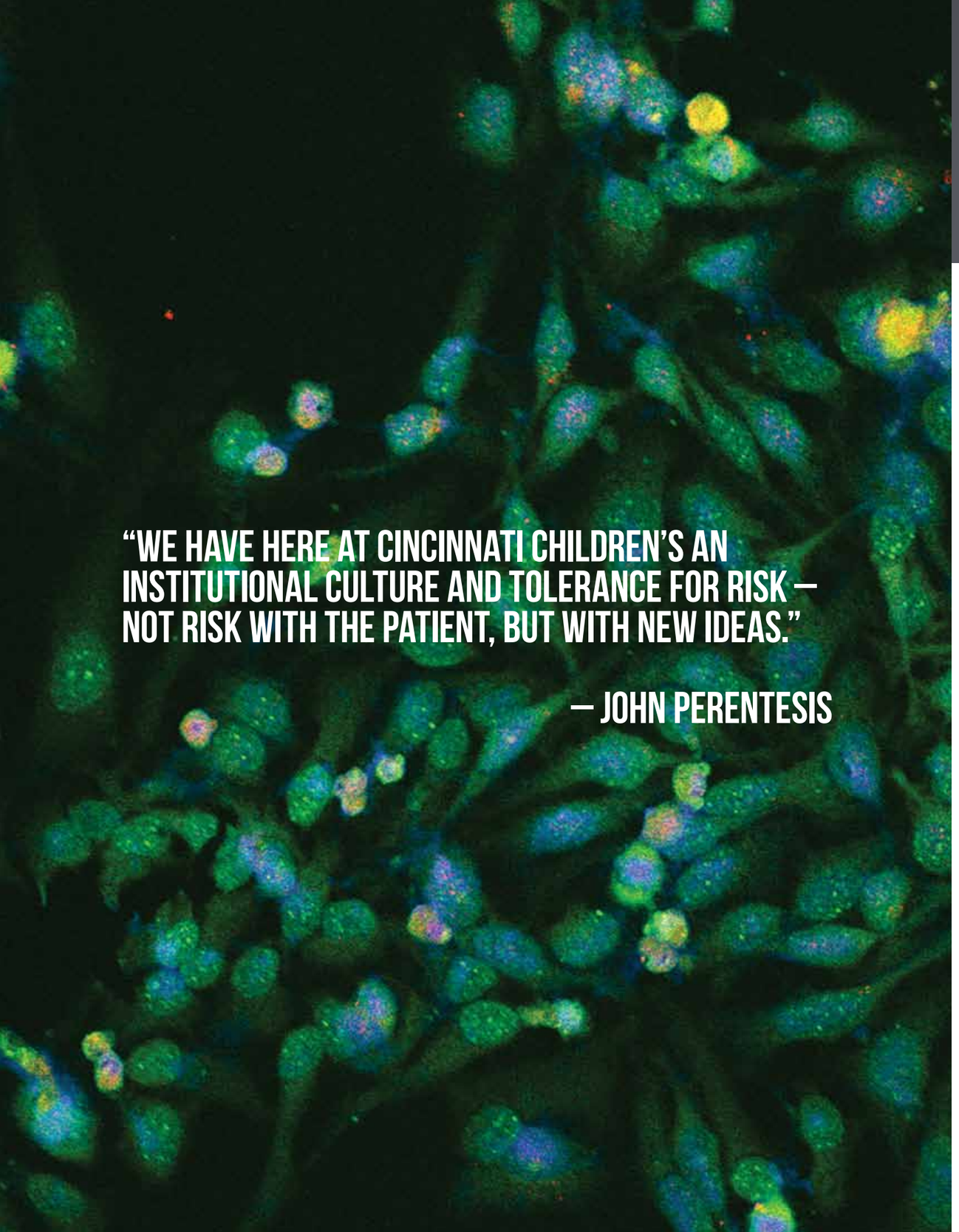
Research Horizons

A PUBLICATION OF THE CINCINNATI CHILDREN'S RESEARCH FOUNDATION
WINTER 2015

Childhood Brain Tumors

Our race to outsmart these thieves of time

Cincinnati Children's®



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Cover: Lauren Hill, photographed with her physician, Dr. Mariko DeWire. Lauren fulfilled her dream of playing as a freshman in Mount St. Joseph University’s season opener basketball game in Cincinnati on November 2, 2014. She had been diagnosed with a fatal diffuse intrinsic pontine glioma (DIPG) brain tumor one year earlier. More on page 31.

Cover photograph courtesy of the National Basketball Association, ©2015 Ron Hoskins/NBA

HONORS

Courtney Brown, MD,
General and Community Pediatrics;

Christopher Dandoy, MD,
Hematology/Oncology;

and Samuel Hanke, MD,
The Heart Institute, graduated from the James M. Anderson Center's Quality Scholars Program in August 2014. The Quality Scholars Program develops researchers and leaders who will transform pediatric health and healthcare delivery.

Beverly Connelly, MD,
Division of Infectious Diseases, received the coveted Cincinnati Pediatric Society Founder's Award in October 2014. Connelly, a professor of clinical pediatrics, is Director of the Fellowship Training Program in Infectious Diseases and the Infection Control Program at Cincinnati Children's.

Sandra Degen, PhD,
was named a finalist in the "Woman of the Year" corporate category of the Cincinnati USA Regional Chamber of Commerce's 9th Annual WE Celebrate Awards. Degen is an accomplished researcher in biochemistry and has developed many programs to advance young women in the sciences.

Alvin Crawford, MD,
Retired Co-Director of the Crawford Spine Center in the Division of Orthopaedic Surgery, received the Morehouse College "Candle in the Dark" award, presented annually to an individual who distinguishes himself in service, achievement, leadership, medicine, business or entertainment. In May 2014, the Scoliosis Research Society named Crawford one of two physicians to receive its Lifetime Achievement Award.

Margaret Hostetter, MD,
Director of the Cincinnati Children's Research Foundation, received the Founder's Award of the Midwest Society for Pediatric Research, the highest award given by that society. The award goes to a senior investigator and member of the society for fostering advances in pediatric research, contributing to research and developing careers of academic pediatric researchers in the Midwest.

Kelsey Logan, MD, MPh,
Director, Division of Sports Medicine, received the Leonard P. Rome Award, which honors a member of the Ohio chapter of the American Academy of Pediatrics whose leadership in a specific program or project furthers its mission.

Sara Meyer, PhD,
Division of Hematology, was one of 20 hematologists chosen to participate in the Translational Research Training in Hematology Program. This joint program of the American Society of Hematology and European Hematology Association provides junior researchers from around the world with a year-long training and mentoring experience to help build research careers.

Peter White, PhD,
Director of Biomedical Informatics, was named the George Rieveschl Jr. Chair for Biomedical Research. White, who joined Cincinnati Children's in July 2014, is leading efforts to develop an academic research program and a service group to support institutional needs for bioinformatics expertise and medical research.

Research Horizons

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

Hamada Named Schmidlapp Scholar

Fumika Hamada, PhD, was named the 2015-16 winner of the Schmidlapp Scholars award. The award provides $50,000 annually for up to two years to women faculty members who show leadership promise. A committee of senior women faculty selects one scholar each year.

