cancer survivors, the result will be growing up with far fewer risks of long-term consequences.

One of several projects seeking to shed light along these lines will involve isolating cancer stem cells from the rest of
80% of children with cancer who need radiation therapy at Cincinnati Children’s will receive proton therapy.

Types of Cancer Well Served by Proton Therapy:
- Ewing’s Sarcoma
- Hodgkin Lymphoma
- Neuroblastoma
- Non-Hodgkin Lymphoma
- Pediatric Brain Tumors
- Rhabdomyosarcoma
- Soft Tissue Sarcomas

“...collaborators from a wide realm of expertise—including investigators from outside Cincinnati Children’s—whose work will take proton therapy to a new level.”

– John Perentesis, MD, Co-Executive Director, Cancer and Blood Diseases Institute

Next Steps
Proton research will be conducted in cooperation with various departments at UC, the University of Cincinnati Physicians, the University of Cincinnati Medical Center, and Varian, the equipment manufacturer. Some collaborations also involve research centers in Germany and Israel, and more multi-institutional partnerships are likely. Initial funding comes from the institutions involved, with the goal of seeking larger grants from the National Cancer Institute, the National Science Foundation, and other sources as pilot projects demonstrate progress.

Proton Therapy

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Proton vs. Photon Radiation

Proton therapy works by extracting positively charged protons from hydrogen gas and accelerating them through a cyclotron up to nearly 2/3 the speed of light. The protons are guided to the tumor site by powerful magnetic and electrical fields. They carry just enough charge to reach a precise point in the tumor, where the particles stop and release nearly all of their energy in a phenomenon known as a Bragg peak.

1/3 of conventional radiation dose winds up in healthy tissue.
Changing the Rules of Engagement

Study Scores Research Win Against Unstoppable Brain Cancers

by Nick Miller

Words like “victory” rarely get used when talking about treatments for aggressive, untreatable childhood brain cancers known as high-grade gliomas and glioblastomas.

The conversation more commonly turns to a sad prognosis focused on how long a child has to live.

So it wasn’t without notice in the world of cancer biology that a recent study led by scientists in our Cancer and Blood Diseases Institute scored an early-stage research win.

In a study published in May 2016 in *Cancer Cell*, scientists tested a form of gene therapy as part of an experimental multi-step treatment. In laboratory mouse models, the therapy changed the cellular makeup of the tumors and allowed further treatment to slow or stop their growth.

The so-called suicide gene therapy shut down the gene Olig2, a gene long-implicated in the formation of high-grade gliomas. In addition to depleting the dividing cells with active Olig2 expression, deleting the gene also yielded key insights into overcoming treatment resistance.

“We found that Olig2 is the molecular arbiter of genetic adaptability that makes high-grade gliomas aggressive and treatment-resistant,” says Qing Richard Lu, PhD, lead investigator and scientific director of the Brain Tumor Center at Cincinnati Children’s. “By inhibiting Olig2 in tumor-forming cells, we were able to change the tumor cells’ makeup and sensitize them to targeted molecular treatment. This suggests a proof-of-principle for stratified therapy in distinct subtypes of malignant gliomas.”

**CREATING TREATABLE TUMORS**

Pro neural tumors form from the cells resembling the early precursors of oligodendrocytes, the brain cells that help generate insulation for neural connections. Olig2 is critical for these cells’ formation at the early stages of brain cell development requiring robust growth. In biopsied human brain cancer cells and mouse models, the researchers observed Olig2 expression in early-stage dividing and replicating cells in tumors.

Olig2 helps transform normal precursor cells into abnormal cancer cells that grow uncontrollably. The gene drives molecular processes that make glioma cells highly adaptable as they form and highly susceptible to the tumor-promoting effects of additional genetic changes.

**GEFITINIB SHOWS PROMISE**

Using laboratory mice genetically engineered to model human brain cancers, the researchers found that using suicide gene therapy to eliminate dividing cells with Olig2 expression (the potential seeding cells for brain tumors) blocks tumor formation and progression. In addition, using gene therapy to remove Olig2 caused the proneural cancer cells to become more like “classical” glioma cells resembling astrocytes, which produce high levels of epidermal growth factor receptor (EGFR). This protein is a common and effective target for chemotherapy drugs used to treat breast cancer and other malignancies. Using the drug gefitinib to block EGFR in mouse models, Lu and his collaborators were able to halt the brain cancer.

