RESEARCH HORIZONS

A Publication of the Cincinnati Children's Research Foundation

FALL 2016

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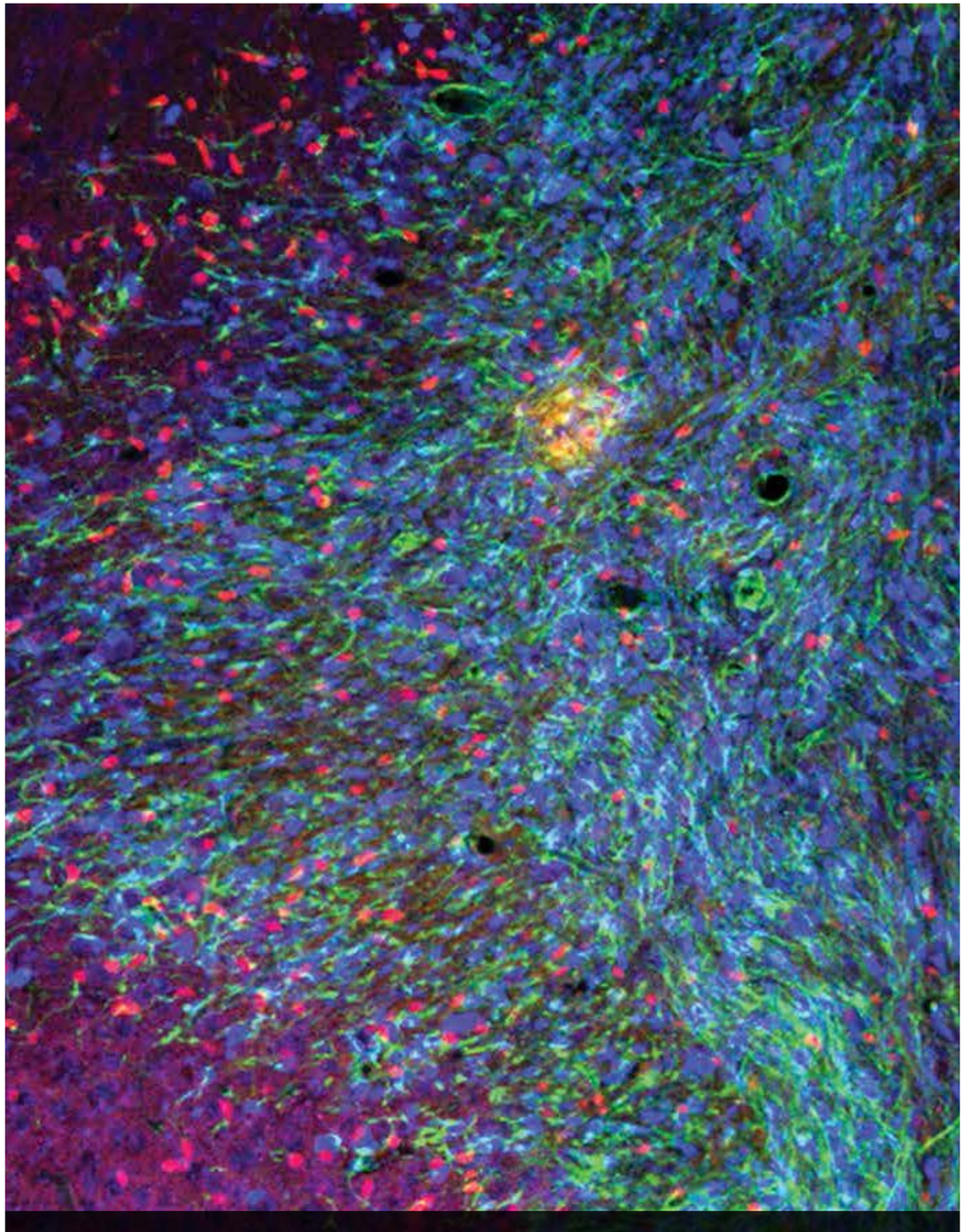
changing the outcome together

Advancing Cancer Care

Taking on the Toughest Cases



This confocal microscope image shows brain cells from adult mice expressing the protein Olig2 (shown in red). Turn to page 12 to read more about how researchers at Cincinnati Children's discovered that inhibiting Olig2 appears to make aggressive, high-grade gliomas significantly more sensitive to treatment.

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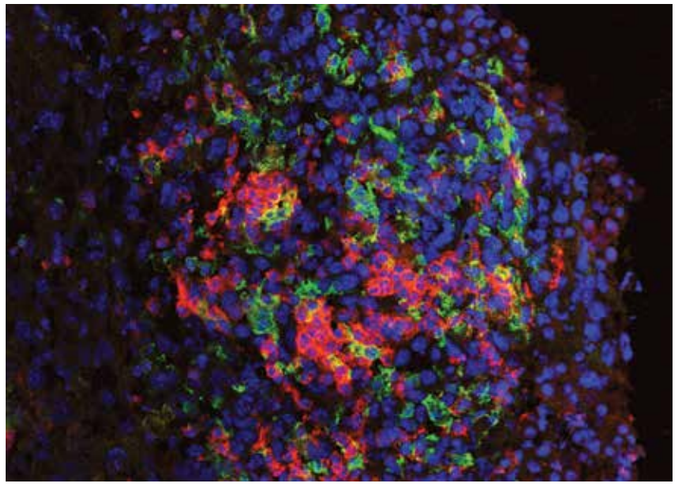


FALL 2016 | Advancing Cancer Care

Cover Image: Exploring the mechanisms of brain tumor formation represents one of several initiatives at Cincinnati Children's to advance cancer research. This computer-enhanced image of a glioblastoma comes from research led by Biplab Dasgupta, PhD, MS.

Fouladi Joins Cancer Moonshot

Read more about Fouladi's brain tumor research.

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.