Hamada, a researcher in the Division of Ophthalmology, studies the correlation between circadian rhythms and body temperature. She will use the scholarship for a mouse study examining how body temperature rhythm (BTR) is critical to essential functions such as generating metabolic energy and sleep.

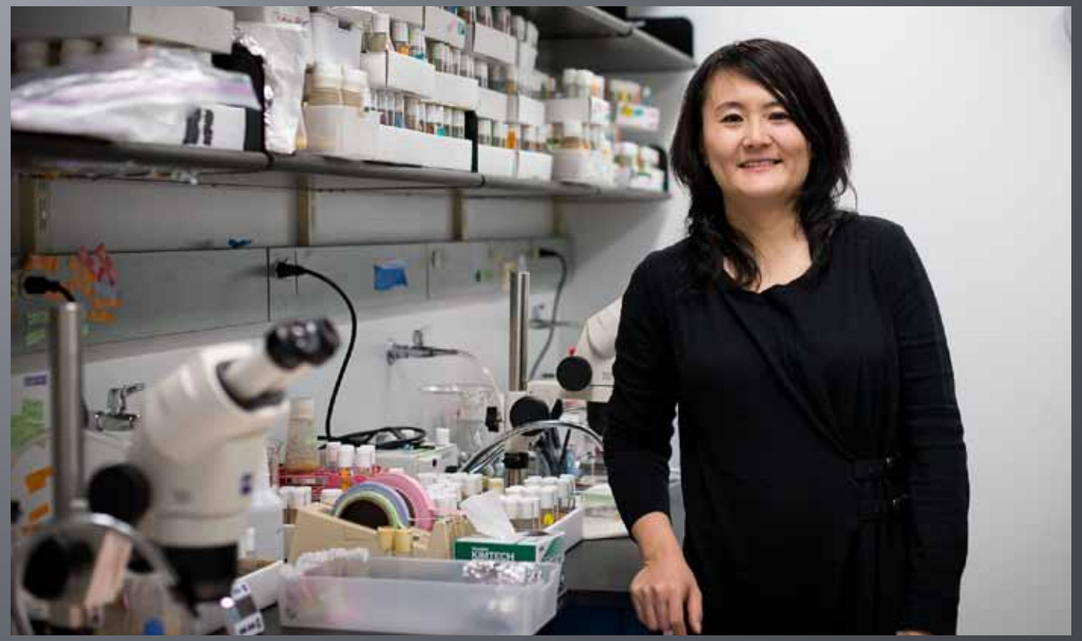
She was a co-lead investigator on a study of heat and pain sensation in fruit flies, demonstrating that a BTR-like mechanism existed. The study was published in *Current Biology* in 2012. Hamada also was co-lead investigator on a 2013 study on temperature integration in the neurons of fruit flies, published in *The Journal of Neuroscience*.

The temperature of the human body is rhythmic over the course of a day, rising during daytime and falling at night. Hamada's goal is to determine if candidate genes identified in fruit flies are comparable to those in mice. "I have realized there is a necessity in developing mice as a model system for BTR research," she says.

Hamada received her PhD from Tokyo University of Science, Japan, in 2004, before serving fellowships at Brandeis University, Harvard and MIT. She came to Cincinnati Children's in 2009.

Receiving the Schmidlapp honor was "so unexpected," she says, "I read the emails again and again."

Dr. Fumika Hamada explores the connections between circadian rhythms, body temperature and metabolism.



GRANTS

Denise Adams, MD,

Oncology, was awarded a four-year, $1.6 million grant from the Food and Drug Administration to conduct a Phase II trial of Vincristine vs. Sirolimus for High Risk Kaposiform Hemangioendothelioma.

Dean Beebe, PhD,

Behavioral Medicine and Clinical Psychology, received a four-year, $1.8 million award from the National Heart, Lung and Blood Institute to study "Sleep Restriction and the Adolescent Diet."

Jorge Bezerra, MD,

Gastroenterology, Hepatology and Nutrition, will study "Biological Basis of Phenotypes and Clinical Outcomes in Biliary Atresia" with a five-year, $2.3 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

Elisa Boscolo, PhD,

Experimental Hematology and Cancer Biology, will pursue the study of "Venous Malformations: A Murine Model to Identify Therapies to Target Aberrant Venous Development" with the help of a four-year, $1.3 million grant from the National Heart, Lung and Blood Institute.

Hermine Brunner, MD,

Rheumatology, received a five-year, $3.3 million grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases to develop the "Cincinnati Center for Innovative Medicine in Adult and Pediatric Rheumatology."

Tiffany Cook, PhD,

Developmental Biology, was awarded $1.9 million over a five-year period by the National Eye Institute for the study of "Molecular Networks Controlling Subtype Specification of Color Photoreceptors."

Senad Divanovic, PhD,

Immunobiology, will study the "Immunopathogenesis of Non-alcoholic Fatty Liver Disease" with the help of a four-year, $1.8 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

Tanya Froelich, MD,

Developmental and Behavioral Pediatrics, will use a five-year, $2.7 million grant from the National Institute of Mental Health to study "Neurobehavioral Effects of Abrupt Methyphenidate Discontinuation."

James Greenberg, MD,

Perinatal Institute, will use a five-year, $3.5 million grant from the Health Resources and Services Administration to work with the Collaboration on Infant Mortality Reduction on "Healthy Start Cincinnati."

Michael Helmrath, MD,

General and Thoracic Surgery, will conduct an "Investigation of Regional Identity in Human Intestinal Stem Cells" with the help of a $1.6 million, five-year grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

Vivian Hwa, PhD,

Endocrinology, will study the "Roles of STAT5b in IGF-1 Production and Human Growth" with the help of a five-year, $1.6 million grant from the National Institute of Child Health and Human Development.

Susmita Kashikar-Zuck, PhD,

Behavioral Medicine and Clinical Psychology, will use a five-year, $1.2 million grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases to study, "Behavioral Interventions and Long-Term Outcomes in Juvenile Fibromyalgia."

Vladimir Kalinichenko, MD, PhD,

Neonatology and Pulmonary Biology, will explore "Transcriptional Regulation of Goblet Cell Metaplasia" with the help of a $1.5 million, four-year grant from the National Heart, Lung and Blood Institute.

Sundeep Keswani, MD,

General and Thoracic Surgery, will use a five-year, $1.5 million grant from the National Institute of General Medicine Sciences to explore "Novel Mechanisms of Regenerative Wound Healing."

Peter Margolis, MD, PhD,

Anderson Center for Health Systems Excellence, will use a one-year award of $1.5 million from the Patient-Centered Outcome Research Institute to establish "A National Pediatric Learning Health System" with Children's Hospital of Philadelphia.

Jeffery Molkentin, PhD,

Molecular Cardiovascular Biology, will focus on "Understanding Cardiovascular Disease Mechanisms." with a five-year, $1.9 million grant from the National Heart, Lung and Blood Institute.

Mark Mitsnefes, PhD,

Nephrology, will use a five-year, $1.1 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases, in collaboration with Children's Mercy Hospital, on the study of "Chronic Kidney Disease in Children."