The researchers stress that a great deal of additional study and testing will be required before this therapeutic strategy can be transitioned to clinical use. Still, the findings do reveal a possible gap in the molecular armor of this deadly brain cancer, Lu says.

**‘INTERESTING’ FINDING DRAWS COMMENTARY**

The May 2016 study by Qing Richard Lu and his colleagues in *Cancer Cell* was significant enough to be the subject of a commentary featured by the journal.

The commentary was written by Rebecca Ihrie, PhD, and Nalin Leelatian, MD, two cancer biology researchers from the Vanderbilt University School of Medicine.

“Interestingly (the study) provides insight into a potential mechanism of molecular subclass shift from proneural to classical glioblastoma, as well as an experimental paradigm that enables further exploration of how tumor phenotypes may evolve during treatment,” they wrote.

The commentary also states that Lu’s study and others that might build upon its findings represent “exciting steps toward identifying, restricting, and killing elusive cell populations that make up this deadly tumor.”

Previous Page: Qing Richard Lu, PhD, lead investigator and scientific director of the Brain Tumor Center at Cincinnati Children’s
The most exciting new cancer-fighting technology in decades has been hiding right inside of us — our own immune systems.

Researchers have suspected for decades that tapping the body’s natural defense mechanism against disease might be a way to slow or stop cancers. A major challenge has been that cancer cells evolve and develop molecular means to evade the immune system.

Now researchers at Cincinnati Children’s — and elsewhere — are testing sophisticated new therapies that overcome these evasive maneuvers against a broad range of pediatric cancers. One immunotherapeutic involves engineered T-cells, hybrid tracking-killing machines that cancers cannot evade. Another involves tweaking the immune system, researchers are also maintaining a careful watch to make sure these therapies do not trigger autoimmune responses in already sick children.

The potential to make a difference is leading to a closer, more formalized collaboration between the Division of Immunobiology and the Cancer and Blood Diseases Institute. Several joint projects in basic and clinical research are underway, according to James Geller, MD, and Edith Janssen, PhD.

“Immune checkpoint inhibitors literally sever the messages to T-cells telling them to go their merry way,” explains Janssen. “But generating an immune response upon destruction of the targeted tumor should allow the elimination of metastases and prevent recurrences. We want to test this.”

And because immunotherapy for cancer involves tweaking the immune system, researchers are also maintaining a careful watch to make sure these therapies do not trigger autoimmune responses in already sick children.

On the clinical side of research, Cincinnati Children’s is leading several multi-center clinical trials that explore immune checkpoint inhibition. One study involves anti-PD-1 therapy, the other focuses on anti-CTLA therapy. Already approved for treating adult solid tumor cancers, these checkpoint inhibitors need to be tested on a wide range of pediatric tumors, according to Geller.

“FROM A BIOMEDICAL AND THERAPEUTIC STANDPOINT THIS IS ONE OF THE MOST IMPORTANT THINGS TO HAPPEN IN CANCER.”

James Geller, MD, and Edith Janssen, PhD, are leading projects to develop ways to harness the immune system to fight cancer.

HEAL THYSELF! Harnessing the Weapon Within to Fight Cancer

by Nick Miller

TO BUILD THE PERFECT T-CELL

Some clinical trials have begun to test the ability of engineered T-cells to target aggressive and treatment-resistant pediatric leukemia and other non-solid tumors. These chimeric antigen receptor (CAR) T-cells, are designed to take advantage of what has been a particular strength of treatment-resistant cancers.

Their tendency to frequently mutate helps these cancers evade treatment, but also constantly generates new proteins. This helps distinguish them from normal healthy cells, and thus makes them detectable to the right type of weapon, Singh says. CAR T-cells are made by using an engineered virus to train a patient’s own T-cells to express a molecule linked to certain types of B-cell blood cancers. This gives the T-cells the ability to track and attack a previously well-hidden enemy.

“Essentially it is a hybrid T-cell that burrows the best part of a B-cell receptor, making it exquisitely specific for certain cancer cells,” says Singh. “Then the T-cell part works in killing the cancer cell.”

In some children, checkpoint inhibitors have shown some positive therapeutic response. But testing remains too preliminary to draw firm conclusions.

“It doesn’t always work, and sometimes it does, but it’s also a tool that does not need to be used in isolation,” says Geller, medical director of the Liver and Kidney Tumors Program.
Cancer researchers here have more than 100 reasons for seeing a new horizon in personalized treatment for children with high-risk and relapsed cancer.