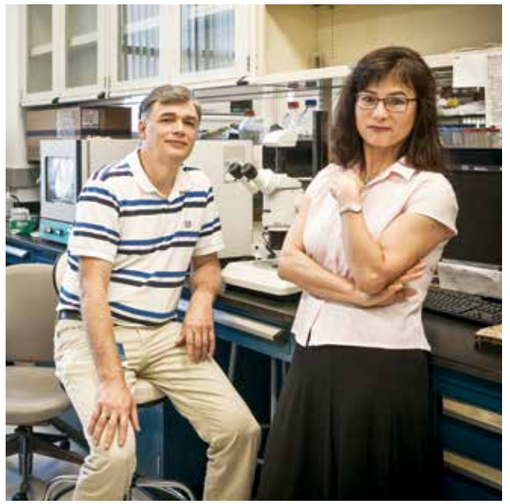
The National Cancer Institute (NCI) has assembled a blue ribbon panel and related working groups to provide expert advice on the vision, proposed scientific goals, and implementation of the National Cancer Moonshot. The panel will use input from the working groups to make recommendations to the NCI director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

"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

Drug Reverses Lung Damage in Mice



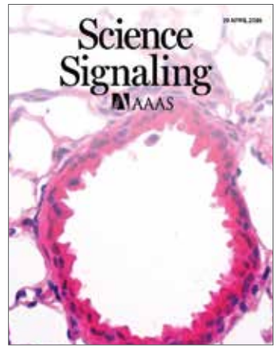
An image from breakthrough lung injury research led by Drs. Kalinichenko and Kalin was featured on the cover of *Science Signaling* (right). Their study identifies a promising compound that could promote lung tissue recovery.

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*.

The algorithm is not yet ready for clinical use, but eventually may help some studies make faster progress while reducing the need to close studies when too few people participate.

Yizhao Ni, PhD

Can Children With EoE Avoid the Endoscope?

Patricia Fulkerson, MD, PhD

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."

Obesity Can Be Predicted At 6 Months

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.

Allison Smego, MD

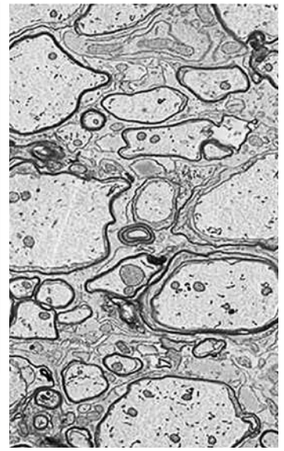
Study Finds a Key Gene Linked to Myelin Production

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."

Qing Richard Lu, PhD



New Model Offers Insights to AML

H. Leighton Grimes, PhD

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.

Studies Stress Need for Careful Screening of iPSCs Before Clinical Use

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.

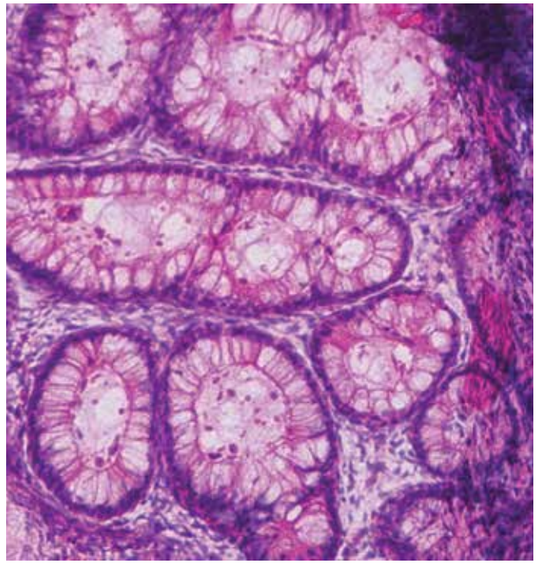
A multi-institutional study appearing June 9 in *Stem Cell Reports*, and led by Cincinnati Children's, found that about 30 percent of tested iPSCs were genetically unstable and otherwise not safe for clinical use. The study analyzed 58 different lines of iPSCs submitted by 10 different research institutions.

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.

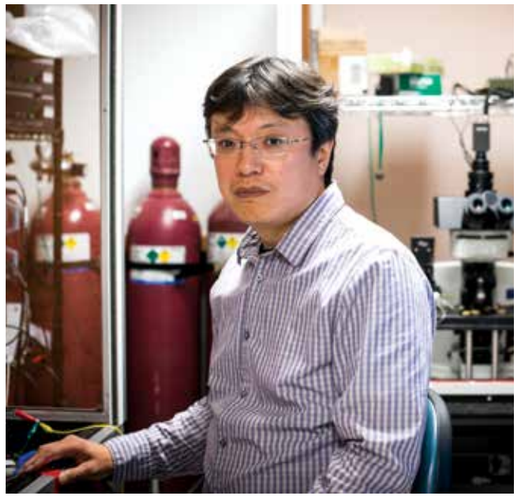
A second study, published April 14 in *Cell Stem Cell,* reports iPSC lines intended for therapeutic use should be screened for age-dependent accumulation of mutations in the mitochondrial genome and DNA – which support energy production and other basic cell functions.

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.



Carolyn Lutzko, PhD, led a multi-center study to help define best practices for producing stem cells for clinical use. The team generated benign teratomas (above) to study how well induced pluripotent stem cells transform into specific tissue types.

New Path to Halting Deadly Infections After Spinal Cord Injury



Yutaka Yoshida, PhD

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.

"Those infections are the leading cause of death for people with spinal cord injuries," adds Yutaka Yoshida, PhD, from Cincinnati Children's Division of Developmental Biology.

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.

How to Stop EoE Tissue Damage? Target Calpain 14

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.

Marc Rothenberg, MD, PhD

TINY PARTICLES

Big Medicine

New Proton Therapy Center Will Transform Cancer Care, Trigger a Wave of Discovery

by Tim Bonfield

Abram Gordon, Executive Director of the Proton Therapy Center, has overseen the complex process of building and preparing the center for service.

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.

"This center will become a national anchor for particle-based cancer research," says John Perentesis, MD, Co-Executive Director, Cancer and Blood Diseases Institute. "The capabilities of this facility will bring together collaborators from a wide realm of expertise – including investigators from outside Cincinnati Children's – whose work will take proton therapy to a new level."

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 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.

"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.

FINE TUNING AN EMERGING TOOL

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

"There is still so much we do not yet understand about the biological effects of proton therapy," Perentesis says.