Ahna Pai, PhD,

Behavioral Medicine and Clinical Psychology, will establish a "Clinic-Based Interdisciplinary Intervention for Parents of Children with Cancer" with a five-year, $3.2 million grant from the National Institute of Nursing Research.

Kieran Phelan, MD,

James Anderson Center for Health Systems Excellence, received a three-year, $3.5 million grant from the National Institute of Child Health and Human Development for "Injury Prevention in a Home Visitation Population."

Steve Potter, PhD,

Developmental Biology, will use a four-year, $1.4 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases to examine "Recombineering-based Analysis of Hox Function in Kidney Development."

Nancy Ratner, PhD,

Experimental Hematology and Cancer Biology, will work with the University of Minnesota to investigate "Disordered Regulation of Wnt/β-catenin Signaling in Malignant Peripheral Nerve Sheath Tumors" with a five-year, $1.3 million grant from the National Institute of Neurological Disorders and Stroke.

Marc Rothenberg, MD, PhD,

Allergy and Immunology, will develop the "Consortium of Eosinophilic Gastrointestinal Disease Research" with a five-year, $2.4 million grant from the National Institute of Allergy and Infectious Diseases (NIAID). He will also pursue the "Regulation of Gastrointestinal Eosinophils" with a five-year, $1.9 million grant from NIAID.

Lisa Shook, MA,

Hematology, will examine "Sickle Treatment and Outcomes Research in the Midwest" with a three-year, $2.5 million grant from the Health Resources and Services Administration.

Earl Siegel, PharmD,

Drug and Poison Information Center, will pursue "Poison Center Support and Enhancement" with the help of a $2.1 million grant from the Health Resource and Services Administration over four years.

Daniel Starczynowski, PhD,

Experimental Hematology and Cancer Biology, will use a four-year, $1.5 million grant from the National Heart, Lung and Blood Institute to study the "Role of TRAF6 in Myeolodysplastic Syndromes."

Jeffrey Towbin, MD,

Heart Institute, will study the "Genetics, Mechanisms and Clinical Phenotypes of Arrhythmias" with a $1.2 million grant over four years from the National Heart, Lung and Blood Institute.

Bruce Trapnell, MD,

Pulmonary Medicine, will use a $3.4 million grant from the National Heart, Lung and Blood Institute to study "RLDC: Molecular Pathway-Driven Diagnostics and Therapeutics for Rare Lung Diseases."

Shari Wade, PhD,

Physical Medicine and Rehabilitation, received a three-year, $2.3 million grant from the Patient-Centered Outcome Research Institute to study "Comparative Effectiveness of Family Problem-Solving Therapy."

Peter White, PhD,

Biomedical Informatics, will join with the American College of Medical Genetics Foundation in a four-year National Institute of Child Health and Human Development award of $2.2 million to develop a "Newborn Screening Translational Research Network."

Brenda Wong, MD,

Neurology, will use a three-year, $1.5 million grant from Pfizer, Inc. to conduct a phase II, randomized, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of PF-06252616 in ambulatory boys with Duchenne muscular dystrophy.

Jessica Woo, PhD,

Biostatistics and Epidemiology, will use a five-year, $13.5 million ward from the National Heart, Lung and Blood Institute to examine "Childhood Cardiovascular Risk and Adult Cardiovascular Disease Outcomes: an International Long-term Follow-up."

Stavra Xanthakos, MD,

Gastroenterology, Hepatology and Nutrition, will use a $3.1 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to study "Outcome of NASH (non-alcoholic steatohepatitis) in Adolescents after Bariatric Surgery." She will also use a five-year, $1.2 million grant from the NIDDK to participate in the "Clinical Research Network in NASH."

Yi Zheng, PhD,

Experimental Hematology and Cancer Biology, will continue work in the Cincinnati Center for Excellence in Molecular Hematology with the help of a $2.8 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

Aaron Zorn, PhD,

Developmental Biology, will study how "Osr Transcription Factors Regulate Embryonic Lung Development" with the help of a $2.1 million, five-year grant from the National Heart, Lung and Blood Institute.

A Surprising Clue to Peripheral Neuropathies

Gene that suppresses tumor growth also plays a role in forming myelin in the nervous system

A research team in the Cancer and Blood Diseases Institute led by Biplab Dasgupta, PhD, found that the tumor suppressor gene Lkb1 helps to myelinate neurons. Disrupting the gene's function causes improper formation of myelin sheath, the coating that protects the neuron and helps conduct electrical signals in nerves. This defect in myelin formation leads to neuropathy in the peripheral nervous system and muscle wasting in mice similar to that found in human diabetic neuropathy and other neurodegenerative conditions. Dasgupta and his team reported their findings Sept. 26, 2014, in *Nature Communications*.

"The finding is unexpected because disruption of this tumor suppressor gene blocked a pathway that is essential for cell proliferation," says Dasgupta, the study's principal investigator. "Additional study is needed, as the function of Lkb1 may have broader implications – not only in normal development, but also in metabolic reprogramming in human pathologies."

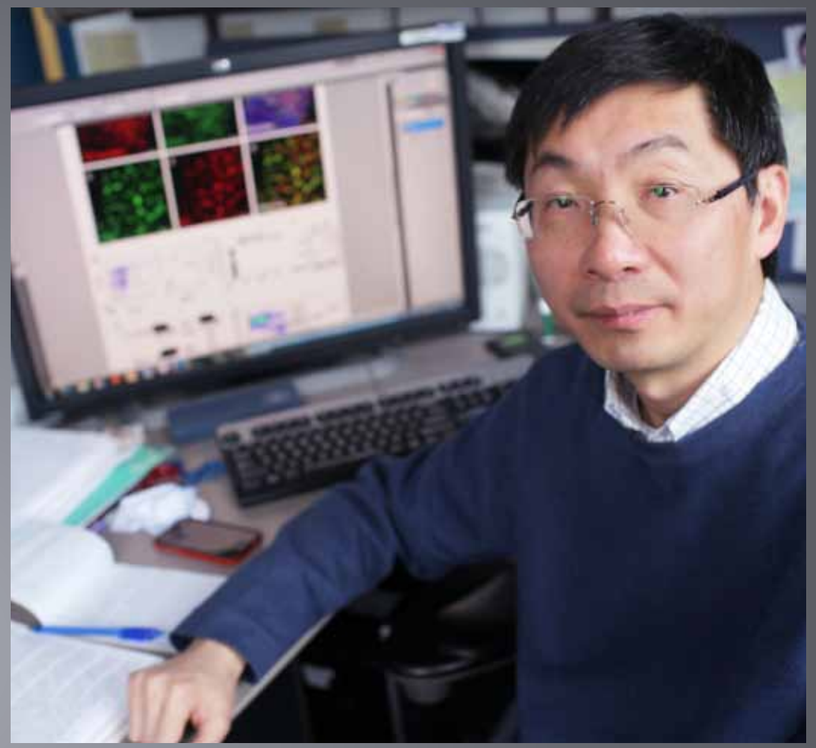
Formation of the myelin sheath by Schwann cells requires high levels of lipid (fat) synthesis because myelin is mostly composed of lipids, says Dasgupta. Lipids are made from citric acid produced in the cells' mitochondria. Success of myelin sheath formation relies on the ability of Schwann cells to switch to Lkb1-dependent mitochondrial metabolism to generate more citric acid, the authors report.