Each of those reasons is reflected in a mouse “avatar,” carefully engrafted with the cancer cells from children whose leukemia cells have been sequenced.

These mice serve as living test platforms, allowing scientists at Cincinnati Children’s to add a new level of precision for determining which treatments are most likely to work against cancers carrying particular genetic mutations.

Since launching the initial research phase of the avatar program in 2015, the team has developed lines of mouse avatars that mimic more than 100 children’s cancers, primarily from patients who developed hematologic cancers such as acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL).

“When you’re down to the level of the genetic mutations that drive the formation of these leukemias, you see that each patient is unique,” says Ben Mizukawa, MD. “If a cluster of avatars share a common mutation or pathway that can be dysregulated, you can test drugs against those specific targets and learn to predict which therapies are likely to succeed in clinical trials.”

He and Jim Mulloy, PhD, both of the Cancer and Blood Diseases Institute (CBDI), are the principal investigators on the avatar project, which involves a group of about 25 collaborators, including clinicians, genomics technicians and experts in biomedical informatics.

Since 2015, the avatar program has developed lines of mice that mimic the cancers of more than 100 children.
HOW THE ENGRAFTMENT PROCESS WORKS

Researchers retrieve cancer cells from patients who have:

A. been diagnosed but not yet begun initial intense rounds of chemotherapy, or,
B. have refractory disease that does not respond to chemotherapy, or,
C. have relapsed disease after being in remission for some time.

After studying the cells’ molecular makeup, gene expression and proteins, the team grows the cells in the avatar and analyzes the effectiveness of different treatment options.

Researchers still face numerous obstacles. Engraftment of the cancer cells fails 25 percent of the time. As a heterogeneous disease, cancer presents something of a moving target.

Scientists envision that one day avatars will help them identify molecular subgroups that show exceptional responses — or just as importantly, drug resistance and toxicity.

The team is also still studying why engraftment works better with aggressive blood cancers than non-aggressive types like myelodysplastic syndromes (see page 20). They’ve also yet to engraft “solid tumors” such as brain tumors, neuroblastoma and sarcoma as part of their program.

“That,” Mulloy says, “is on the horizon.”

Right: Ben Mizukawa, MD, and Jim Mulloy, PhD, both of the Cancer and Blood Diseases Institute, are the principal investigators on the avatar project.
The drug lenalidomide — a safe derivative of the infamous thalidomide that caused horrific birth defects a half-century ago — turned out to be a curiously effective fighter of certain blood malignancies.

But in the case of bone marrow disorders called myelodysplastic syndromes (MDS), researchers did not fully understand the mechanisms of its imperfect success. Or how to improve on it. That just changed in several unexpected ways, thanks to a team of scientists at Cincinnati Children’s.

In a study published online June 13 in *Nature Medicine*, researchers detailed a complex interaction involving a calcium- and calpain-dependent pathway and the disease’s progression. Lenalidomide, it turns out, kills mutation-bearing MDS cells by increasing expression of the G-protein-coupled receptor GPR68. This increases intracellular calcium concentrations and activates the protein calpain. Mystery solved.

“That was unexpected,” says senior author Dan Starczynowski, PhD, Division of Experimental Hematology and Cancer Biology. “There were a couple of ‘ah-hah’ moments. That was one.”

Understanding how the drug works could help clinicians maximize the potential of drug combinations currently in use, and minimize the toxicity and other adverse effects that occur frequently when treating MDS patients. As a group, these bone marrow disorders are primarily a function of aging. The overwhelming majority of MDS patients are older than 65. With MDS, bone marrow begins producing insufficient numbers of healthy blood cells, which can be fatal. “The nature of the disease is very different for kids, and is much more complicated,” Starczynowski says.
The mechanisms behind lenalidomide sensitivity in patients with MDS

When other serious illnesses take hold, MDS is one of the most common hematologic malignancies in the aging population. Pediatric care for MDS is complicated by the fact that it typically occurs with congenital disorders, such as Fanconi anemia and Schwachman-Diamond syndrome, or after chemotherapy or radiation to treat an unrelated cancer. So children's systems are already under siege when MDS takes hold, fueled by a genetic predisposition to blood disorders.