Susanne Wells, PhD, directs the Epithelial Carcinogenesis and Stem Cell Program at Cincinnati Children's. She is part of a growing team of experts from Cincinnati Children's and the University of Cincinnati (UC) who are launching proton-related research projects.

"We want to be as sophisticated as possible in making use of the tremendous resources that we have," Wells says. "We are employing genomics, metabolomics and other large-scale approaches to get down to the details of proton radiation biology. All of these aspects have been vastly understudied in comparison to conventional photon radiation."

AN AMBITIOUS AGENDA

Research planned for the Proton Therapy Center will follow several tracks, including:

Basic biological research: How exactly do protons kill cancer cells? Scientists have long studied how ionizing radiation from photons disrupts DNA and causes cell death. But few have yet taken deep dives into the genetic and molecular pathways that protons can affect.

The scientific literature already reports, for example, that RNA responses differ when a cell is radiated with photons, protons or carbon ions. This has potential far-reaching implications for determining the most effective doses for specific types of cancer occurring in specific types of tissue.

One of several projects seeking to shed light along these lines will involve isolating cancer stem cells from the rest of

"The capabilities of this facility will bring together 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

a tumor, then testing that population's reaction to proton vs. photon radiation.

Applied research and development: Currently, proton devices magnetically bend proton streams into pencil-like beams that can paint a tumor, layer by layer, with tiny bursts of radiation. The cell-killing damage can be confined to less than a millimeter of tissue.

Yet as impressive as that may be, even more precision is desired. When patients receive as many as 40 treatment sessions across several weeks, a variety of critical events can occur. Children grow. People lose or gain weight. The tumor itself can shift – and hopefully – shrink as treatment progresses, being replaced by healthy tissues.

The research gantry at Cincinnati Children's will serve as a real-world test platform for evaluating imaging methods, computer targeting technologies, patient positioning techniques, and more. The goal: improve treatment plans created and updated at specific points in time into an even more flexible approach that keeps constant precise track of the size and location of a tumor.

Translational research: A major goal for proton research here is to develop and refine radio-sensitizing treatments that can augment proton therapy. These are drugs that can be given in conjunction with radiation treatments that increase the likelihood of cell death when hit by radiation. A number of such agents already exist, but their effects can vary with the types of cancer and radiation source, and few of these properties have been documented for children.

How proton therapy can work best in conjunction with evolving chemotherapy regimens and emerging immune therapy approaches remains to be explored. Engineering experts at UC are especially interested in exploring nanoparticles that could make it easier to target cancer cells or fortify healthy tissues near a tumor site.

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.

"Ultimately, the clinical goal is to figure out which people will be most responsive to proton therapy," Wells says. "What tumors, which individuals will benefit the most?" ■

PROTON THERAPY

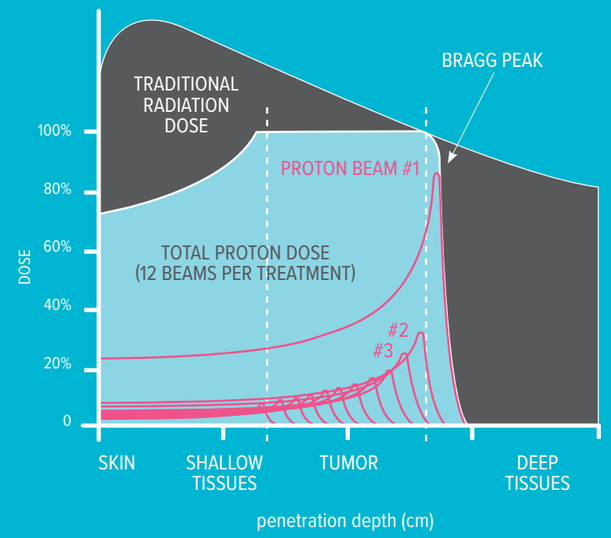
Types of Cancer Well Served by Proton Therapy:

Ewing's Sarcoma
Hodgkin Lymphoma
Neuroblastoma
Non-Hodgkin Lymphoma
Pediatric Brain Tumors
Rhabdomyosarcoma
Soft Tissue Sarcomas

80% of children with cancer who need radiation therapy at Cincinnati Children's will receive proton therapy.

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.