The researchers used mice in which Lkb1 was deleted in the myelinating cells. This allowed them to analyze the gene's role in Schwann cell metabolism and myelin sheath formation.

Deletion of Lkb1 in the mice resulted in a thinner myelin sheath on the nerves and caused muscle atrophy, hind limb dysfunction, peripheral neuropathy and even premature death.

Dasgupta and his colleagues are currently testing whether increasing the fat content in the diet of these mutant mice would improve myelination defects. They will pursue additional research to extend the relevance of their findings to human diseases like diabetic neuropathy.

Dr. Biplab Dasgupta and his team will explore other uses for the tumor-suppressing Lkb1 gene.



New Compound Blocks Rapid Cell Growth

Study may lead to treatments for several types of cancer and rare 'Rasopathies'

Scientists have known for years that the Ras molecular signaling pathway plays a central role in how cells grow and divide, and that genetic mutations in this process can lead to the uncontrolled cell proliferation common to many forms of cancer.

Now researchers at Cincinnati Children's have identified a compound that shows promise in blocking that process. If further testing confirms the early findings, the compound may become a new weapon against breast, prostate and several other forms of cancer as well as a group of nine related developmental syndromes called "Rasopathies."

According to findings published Nov. 20, 2014, in *Chemistry & Biology*, the compound (NSC-658497) targets SOS1, a key enzyme involved in activating the Ras molecular signaling pathway.

"While Ras pathway activation is a dominant event happening in many diseases, so far, the immediate signaling module of the Ras pathway has been difficult to target. Most strategies for treatment have been geared toward hitting molecular effectors that are farther downstream," says Yi Zheng, PhD, principal author and director of Experimental Hematology and Cancer Biology at Cincinnati Children's.

The research team found the new compound by screening more than 30,000 candidate compounds from a database maintained by the National Cancer Institute. Next steps include testing the compound in mice bred to exhibit various cancers and Rasopathies. Zheng says human application of the findings remains several years away.

Dr. Yi Zheng's research team will continue to explore a drug that appears to block uncontrolled cancer cell growth.

Cell Therapy Shows Promise in Treating Rare Lung Disease

Researchers at Cincinnati Children's have corrected a rare lung disease by transplanting healthy immune cells into mice. They reported their findings online Oct. 1 in *Nature.*

Using mice bred to mimic the rare human lung disease hereditary pulmonary alveolar proteinosis (hPAP), the scientists transplanted healthy macrophages – immune cells that collect and remove cell debris from the body – into the respiratory tracts of the animals. Their hope is that the treatment could be used to treat hPAP and other human lung diseases caused by dysfunctional immune cells.

The scientists found that transplanting either normal or gene-corrected macrophages into the respiratory tracts of the mice corrected the disease.

"These are significant findings with potential implications beyond the treatment of a rare lung disease," says Bruce Trapnell, MD, Division of Neonatology and Pulmonary Biology and the study's senior author. "Our findings support the concept of pulmonary macrophage transplantation as the first specific therapy for children with hPAP."

"Results also identified mechanisms regulating the numbers and phenotype of macrophages in the tiny air sacs of the lungs (called alveoli) in health and disease," adds Takuji Suzuki, MD, PhD, the study's first author.

Just one administration corrected the disease and prevented disease-specific mortality for at least one year. Researchers must still confirm how the body processes the therapy, and determine appropriate dosage levels and duration following treatment. Preclinical studies are now in progress and planning for human studies is underway.

Swapping healthy immune cells for dysfunctional ones could be the answer for rare lung disease, says Dr. Bruce Trapnell.

Oral Antibiotics as Good as IV, Without Complications

Oral and intravenous (IV) antibiotics are equally effective for treating osteomyelitis in children, and oral delivery avoids the complications of a peripherally inserted central catheter (PICC line).

Results of a multi-institutional study led by Cincinnati Children's and Children's Hospital of Philadelphia appeared Dec. 15 in *JAMA Pediatrics*. Findings led researchers to suggest that physicians reconsider the use of an IV to deliver antibiotics for the bone infection that affects about 1 in 5,000 children each year.

"Complications with PICC lines include blood clots and sepsis," says Samir Shah, MD, MSCE, Director of Hospital Medicine and study co-author. "We can avoid such complications by using oral antibiotics, with excellent outcomes."

The study reviewed medical records of 2,060 children hospitalized over a three-year period in 36 pediatric hospitals. Overall, outcomes were the same and there were fewer than 4 percent adverse drug reactions. But 15 percent of the children with PICC lines developed a PICC-related complication that required an emergency visit or re-hospitalization.

Study of antibiotic delivery will now expand to pneumonia and appendicitis, says Dr. Samir Shah.

Redington Named Heart Institute Co-Director

Andrew Redington, MD, is the Heart Institute's new executive co-director. He joined Cincinnati Children's in November 2014 after serving as Head of Cardiology at The Hospital for Sick Children in Toronto since August 2001.

Redington's research interests include the pathophysiology of congenital heart disease, ventricular function and cardiovascular physiology and ischemic preconditioning. He has written more than 230 peer-reviewed publications and more than 20 book chapters, and has co-edited six books. He serves on the editorial boards of *Cardiology in the Young* and *Heart and Vessels*.

A 1981 graduate of the University of London, he obtained his MRCP (Membership in the Royal College of Physicians) diploma in Internal Medicine in 1984 and his doctorate of medicine in 1988. He was consultant pediatric cardiologist at the Royal Brompton Hospital, London, in 1990 and was awarded a fellowship of the Royal College of Physicians in 1994. In 1998, he transferred his clinical and research teams to Great Ormond Street Hospital in London, where he remained until moving to Toronto in 2001.

Redington sees opportunities for transformational research and discovery in the Heart Institute. He looks forward to improving efficiencies and fostering the ideas of faculty and fellows.

"There are very few jobs I would have left Toronto for," he says. "But the people in the Heart Institute impressed and inspired me. They have the talent and the desire to be the best. But they also have the resources to make it happen, including the support of hospital leadership."

Expanding the Heart Institute's research and services is part of Dr. Andrew Redington's plan.

Progress on Two Organ-In-A-Dish Projects

Scientists generate functional stomach tissue in the lab and coax intestinal organoids to grow in mice

Someday, the tiny stomachs and mini-intestines grown at Cincinnati Children's may pave the way for helping people with a wide range of digestive diseases grow their own replacement tissues.

But first, these organoid projects could advance laboratory research by providing human organ models for use in drug development and basic developmental studies. Two recent papers demonstrate how quickly this technology is moving forward.

Stomach tissue from stem cells

A paper published Oct. 29 in *Nature* explains how scientists here managed to grow gastric organoids in the laboratory.

"Until this study, no one had generated gastric cells from human pluripotent stem cells (hPSCs)," says James Wells, PhD, principal investigator and a scientist in the divisions of Developmental Biology and Endocrinology. "We discovered how to promote formation of three-dimensional gastric tissue with complex architecture and cellular composition."

The pea-sized stomachs will help explore questions scientists could not probe with traditional technology. They will shed light on *H. pylori* bacterial infections, a major cause of peptic ulcer disease and stomach cancer. And the techniques used to grow the stomach tissue may advance efforts to generate other organs that trace their roots to the foregut, such as the lungs and pancreas.