Starczynowski’s study was primarily focused on adult MDS but could be instrumental in improving pediatric care if researched. “We need to figure out how the mechanisms differ between adults and children.” If left untreated, MDS leads to acute myelogenous leukemia (AML) in about 30 percent of pediatric cases. AML, a fast-growing cancer of the bone marrow cells, kills 10,430 people a year, nearly all of them adults, according to the American Cancer Society.

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The crucial role of calcium-dependent calpain activity

The mechanisms behind lenalidomide sensitivity in patients with MDS

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“Part of it is understanding the gene-regulatory networks that govern the cancers. Through them, we can find the Achilles’ heels that make the cells vulnerable.”

MOUSE AVATARS

Serve as key collaborators

The team was assisted by mouse avatars, implanted with MDS cells. A lot of people are working on this and I imagine we will be able to move on to treating children’s cancers in the next few years.”

Keywords

MDS, mouse avatars, personalized medicine

The multi-step pursuit of MDS solutions

For Dan Starczynowski and colleagues, the nature medicine study is the latest in a series of high-impact papers on MDS.

Their work also includes:

• A 2015 study in *The Journal of Experimental Medicine* that explored how an uncharacterized del(5q) MDS gene, TIFAB, alters hematopoiesis through signaling depression of innate immune signaling pathways.

• A 2014 study in *Cell Report* that described the first pre-clinical model using MDS cell line for novel drug studies.

• A 2013 study in *Leukemia* that analyzed a novel therapeutic approach that targets a protein-coding gene called IRAK1.

Next-generation sequencing is routine in cancer drug studies.
Building a new cancer care center at our Liberty Campus involved quite a bit more than walls and wires. Our planning also strived to incorporate an atmosphere of innovation into nearly every activity occurring within the building, right down to how doctors explain cancer to kids.

“As we take care of the toughest cases, we employ all the latest technologies from proton therapy to immune therapy to genomic-guided precision medicine,” says John Perentesis, MD, Co-Executive Director of the Cancer and Blood Diseases Institute at Cincinnati Children’s. “Likewise, we expect our facility to offer an excellent experience for patients and families.”

To that end, Cincinnati Children’s partnered with the Live Well Collaborative, a non-profit product and service research program launched in 2007 by the University of Cincinnati (UC) and Procter & Gamble. Its work with Cincinnati Children’s involves more than a dozen projects, including several focused on cancer care.
WHAT’S NEXT? Teams will collect data to analyze how these innovations affect outcomes and satisfaction. The most successful ideas will be rolled out to the rest of Cincinnati Children’s. Eventually, some concepts may be offered as potential national models for improving care.

DIGITAL THERAPY PROTOCOL CALENDAR: Staff members currently devote many hours to providing families with personalized calendars that spell out the details of complex treatment regimens. Schedule adjustments, which occur frequently, can require time-consuming re-writes. A Live Well team produced a digital alternative that saves time by automatically adjusting the rest of the calendar when changes are inserted.

HEALTHY REWARDS SYSTEM: This initiative digitizes a paper-based “1-2-3 Initiative” developed by Christopher Dandoy, MD. A wall-mounted device used in combination with an RFID decal worn on a hospital band will track desired behaviors during inpatient stays. Children can collect reward points for showering daily, rising from bed at least twice daily, and brushing their teeth three times a day.

LIBERTY CAMPUS VIRTUAL TOUR: Children and parents soon will be able to take a virtual reality video tour using their own laptops or smartphones, even before setting foot in the new center.

EDUCATIONAL VIDEOS: Animated, sharable, patient-friendly videos focus on topics including the basics of leukemia, the importance of supplemental tube feeding, the relationship between nutrition and cancer therapy, and options for fertility preservation. The videos were created to help make information about complex topics more accessible and increase the health literacy of adolescent cancer patients and their families. Live Well has produced six videos so far.

HOME MONITORING: We are adopting a remote care system to deliver temperature, blood pressure and other vital signs data from home to hospital staff. The system prompts rapid intervention at the earliest signs of infection and other complications.
Raouf Amin, MD, Pulmonary Medicine, will study the impact of treatment of mild sleep-disordered breathing with a $1.1 million grant from the National Heart, Lung, and Blood Institute.

Bruns Blaxall, PhD, Heart Institute, was awarded a four-year, $1.67 million grant from the National Heart, Lung, and Blood Institute to study targeted signaling in fibrin remodeling.