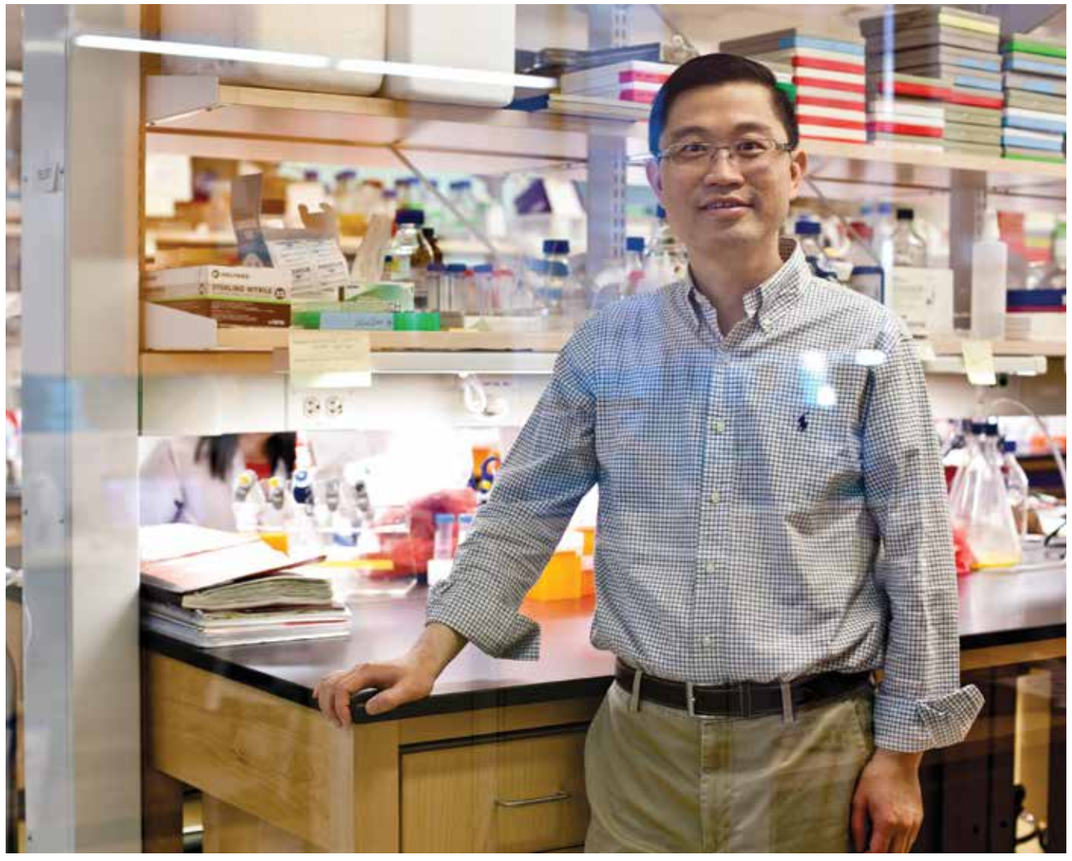


1/3 of conventional radiation dose winds up in healthy tissue.

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

Proneural 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. ■

Previous Page: Qing Richard Lu, PhD, lead investigator and scientific director of the Brain Tumor Center at Cincinnati Children's

'INTRIGUING' 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.

"Intriguingly (the study) provides insight into a potential mechanism of molecular subclass shift from proneural to classical glioblastoma, as well 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."


Cancer Cell
Previews

Head of the Class: OLIG2 and Glioblastoma Phenotype

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

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 approach involves a new class of cellular therapies that can block immune checkpoint inhibition — a braking mechanism in the immune system that researchers have learned cancer cells hijack to avoid detection.

"From a biomedical and therapeutic standpoint this is one of the most important things to happen in cancer," says Harinder Singh, PhD, Director of the Division of Immunobiology at Cincinnati Children's.

Immunotherapy is not considered a cure-all solution. Instead, it could become a potent new weapon in combination with radiation, chemotherapy, proton beams and high-intensity ultrasound.

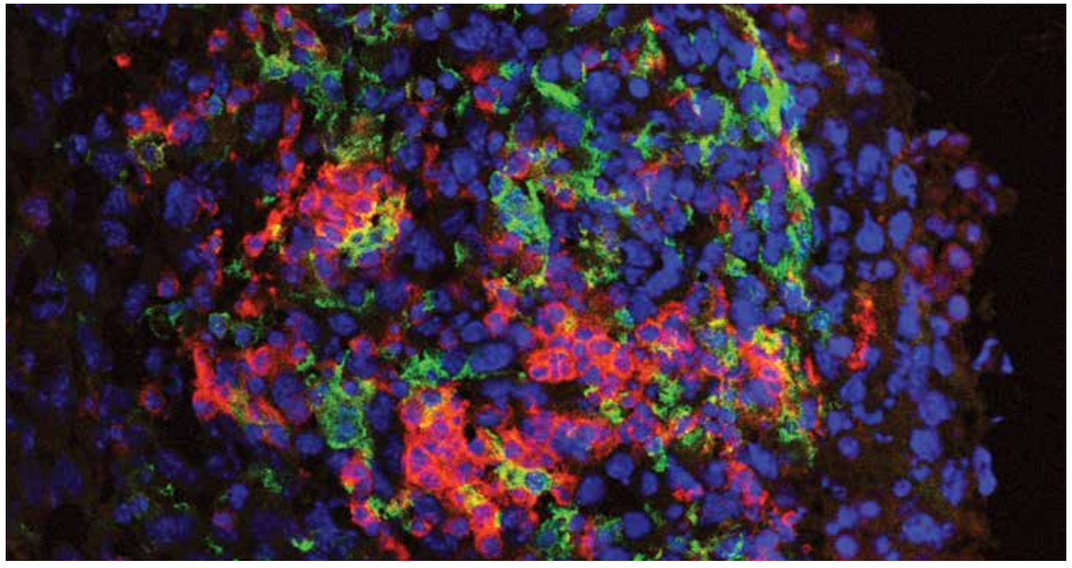
"There was a lot of frustration 10 years ago," recalls Singh. "We had a war on cancer, we had invested tremendous resources, we made great progress in understanding cancer mechanisms, but therapeutically we were still stuck. Then we got smarter and developed targeted molecular therapies. Unfortunately cancers mutate and learn to evade targeted therapy. Now we see indications that combining targeted therapies and others with emerging immunotherapies may bring the next generation of cures for all kinds of cancers."

NEW COLLABORATIONS TO EVALUATE A NEW APPROACH

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.

Geller, a pediatric oncologist here, and Janssen, an immunobiologist, are assembling a collaborative research structure as teams expand efforts to develop deeper understanding of how the immune system can be harnessed to battle malignant disease.

Some research projects explore how cancer treatments — ranging from chemo to proton therapy —affect the immune system and the patient. Janssen is particularly interested in studying how the immune system reacts after a proton beam or high-intensity ultrasound wave zaps a tumor.



This confocal microscope image shows immune system dendritic cells and macrophages (highlighted in red and green) invading a tumor in the skin of a mouse.

"These treatments target the tumors locally but any metastases that are not in the treatment field will be unaffected and keep growing," Janssen explains. "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."

HOW TO HEAD OFF A HIJACKING

The body uses immune checkpoints to prevent T-cells and their allies — which exist to find and destroy viruses and other pathogens — from attacking the body's normal healthy tissues. But cancer cells hijack this process to avoid detection, using the proteins PD-1 and CTLA-4 to send these messages.

"These proteins on the outside membranes of the cells send messages to T-cells telling them to go their merry way," explains Geller. "Immune checkpoint inhibitors literally sever the message that tumors send, allowing the immune system to react to the tumor in a way it otherwise could not."

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.

TO BUILD THE PERFECT T-CELL

Some clinical trials have begun to test the ability of engineered T-cells to treat 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 borrows 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." ■

Mice As Mirrors

Avatars Provide Unique Window Into the Crucial Pathways Connecting Each Patient's Cancer Cells and Genetic Mutations

by Tom O'Neill

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.