Intestine organoids reach mature form in mice

Before the latest progress with stomach organoids, Wells and colleagues had reported similar successes growing intestine tissue from iPSCs. Now that line of research has taken another step.

A study published online Oct. 19 in *Nature Medicine* details how researchers here successfully transplanted laboratory-grown organoids of human intestinal tissue into mice. The mouse blood supply allowed the organoids to grow into mature, functioning tissue, including muscle layers and mucosa, with absorptive and digestive abilities.

"This provides a new way to study the many diseases and conditions that can cause intestinal failure, from genetic disorders appearing at birth to conditions that strike later in life, such as cancer and Crohn's disease," says Michael Helmrath, MD, MS, lead investigator and surgical director of the Intestinal Rehabilitation Program at Cincinnati Children's. "These studies also advance the longer-term goal of growing tissues that can replace damaged human intestine."

Dr. Michael Helmrath looks to the day when laboratory-grown tissue will replace children's damaged intestines.

Sanitation, Cultural Issues in Poor Countries at Root of Disparity in Children's Health

In countries with poor sanitation, even children with enough to eat are often malnourished, falling far behind in height, weight, and physical and mental development. And vaccines are less effective among these children.

Sean Moore, MD, MS, a gastroenterologist at Cincinnati Children's, and colleagues are using a mouse model to study the problem, thanks to a $1 million Phase II grant from Grand Challenges Explorations, an initiative of the Bill and Melinda Gates Foundation. Collaborators include scientists at Cornell University and Baylor College of Medicine.

Moore uses mouse models to study environmental enteropathy — the way the lining of the gut is damaged by consuming contaminated food and water, leading to inflammation and malabsorption.

"The best solution would be that everyone has access to clean water and food," Moore says. "But in the meantime, targeted interventions that help kids be their best in challenging environments is the goal."

Those interventions, Moore says, could range from antibiotics and vaccines to nutritional supplements and working to change attitudes toward sanitation.

Taking in contaminated food and water also might be why children in these environments become resistant to life-saving vaccines. The Rotarix™ vaccine against rotavirus, developed at Cincinnati Children's, is effective in 98 percent of children in the U.S., but only half as effective in the world's poorest countries.

"Vaccines are so important to public health, but so much vaccine development happens in industrialized countries like the U.S. and in Europe," Moore says.

Dr. Sean Moore uses a Gates Foundation grant to explore how to keep kids healthy in countries where sanitation is poor.

Grant Will Improve Sickle Cell Treatment, Expand Care

Cincinnati Children's is developing a six-state network to improve the treatment of sickle cell disease and increase the number of people with access to care.

The "Sickle Treatment and Outcomes Research in the Midwest" (STORM) project recently earned a three-year, $2.5 million grant from the Health Resources and Services Administration (HRSA). Lisa Shook, MA, MCHES, in the Division of Hematology, serves as principal investigator.

The new network will share data, educate, and connect primary care providers with specialists to improve outcomes for adults and children with sickle cell disease, particularly those challenged by chronic poverty or who live in rural areas with limited access to treatment.

The project seeks to expand the availability of disease-modifying therapies, specifically hydroxyurea and periodic blood transfusions, and plans to address the disparities in care for adult patients in acute-care settings.

Shook, who specializes in newborn screening and chronic disease management, is also principal investigator for the Cincinnati Sickle Cell Newborn Screening Network, another HRSA-funded project.

The STORM network is modeled after several Cincinnati Children's initiatives to treat chronic illnesses, each supported by the James M. Anderson Center for Health Systems Excellence.

"We will utilize strategies and lessons learned from these other projects," says Shook. "Leveraging partnerships throughout the region will be an important step in reaching as many providers and underserved patients as possible."

The project will serve Ohio, Indiana, Illinois, Michigan, Minnesota and Wisconsin, providing a central information system to engage state health departments, newborn screening programs, community-based organizations, advocacy groups and patients.

Lisa Shook will oversee a $2.5 million HRSA grant to improve care for people with sickle cell disease.

Study IDs Gene Network That Fuels Untreatable Leukemia

A gene network that fuels an aggressive form of leukemia may be the key to developing a more effective treatment.

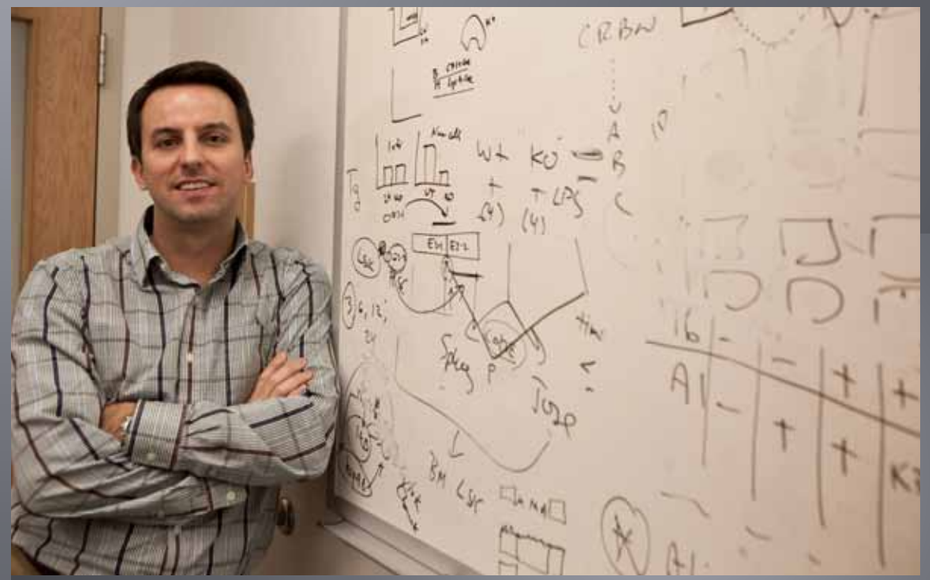
Scientists from the Cancer and Blood Diseases Institute here say new strategies are crucial because acute myeloid leukemia (AML) and its precursor disease, myelodysplastic syndrome (MDS), are so resistant to chemotherapy and radiation. Their findings were posted online Sept. 4 by *Cell Reports*.

The study focused on patients with a form of AML and MDS in which the chromosome del(5q) was deleted. Patients with less aggressive forms of del(5q) MDS tend to have fewer immature leukemia blasts, or cells, in their bone marrow and their prognosis is generally good.

"Unfortunately, a large portion of AML and MDS patients with del(5q) have an increased number of bone marrow blasts and additional chromosomal mutations," says lead investigator Daniel Starczynowski, PhD, a researcher in Experimental Hematology and Cancer Biology. "Finding new therapies is important and this study identifies new therapeutic possibilities."

In studies of human cells and mouse models, researchers found that reduced expression of the blood cell gene miR-146a activated a molecular protein, p62, which is critical to certain cancers. When they deleted the gene in the mice, it activated p62 and prompted aggressive leukemia cell growth. By targeting p62, researchers prevented expansion of leukemic cells in mouse models and reduced the number of leukemia cell colonies by 80 percent in human AML/MDS cells. It suggested that scientists could develop a "workaround solution" to the interaction between the gene and protein.