James Bridges, PhD, Perinatal Institute, will study the role of the GPR16 signaling pathway that controls alveolar homeostasis, or self-regulating process, using a five-year, $2 million grant from the National Heart, Lung, and Blood Institute.

Jeff Epstein, PhD, Behavioral Medicine and Clinical Psychology, received a five-year, $3.4 million grant from the National Institute of Child Health and Human Development, to explore ways to improve the driving skills of teens with ADHD.

Stuart Goldstein, MD, Nephrology, received a four-year, $1 million grant from Innovative Biotherapies, Inc, to study a selective cytopheretic device for the treatment of acute kidney injury.

Christina Gross, PhD, Neurology, received a four-year, $1.9 million grant from the National Institute of Neurological Disorders and Stroke, to study MicroRNA-mediated silencing of the Kv4.2 complex in epilepsy patients.

Michael Helmrath, MD, Pediatric General and Thoracic Surgery, will study the regional identity of human intestinal stem cells, with a five-year, $2.5 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

Gurjit Khurana Hershey, MD, PhD, Director, Asthma Research, received a two-year, $1 million grant from the Ohio Children’s Hospital Association for her work on its asthma task force.

Eileen King, PhD, Biostatistics and Epidemiology, received a four-year, $19.2 million grant from the National Heart, Lung, and Blood Institute for her research with the agency’s Administrative Coordinating Center: Cardiovascular Development and Pediatric Cardiac Genomics Consortia.

Raphael Kopan, PhD, Director, Developmental Biology, will study the mechanism that regulates renal progenitor aging, using a four-year, $2.5 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

Carole Lannon, MD, MPH, James M. Anderson Center for Health Systems Excellence, received a five-year, $1.7 million grant from the Health Resources and Services Administration for her work with the Autism Treatment Network, a collaboration of Autism Speaks and pediatric hospitals.

Yu Li, PhD, Radiology, will study real-time pediatric cardiovascular MRI without breath-holding, using a four-year, $1.4 million grant from the National Institute of Biomedical Imaging and Bioengineering.

Tesfaye Mersha, PhD, Asthma Research, received a five-year, $3.4 million grant from the National Heart, Lung, and Blood Institute to study the interactions of ancestry and environmental exposure in childhood asthma.

Sean Moore, MD, MS, Gastroenterology, Hepatology and Nutrition, will study environmental enteropathy and malnutrition using a four-year, $4.4 million grant from the Bill & Melinda Gates Foundation.

Louis Muglia, MD, PhD, Co-Director, Perinatal Institute, received a one-year, $2 million grant from the March of Dimes for his leadership role with its Cooperative Multicenter Neonatal Research Network.

Brenda Poindexter, MD, MS, Perinatal Institute, received a five-year, $1.4 million grant from the National Institute of Child Health and Human Development, for her work with its Cooperative Multicenter Neonatal Research Network.

Joseph Palumbo, MD, Hematology, received two five-year, $1.8 million grants from the National Cancer Institute. He will study hematopoietic factors that drive the development of prostate cancer, and the modifying factors of coagulation in colon cancer.

Brenda Poindexter, MD, MS, Perinatal Institute, received a five-year, $1.4 million grant from the National Institute of Child Health and Human Development, for her work with its Cooperative Multicenter Neonatal Research Network.

Cincinnati Children’s Joins Bench to Bassinet Program

Thanks to a $32.5 million, five-year grant from the Bench to Bassinet Program of the National Institutes of Health (NIH), researchers here will help determine why children are born with heart problems.

Cincinnati Children’s will serve as administrative coordinating center for the program, ensuring transfer of promising research from the laboratory to the clinic. We will also be the hub for more than 150 terabytes of molecular data to be shared by the cardiac research community.

Eileen King, PhD, Biostatistics and Epidemiology, and Peter White, PhD, Director, Biomedical Informatics, are co-principal investigators for the project, which the NIH launched to accelerate pediatric cardiovascular research from the laboratory to the clinic.

To date, the Bench to Bassinet Program has collected clinical, environmental, and genomic data for more than 10,000 children with heart defects through a collaboration involving nine academic health centers.
Keri Drake, MD, shares the latest in kidney development at the Pediatric Academic Societies meeting.