THE TEAM PUTS TRIAL-AND-ERROR ON TRIAL

The program is rooted in the innovative goals of John Perentesis, MD, Co-Executive Director of CBDI.

"John had the foresight years ago to routinely send for genetic sequence testing on cancer patients," Mizukawa says. "So we have hundreds of patients where we can see the

Since 2015, the avatar program has developed lines of mice that mimic the cancers of more than 100 children.

specific gene mutation, and match drug options to it. Traditionally, there was just an empiric approach, very trial-and-error."

Avatars reflect a step beyond the standard method of evaluating human cancer cell lines in culture. Although growing cells in a petri dish can be informative, the process produces limited numbers of cell lines. Such cells also tend to adapt to the culture conditions, acquiring additional mutations to grow, which makes them less like their source over time.

Interestingly, cancer progresses faster in mice than it does in humans, allowing the researchers to test multiple different treatments in an avatar in less time than it would take to test a single treatment in humans.

"Typically, we use drugs that are targeting cells that are growing and dividing quickly," Mizukawa says. "They're not tailored to any particular biology of the cancer cell. With some leukemias, that has worked. Yet others do not respond, or the patient relapses and the tumor becomes harder to treat. There is now more emphasis on predicting who is going to respond well and who needs new approaches."

RESEARCHERS ENVISION MULTIPLE MICE FOR EACH CHILD

Engraftment of as few as 10,000 cells can expand to millions in a mouse, which can then be engrafted into a second-generation of mice that are also genetic mimics of that patient.

"And we're interested to know," Mulloy says, "whether the sub clone that grows out from the minimal residual disease samples is actually the relapse clone that shows up months to years later in the patient."

If the answer is yes, deep sequencing of the clone may answer why it is chemo-resistant, and whether specific mutations might be targets of new therapies. Deep sequencing acquires more information than standard sequencing, and lessens the chance that rare mutations are missed.

For now, data from the avatars are too new to begin guiding patient therapies. 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.

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 make-up, gene expression and proteins, the team grows the cells in the avatar and analyzes the effectiveness of different treatment options.

TRAVELING the Pathways of MDS FOR ANSWERS

Researchers Unlock the Mechanisms Behind Myelodysplastic Syndromes, and Explain Why a Drug with an Unusual Pedigree Makes a Difference

by Tom O'Neill

Dan Starczynowski, PhD

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.

Lenalidomide's Improbable Rise From the Ashes of Medical Tragedy

When Dan Starczynowski, PhD, was a high school kid in Vancouver, he had a book on medical disasters and was taken aback by photos from the 1950s of newborns with ghastly deformities.

"I remember how devastating it was to see babies born with no arms or legs," he recalls.

Thalidomide was prescribed to pregnant women to alleviate morning sickness and anxiety, but scientists were unaware that it could penetrate the placental barrier. It affected 10,000 children around the world, thousands of whom died. Thalidomide survived only as a treatment for leprosy and, in time, as a cancer-fighter.

In 2005, the FDA approved the first analog of the drug, lenalidomide, for blood diseases, for which Starczynowski is a leading researcher.

As for that medical disaster book that so impacted Starczynowski in his youth, he still has it.

PEDIATRIC MDS EMERGES 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 researchers can determine 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. MDS is curable only through a bone marrow transplant.

To understand the mysterious pathways MDS follows, researchers at Cincinnati Children's took a global approach by analyzing all of the approximately 20,000 genes that comprise the human genome.

They started by performing a screen of interfering RNA to delineate gene regulatory networks that might mediate lenalidomide responsiveness in MDS cells. The team also identified a G-protein-coupled receptor pathway, and noted that eliminating it neutralized the cell's response to lenalidomide.

"This is at the heart of trying to understand why this drug works," he says. "With this knowledge, we can identify patients who are receptive to it and also those who are sensitive to it." Researchers also identified a direct link (GPR68) between the enzyme and the calcium pathway, another 'ah-hah' moment. "So we connected a lot of the dots that previously were part of a big black box," Starczynowski says.

MOUSE AVATARS SERVE AS KEY COLLABORATORS

The team was assisted by mouse avatars, implanted with MDS cell lines derived from patients (see page 16). The program is at the forefront of personalized medicine. But there too lies an obstacle. MDS cells engraft, or grow new cells, less efficiently than they do with more aggressive blood cancers, like leukemia.

"We need to figure out how to overcome this limitation," says Jim Mulloy, PhD, of the Cancer and Blood Diseases Institute. He directs the Humanized Mouse Resource Core. "We're having some success with co-injection of supporting human stromal cells. A lot of people are working on this and I imagine we will solve the problem."

Mouse avatars are just one aspect of the science behind personalized medicine, a once futuristic-sounding medical theory.

"I think we're on the cusp of major breakthroughs," Starczynowski says. "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." ■

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 examined how myeloid malignancies with chromosome 5q deletions acquire a dependency on an intrachromosomal gene network.
- A 2014 study in *Leukemia* that described the first pre-clinical model using an MDS cell line for novel drug studies.
- A 2013 study in *Cancer Cell* that analyzed a novel therapeutic approach that targets a protein-coding gene called IRAK1.

NEXT-GENERATION SEQUENCING SHOWS PROMISE

Research at Cincinnati Children's shows that about 50 percent of children with high-risk forms of cancer receiving genomics-guided treatment experienced dramatic tumor shrinkage, compared to just 6 percent of those who did not.

Brian Turpin, DO, Division of Oncology, presented the findings at the 2015 annual meeting of the American Society of Clinical Oncology.

Next-generation sequencing is routine in treating certain adult malignancies, but pediatric research is still emerging. The most common actionable pathways include cell-cycle regulation/DNA repair.