Starczynowski cautioned that further study is needed because the molecular processes involved in mice do not necessarily translate to humans.



Dr. Daniel Starczynowski and team have discovered a gene-protein interaction that might halt aggressive leukemia cell growth.

Project Reduces Hospital Alarm Fatigue by 80 Percent

Monitor alarms in hospitals can save patients' lives, but the frequent beeping can also lead to alarm fatigue among caregivers.

Researchers at Cincinnati Children's have sharply reduced the frequency of false cardiac monitor alarms, according to a study posted online Nov. 10, 2014, in *Pediatrics*. A standardized approach developed by a team working in a 24-bed pediatric bone marrow transplant unit reduced the median number of daily cardiac alarms from 180 to 40, and increased caregiver compliance with the process from 38 percent to 95 percent.

"Cardiac monitors constitute the majority of alarms throughout the hospital," says Christopher Dandoy, MD, a physician in the Cancer and Blood Diseases Institute and lead author of the study. "We think our approach to reducing monitor alarms can serve as a model for other hospitals throughout the country."

The project involved a process for initial ordering of monitors based on age-appropriate standards, replacing electrodes daily in a manner that was pain-free for patients, individualized daily assessment of cardiac monitor parameters and a reliable method for discontinuing the monitors.

Dr. Christopher Dandoy's project to reduce unnecessary alarms could become a national model.

Funding Helps Study of Rare Diseases

Denise Adams, MD, a researcher in the Cancer and Blood Diseases Institute, was awarded one of 15 grants by the U.S. Food and Drug Administration (FDA) to help in the study of rare diseases.

Adams' award of $1.6 million over four years will support a Phase II study of "Vincristine vs. Sirolimus for the Treatment of High Risk Kaposiform Hemangioendothelioma (KHE)." KHE is a rare vascular tumor that causes a significant bleeding disorder with increased morbidity and mortality.

The 15 grants, totaling $19 million, are intended to boost the development of medical devices, drugs, and biological products for patients with rare diseases. At least one-quarter of the funding went to studies focused solely on pediatrics.

According to Gayatri Rao, MD, director of the FDA's Office of Orphan Product Development, "The grants awarded this year support much-needed research in difficult-to-treat diseases that have little, or no, available treatment options."

The FDA's Orphan Products Grants Program was created by the Orphan Drug Act in 1983 to promote the development of products for rare diseases. Since its inception, the program has given more than $330 million to 530 new clinical studies for rare diseases and has been used to bring more than 50 products to market approval.

A panel of independent experts with experience in the disease-related fields reviewed the grant applications and made recommendations to the FDA.

Dr. Denise Adams will pursue treatment for a deadly vascular tumor.

Clinical Sciences Building Will Open This June

Cincinnati Children's newest research tower, the Clinical Sciences Building, will quite literally serve as a bridge between research and care.

The building represents a deeply held aspect of the medical center's culture – close cooperation between physicians and scientists to move the latest innovations rapidly from the lab to the bedside.

"This building symbolizes translational research in every way - geographically, structurally, and functionally," says Kristine Justus, PhD, Vice President of Research Operations and Assistant Director of the Research Foundation. "This is the piece that connects our research to our clinical care in a fundamental way."

Laboratory spaces are organized in "neighborhoods" to encourage collaboration, and research divisions that work together frequently will be located near each other. "Beehive" spaces will be equipped with conference rooms and 24-hour refreshment areas to support impromptu gatherings.

After three years of work, the 15-story, 425,000-square-foot building will connect the hospital's main clinical center to the William Cooper Procter Research Tower, which opened in 2008. The new tower brings our total square footage in research buildings to more than 1.4 million square feet, making Cincinnati Children's one of the country's largest pediatric research centers. More than 1,500 physicians, scientists and support staff will work here.

From spaces for advanced imaging research to clinics for participants in clinical studies, the new tower will be a nexus to bring children and science together. The first three floors will feature a soaring, open atrium where families participating in clinical trials will find a one-stop shop to receive study-related exams, scans and tests. Some of its highlights include a pharmacy to compound and manage investigational medications, a shipping area where clinical samples can be quickly packed in dry ice, and a metabolic kitchen where families can learn how to prepare foods for children with special dietary needs.

Building Highlights

Cost: $205 million
Height: 201 feet
Funding Sources: Operating cash, investments and philanthropy
Architects: GBBN, GBR, HDR
Builder: Messer Construction
Key Features:

- New labs for clinical and translational research
- Research imaging facility
- Research focused outpatient clinic
- Collaborative space known as the Beehive
- Rooftop respite garden
- Office space for executive leadership and staff

Nothing Ordinary About It

FOR OUR CANCER AND BLOOD DISEASES INSTITUTE, LIMITED THINKING IS OFF-LIMITS

by Mary Silva

There is something fundamentally wrong about a child having cancer. At least when cancer strikes in adulthood, we can often blame years of smoking, eating the wrong foods or generally indulging in ways we should not.

But for a child, there are no such explanations. Cancer in a child disrupts the order of the universe. Which might be why John Perentesis, MD, uses the word "disruptive" to describe the work of the Cancer and Blood Diseases Institute (CBDI).

Perentesis is head of the Division of Oncology and one of four co-directors of the Institute, which cares for several hundred children each year who are newly diagnosed with cancer. The Institute's 100 faculty and nearly 400 support staff treat children who have cancers in their blood cells, bones, lymphatic system, kidneys, liver, eyes – you name it. Some of these cancers are more treatable than others; many are curable. But few are as little understood, or as impervious to treatment, as brain tumors.

Brain tumors, particularly the high-grade, incurable ones, are daunting, and Perentesis has assembled a powerful team to take them on. Maryam Fouladi, MD, heads the Brain Tumor Program; a team of researchers led by scientific director Qing Richard Lu, PhD, carry out the science. Neuroradiologists image the tumors; neurosurgeons perform the resections; pathologists interpret the biopsies. Many others provide an array of clinical support. Underlying it all is a tenet of close collaboration.

"One of our ethics is team science," Perentesis says. "We spend a lot of resources to cover people's time and effort so they can spend more time working as a team. And we fund high-risk research with transformational potential that would be hard to fund through traditional funding mechanisms."