Robert Kahn, MD, MPH, is the Fellowship Director for Sports Medicine and has been awarded the 38th Louis Molkentin, PhD, Molecular Cardiovascular Biology, Section of the American Physical Therapy Association and the Kappa Delta Occupational Therapy and Physical Therapy, prestigious honors: the Excellence in Research Award from the Sports Medicine. Ruddy now serves as medical director of our Liberty Campus.

Andrew Lindsley, MD, PhD, Allergy and Immunology and Asthma Research, has received a Faculty Development Award from the American Academy of Allergy, Asthma & Immunology Foundation.

Kelsey Logan, MD, MPH, Director, Sports Medicine, was elected to the Board of Directors of the American Medical Society for Sports Medicine.

Monica Mitchell, PhD, Behavioral Medicine and Clinical Psychology, was awarded the Society of Pediatric Psychology's Award for Distinguished Contributions to Diversity in Pediatric Psychology.

Jeffrey Anderson, MD, MPH, Heart Institute, has been awarded the Paul V. Miles Fellowship from the American Board of Pediatrics.

Keri Drake, MD, Nephrology, received a Fellows' Basic Science Research Award from the Society for Pediatric Research. In May, she presented an abstract of her latest work in kidney development at the annual Pediatric Academic Societies meeting.

Paul Guberman, MD, MPH, Fellowship Director, Sports Medicine, was elected chair of the 2016 Fellows' Conference for the American Medical Society for Sports Medicine.

Robert Kahn, MD, MPH, General and Community Pediatrics and Adrienne Heinze, JD, Program Manager, Child HeLP, received the Outstanding Medical-Legal Partnership Award from the National Center for Medical-Legal Partnerships, in recognition of the successful Child HeLP program at Cincinnati Children's.

Melissa Klein, MD, MEd, Director, General Pediatric Master Educator Fellowship, recently received the Academic Pediatric Association's 2016 Faculty Teaching Award for mid-level faculty. Klein's scholarly career focuses on educating others about the impact of the social determinants of health on children.

Aronow Receives New Hutton Chair

Bruce Aronow, PhD, Biomedical Informatics, is the first recipient of the new John J. Hutton, MD, Chair for Biomedical Informatics at Cincinnati Children's. Hutton, Aronow and John Pestian, PhD, helped found the Division of Biomedical Informatics here. Aronow's groundbreaking work in computational biology includes working with colleague, Anil Jegga, DVM, to develop the ToppGene Suite, a tool used by thousands of scientists worldwide to identify new molecular functions and gain insights into disease processes.

Aronow Receives New Hutton Chair

Bruce Aronow, PhD

Porter to Lead Emergency Medicine

Stephen Porter, MD, returned to his hometown in June to become director of the Division of Emergency Medicine at Cincinnati Children's. He succeeds Richard Ruddy, MD, who spent 24 years leading Emergency Medicine. Ruddy now serves as medical director of our Liberty Campus.

Porter grew up in the Cincinnati suburb of Terrace Park and earned his medical degree from the UC College of Medicine in 1993. "As a native son, I've always kept my eye on Cincinnati Children's," Porter says. "Even from hundreds of miles away, the excellence has been very clear — the spirit of collaboration, improvement and clinical expertise."

Porter completed his residency at the Children's Hospital of Philadelphia, his fellowship at Boston Children's, and has earned two master's degrees. He served on the faculty at Harvard for 15 years until 2010, when he left to direct pediatric emergency medicine at The Hospital for Sick Children in Toronto.

Aronow Receives New Hutton Chair

Bruce Aronow, PhD

Porter to Lead Emergency Medicine

Stephen Porter, MD
A 90-ton cyclotron and a 100-yard beam line (shown here) produce and guide the proton particles that will be used to treat children at the new Proton Therapy Center.

Oct. 6, 2016
at the Northern Kentucky Convention Center

Clinical investigators, research support staff, research sponsors, contract research organizations, government regulators, and others are invited to hear top speakers in the field discuss the latest issues regarding the protection of human subjects.

* Includes material, CME and CEU credit, meals and refreshments.
* An early registration discounted rate of $125 is available to employees of the following co-sponsors: UC, UK, and Cincinnati Children’s. This early registration discount ends Sept. 8.
* Registration ends Sept. 29. All payments are non-refundable.

To register online, visit www.cincinnatichildrens.org/cme and click the “Continuing Education Portal” link.
Questions? Please email hspconference@sairb.com or contact Angela Kovatch, 513.761.4100.

COST: $175

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