The mechanisms behind lenalidomide sensitivity in patients with MDS

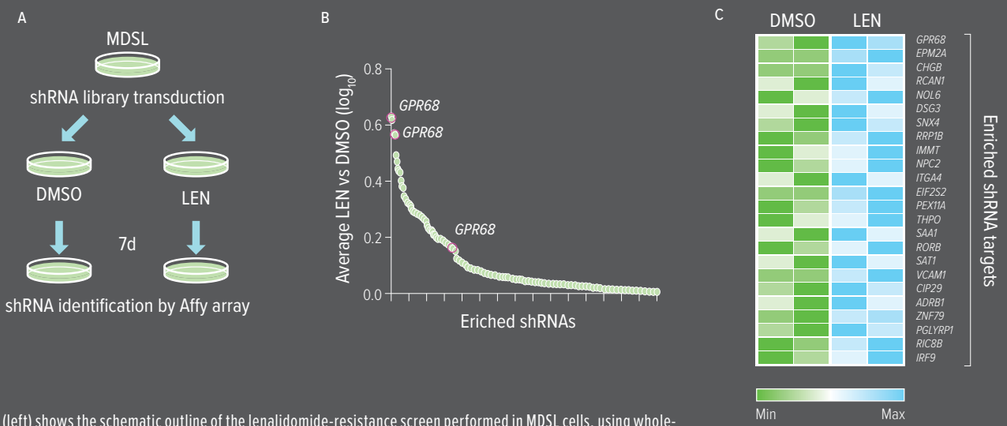


Figure A (left) shows the schematic outline of the lenalidomide-resistance screen performed in MDSL cells, using whole-transcriptome human lentiviral-packaged short hairpin RNAs (shRNA). Figure B (center) shows the ratios for the abundance of individual shRNAs in MDSL cells treated with lenalidomide compared to those treated with dimethyl sulfoxide (DMSO) Each dot represents an enriched individual shRNA. In Figure C (right) enriched shRNAs are shown in a heat map for two independent biological replicates of the RNAi-screen.

The crucial role of calcium-dependent calpain activity

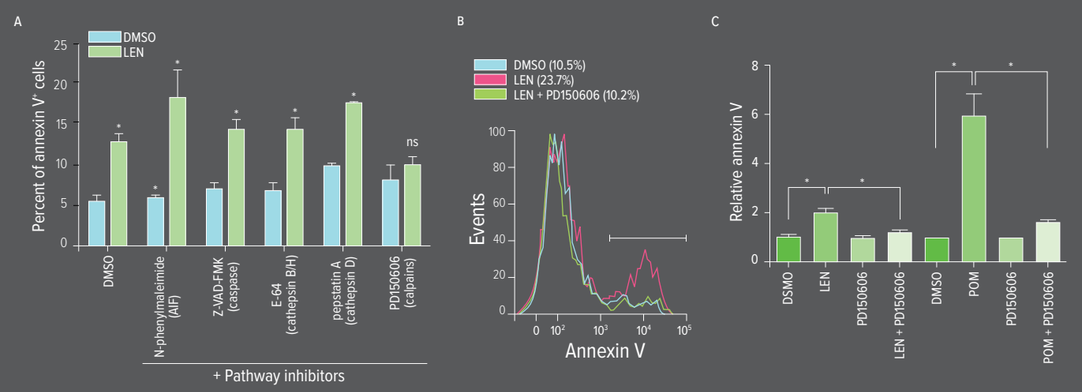
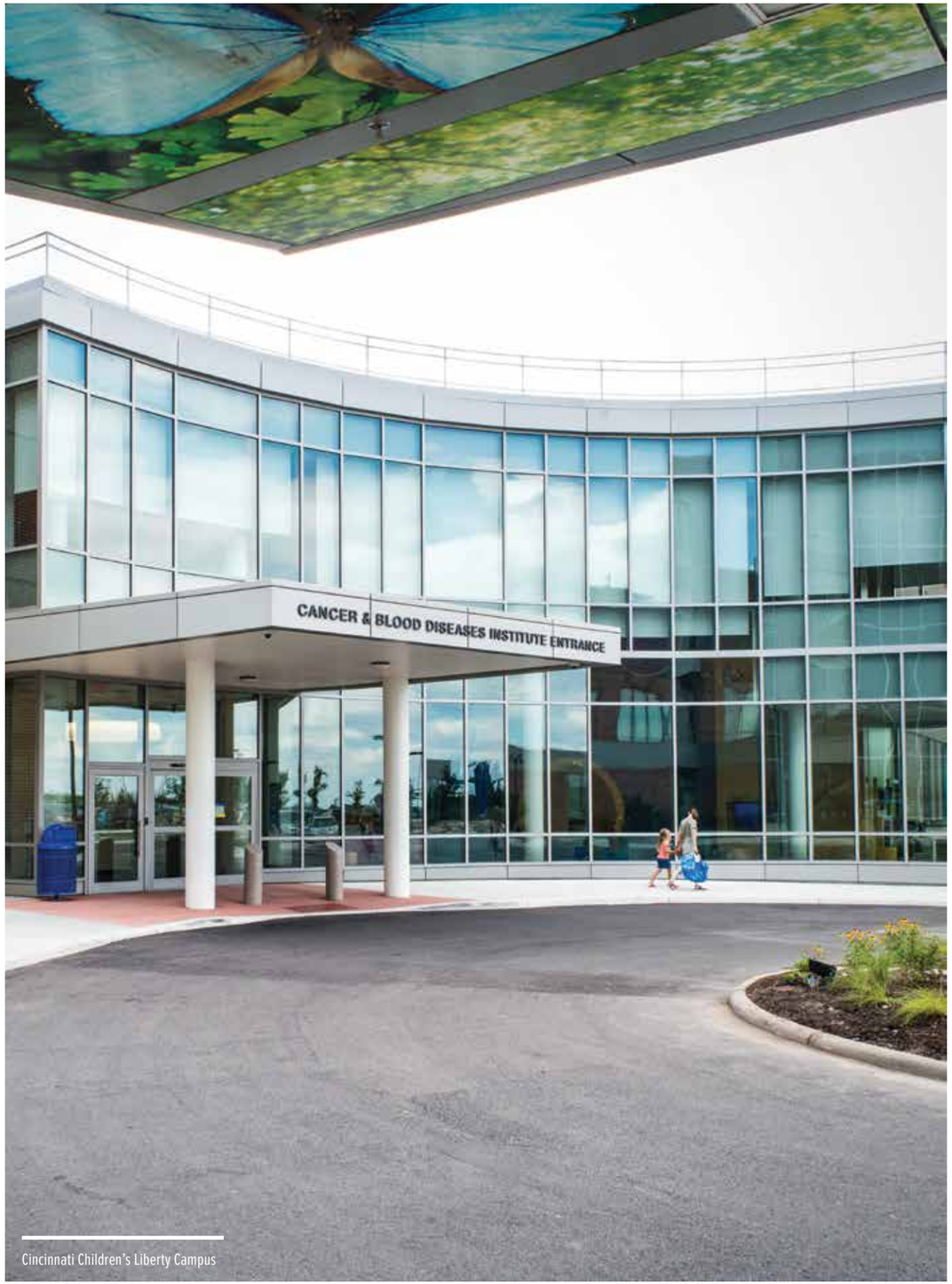