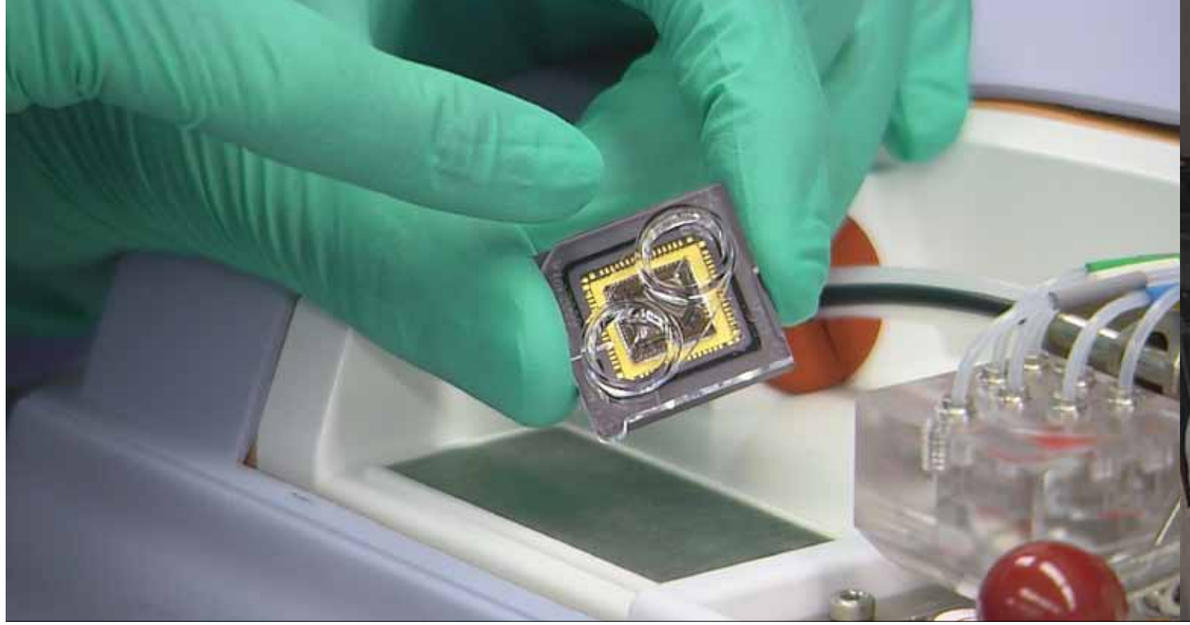
The results of this approach speak for themselves. Perentesis recites a litany of prestigious publications that have published findings of his scientific team. He calls an article published last summer by Lu in *Nature Medicine* a "tour de force." Lu and his team discovered that an anti-depressant medication can combat medulloblastoma, an aggressive and often fatal brain tumor.

ENCOURAGING DISRUPTION

That discovery, Perentesis says, is a perfect example of the outside-the-norm thinking encouraged within the Institute.

"A lot of our internal resources go toward disruptive technologies and research," Perentesis says, using that word again. "'Disruptive' is an important thing in these times. Science moves forward in two ways. One is incremental – methodically, carefully. The other is to pull in new ideas from different fields and to think in new and different ways."

The only rule for outwitting childhood cancers, says Dr. John Perentesis, is that there are no rules. He encourages his team to stop at nothing in their search for answers.



It only takes minutes for research assistant Otis Pinkard to run genetic information from tumors against tens of thousands of compounds to find the best match for treatment.

A NEW DIRECTION IN TREATMENT

Perentesis and his group lean heavily toward the latter approach. One of their new and different ways of approaching cancer treatment is currently under construction: a Proton Therapy Center at Cincinnati Children's location in Liberty Township, Ohio. Perentesis considers proton therapy an essential tool for treating childhood cancers. And, he adds, this center will be the only one in the world with a dedicated research facility (see page 38).

Along with the Proton Therapy Center, the Cancer Institute is expanding inpatient and outpatient services at the Liberty Campus. The Institute has enlisted faculty from the University of Cincinnati's College of Design, Art, Architecture and Planning to work with families of children with cancer, to design a facility that truly meets their needs.

CUSTOM-DESIGNED DRUGS

Perentesis' own area of research is in drug discovery and development, where he takes advantage of the latest genomic technology to move science along. His laboratory today is a far cry from the early days of his career. "We would spend up to a year doing things that we can do in less than 10 minutes today in our sequencing lab."

Now, just one flight of stairs down from his office, is a laboratory packed with $3 million worth of the latest gene sequencing equipment. The sequencers analyze each child's tumor to see what makes it tick and researchers run the findings against tens of thousands of compounds in a matter of minutes to find the ideal match for treatment.

"We used to think about cancers as being a series of broken 'on' switches. And if you blocked those switches, you could cure the cancer," Perentesis says. "It turns out to be much more specific than that. You have to do a designer solution for each type of cancer. And even the same cancers might react to a drug differently, depending on the child."

At a time when pharmaceutical companies are not developing new drugs for pediatric cancers, the Institute's research team has decided to take it on themselves. Yi Zheng, PhD, who heads the Institute's Division of Experimental Hematology and Cancer Biology, is using information generated by our gene sequencing laboratories to understand the molecular underpinnings of certain cancers and to identify compounds that could revolutionize their treatment. One of his discoveries was published Nov. 20, 2014 in *Chemistry & Biology* – a compound that appears to block the Ras signaling pathway, implicated in a variety of diseases, including cancer.

Adopting promising therapies for pediatric use is a step Perentesis expedites through his role on the National Cancer Institute's Investigational Drug Steering Committee, and as a member of the executive committee of the Children's Oncology Group.

FOR EVERY CHILD, AN AVATAR

Perentesis' latest disruptive idea is adopting a "Pediatric Cancer Avatar Program." Doctors sequence a biopsy of a child's tumor to find what is driving the cancer. Tumor samples are then implanted into mouse "avatars" to grow and be treated with the same chemotherapies as the child. Researchers observe how the mouse model reacts to treatment and anticipate what the response might be in the child.

"Although this program is still in the research stages, the potential is here for next-generation advances for children with high-risk and relapsed cancers," Perentesis says. "The goal is to develop curative and precise therapies individualized for a patient and his tumor. It is turning oncology on its side."

Turning things on their side seems more than reasonable when your life's work is treating children with a disease for which there is no explanation and all too frequently, little hope.

Perentesis feels fortunate to be part of an organization that understands the value of such thinking.

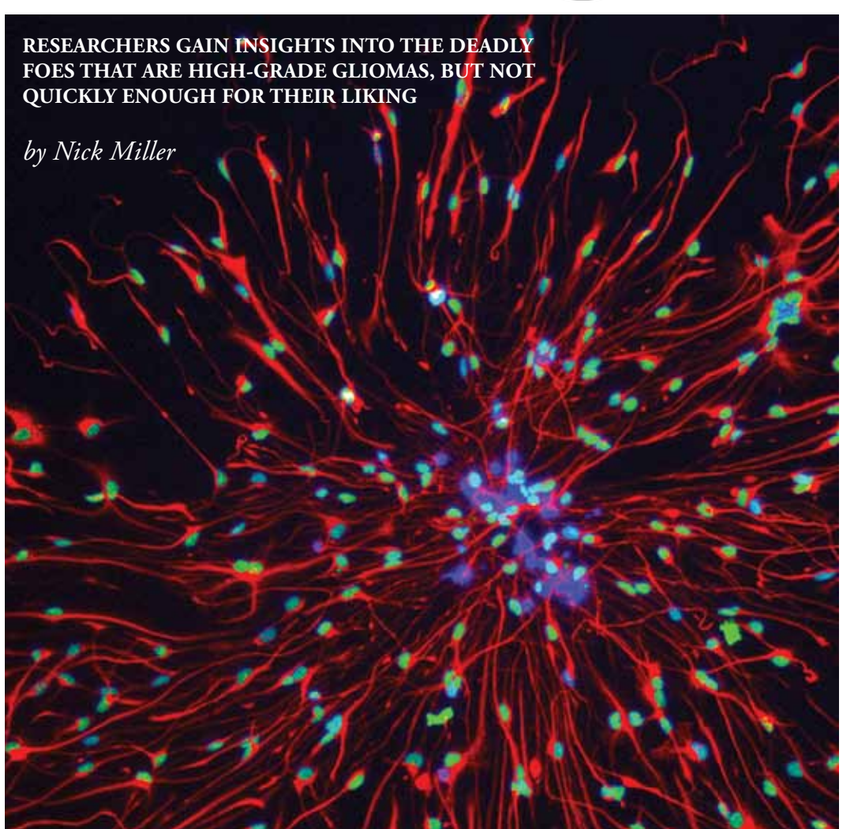
"We have here at Cincinnati Children's an institutional culture and tolerance for risk – not risk with the patient, but with new ideas. And if it is a good idea, to put resources behind it," Perentesis says. ■

The Pediatric Avatar Program pairs each child with a mouse bearing a biopsied sample of his tumor. The mouse's reaction to treatment helps predict response in the child.