Figure A (left) shows how staining of MDSL cells with cellular protein called annexin V differs in treatment with lenalidomide and dimethyl sulfoxide (DMSO). Figure B (center) represents the histograms of annexin V staining of MDSL cells that were treated with DMSO, lenalidomide or a combination of lenalidomide and a calpain inhibitor called PD150606. Figure C (right) shows the relative levels of annexin V staining of MDSL cells given the different treatment options.



Cincinnati Children's Liberty Campus

BUILDING
AN INNOVATION LAB FOR PEDIATRIC CANCER CARE

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.

by Tim Bonfield

"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.

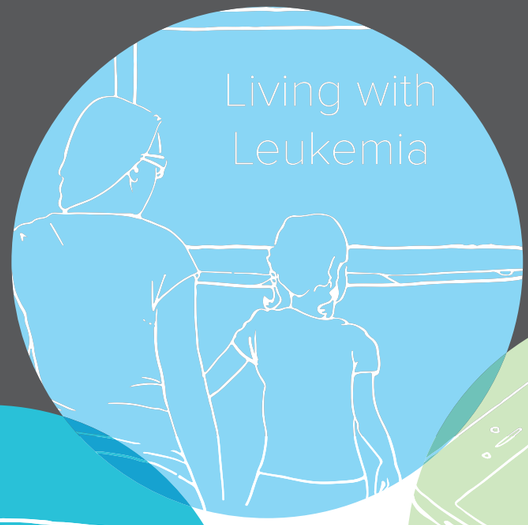
ANN BLACK, the University of Cincinnati faculty advisor for the Live Well Collaborative, and her colleague Todd Timney, an expert on communication design, guided teams of Cincinnati Children's and UC experts to enhance how patients and families navigate their cancer journeys. The work included highly focused 15-week projects — supported by our Center for Clinical and Translational Science and Training (CCTST) — to convert promising ideas into products and services that leverage new technologies to improve patient and family experience. THE PROJECTS INCLUDE:

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.

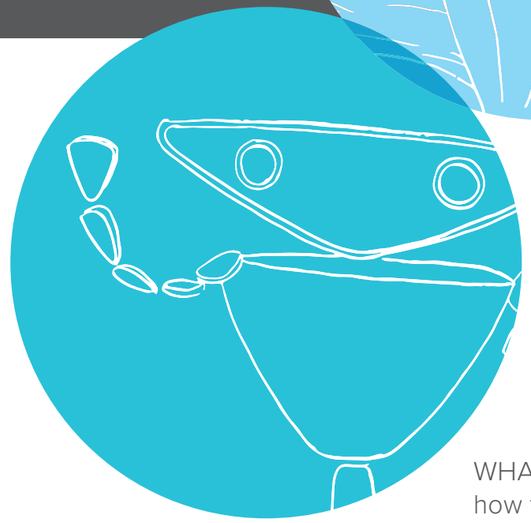
HEALTHY REWARDS SYSTEM: This initiative digitizes a paper-based "1-2-3 Initiative" developed by Christopher Dandoy, MD. A wall-mounted device used in combination with an RFID decal worn on a hospital band will track desired behaviors during inpatient stays. Children can collect reward points for showering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

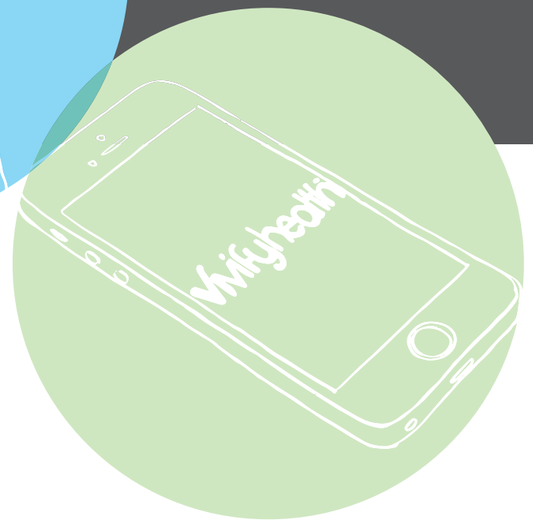
LIBERTY CAMPUS VIRTUAL TOUR: Children and parents soon will be able to take a virtual reality video tour using their own laptops or smartphones, even before setting foot in the new center.

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.





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.

GRANTS

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.

Burns 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 fibrotic remodeling.

James Bridges, PhD,

Perinatal Institute, will study the role of the GPR116 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, MS,

Pediatric General and Thoracic Surgery, will study the regional identity in human intestinal stem cells, with a five-year, $1.7 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 five-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 Prematurity Research Center Ohio Collaborative.

Dao Pan, PhD,

Experimental Hematology and Cancer Biology, will study enzyme replacement therapy that penetrates the blood-brain barrier, using a two-year, $1.4 million grant from Shire International GmbH.

GRANTS

Joseph Palumbo, MD,

Hematology, received two five-year, $1.8 million grants from the National Cancer Institute. He will study hemostatic 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.

Michael Seid, PhD,

Pulmonary Medicine, received a two-year, $2.4 million grant from the Cystic Fibrosis Foundation Therapeutics, Inc, for his work in creating better care models at the Collaborative Chronic Care Network.

Mei Xin, PhD,

Experimental Hematology and Cancer Biology, will study Hippo signaling in heart development and repair with a five-year, $2 million grant from National Heart, Lung, and Blood Institute. Hippo signaling controls organ size by regulating cell proliferation and the self-renewal of stem cells.

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 discovery to clinical testing of treatments. 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.

Eileen King, PhD

Peter White, PhD

HONORS

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 Gubanich, 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.

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.

Jeffery Molkentin, PhD,
Molecular Cardiovascular Biology, recently received the 38th Louis and Artur Lucian Award for Research in Circulatory Diseases from McGill University in Montreal. In addition, Molkentin and Daniel Nebert, MD, professor emeritus, UC College of Medicine, Department of Environmental Health, have been listed among 1,040 of the world's most highly cited researchers, according to the "Webometrics Ranking of World Universities." Nebert was ranked No. 652 with 51,585 citations and Molkentin was ranked No. 751 with 38,655 citations.


Bruce Aronow, PhD

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.

HONORS

Amy Nathan, MD,
Perinatal Institute, and a team of 16 colleagues received the 2015 Distinctive Achievement Award from the Children's Hospital Association in March for using quality improvement techniques to achieve an 83 percent reduction in the regional rate of necrotizing enterocolitis (NEC).

Mark Paterno, PT, PhD,
Occupational Therapy and Physical Therapy, recently received two prestigious honors: the Excellence in Research Award from the Sports Section of the American Physical Therapy Association and the Kappa Delta Clinical Research Award from the Orthopaedic Research and Education Foundation of the American Academy of Orthopaedic Surgeons.

Javier Gonzalez del Rey, MD, MEd,
Director, Pediatric Residency Program, was elected president of the Association of Pediatric Program Directors. The association, formed in 1985, works to advance excellence in pediatric medical education.

Kenneth Setchell, PhD,
Pathology, was selected to receive the 2016 Distinguished Contribution Award from the Association for Mass Spectrometry: Applications to the Clinical Laboratory.

Amy Shah, MD,
Endocrinology, has received an Early Career Development Award from the Central Society for Clinical and Translational Research. She also is one of 40 investigators nationwide to receive a Young Physician-Scientist Award from the American Society for Clinical Investigation.

Russell Ware, MD, PhD,
Director, Hematology, and Jennifer Tymon, a medical student at Loyola of Chicago, were selected in April as one of nine mentor-mentee pairs nationwide to receive Clinical Research Mentorship grants from the Doris Duke Charitable Foundation. Ware and Tymon plan to devote a year to studying the effects of hydroxyurea treatment on stroke risk in children with sickle cell disease.

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.


Stephen Porter, MD

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.

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www.cincinnatichildrens.org/cme
and click the "Continuing Education Portal" link.
Questions? Please email
hspconference@sairb.com or
contact Angela Kovatch, 513.761.4100.

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Cincinnati Children's is a teaching affiliate of the University of Cincinnati College of Medicine.

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.

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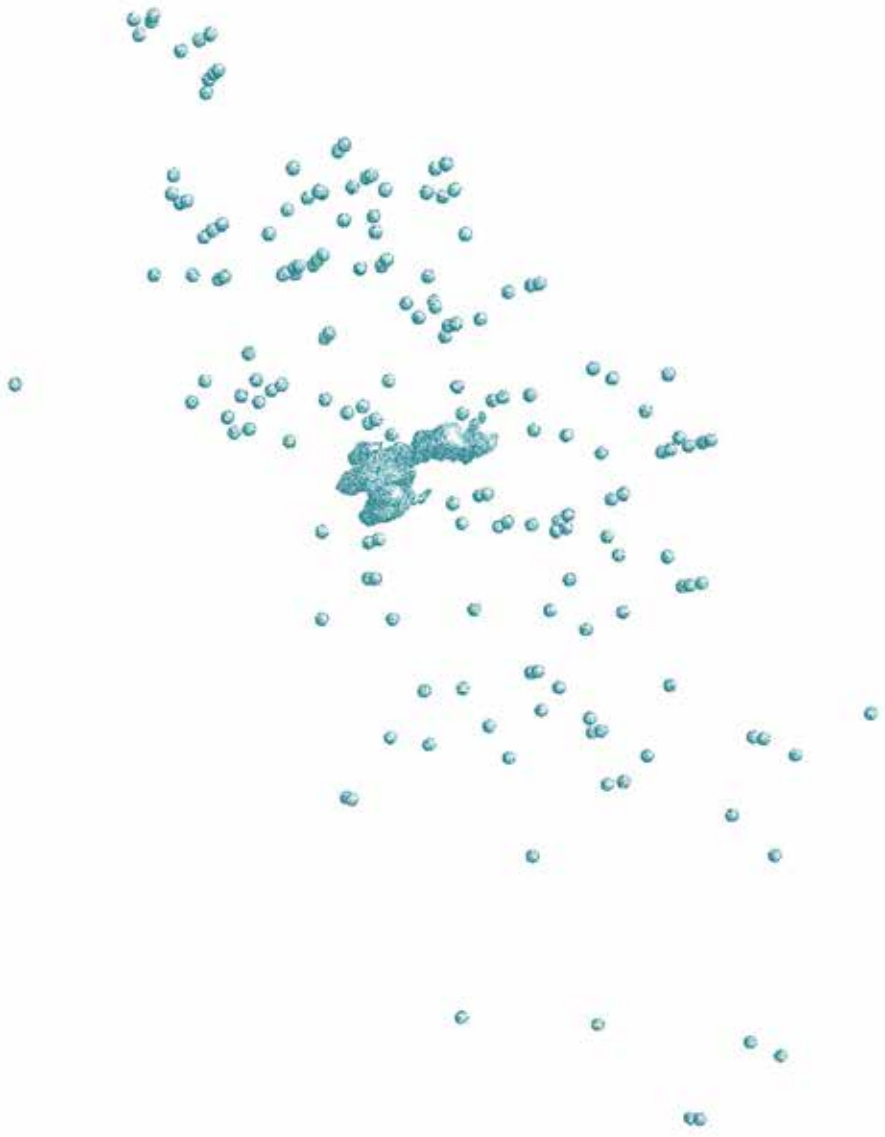

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