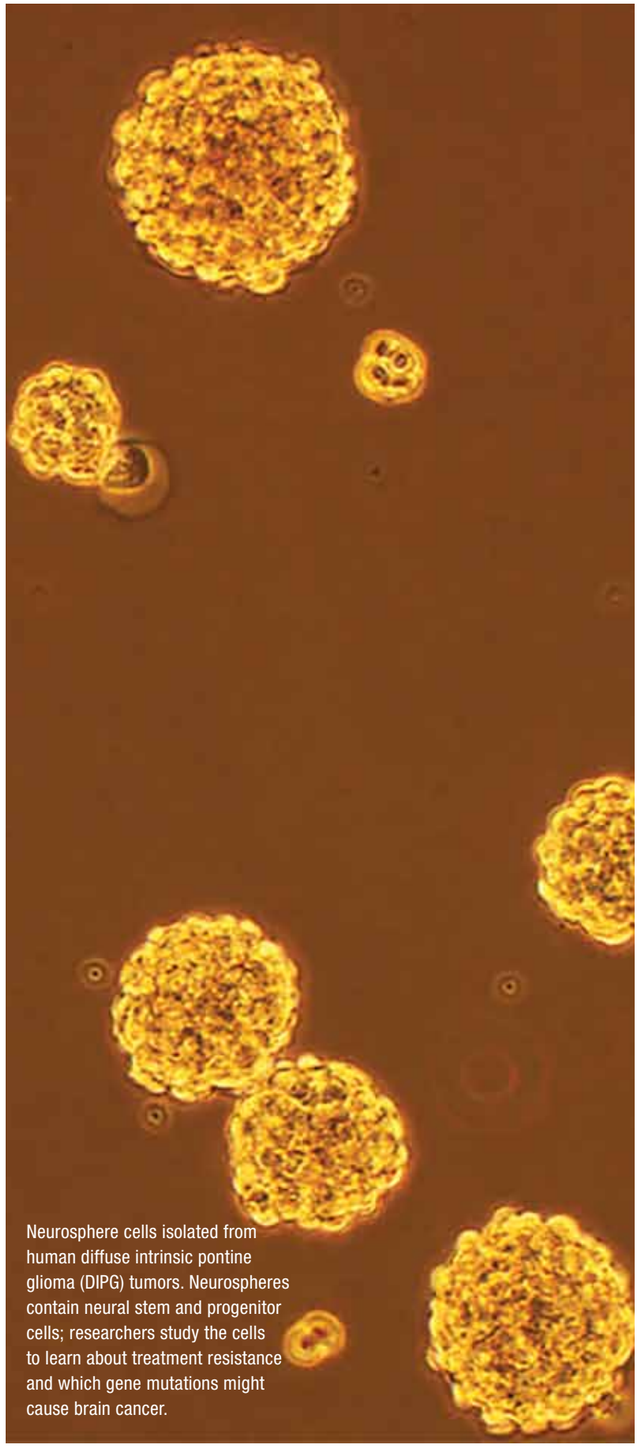
KNOWING THE ENEMY

RESEARCHERS GAIN INSIGHTS INTO THE DEADLY FOES THAT ARE HIGH-GRADE GLIOMAS, BUT NOT QUICKLY ENOUGH FOR THEIR LIKING

by Nick Miller



From the left: Drs. Lionel Chow, Rachid Drissi, and Biplab Dasgupta



Neurosphere cells isolated from human diffuse intrinsic pontine glioma (DIPG) tumors. Neurospheres contain neural stem and progenitor cells; researchers study the cells to learn about treatment resistance and which gene mutations might cause brain cancer.

All cancers are not created equal. So when physicians and scientists who study cancer biology talk about making strides in cure rates for many childhood cancers, there is that "other" list — the cancers that cannot be cured, or even treated with reasonable effectiveness.

Of the dozen or so different types of pediatric brain cancers, high-grade gliomas (HGG) are particularly treatment-resistant. They account for just 8 to 10 percent of central nervous system tumors in children, with an incidence rate of 0.85 cases per 100,000, according to the U.S. Central Brain Tumor Registry. Five-year survival rates are only 15 to 30 percent.

Lionel Chow, MD, PhD, is an oncologist and researcher in the Cancer and Blood Diseases Institute. He treats children with these tumors and spends long hours with research colleagues studying HGGs. The scientists are relentless in their search for better ways to treat HGG and other brain cancers. But they have yet to determine what causes them, or how to stop them.

What they do know is that they look forward to the day when they will not have to deliver the dismal prognosis that accompanies a diagnosis of an HGG to a family.

"It is extremely difficult and disheartening to deliver a diagnosis of a high-grade glioma to patients and families," says Chow. "These are such aggressive cancers and our options for treatment are few and ineffective. We try to offer hope with new therapies and clinical trials, but we know that the patient's outcome is determined with the diagnosis. Parents should not have to watch their child endure the suffering that this disease causes. I am a parent myself and I cannot imagine outliving my kids."

Chow is part of a team of Cincinnati Children's researchers who make defeating pediatric HGG their life mission. They are joined in this effort by colleagues across the globe in a variety of collaborative efforts, in particular the Pediatric Brain Tumor Consortium (PBTC), led by Maryam Fouladi, MD, who heads our Brain Tumor Program. The PBTC emphasizes a strong blend of basic cancer biology and clinical investigation.

WHAT RESEARCHERS KNOW

Pediatric HGG tumors look similar at the microscopic level when compared to their adult counterparts, so at one time it was thought they might be driven by genetic and biologic factors similar to those seen in the adult disease. But advances in the ability to identify the precise genetic signatures of different tumors have changed this thinking.

"There is a big difference between pediatric brain tumors and adult brain tumors," says Rachid Drissi, PhD, a scientist in the Division of Experimental Hematology and Cancer Biology. "They may look the same under the microscope, but the genetic and molecular pathways that lead to these tumors are not the same."

Arising from glial, oligodendrocyte and ependymal brain cells, high-grade gliomas vary in their genetic drivers and molecular signatures. The precise combination of mutations that leads to HGG can depend on the type of cell being targeted or region of the brain in which the cancer originates, or even the patient's genetic background.

Many believe these cancers have their origins from flexible progenitor cells of the central nervous system. Progenitor cells are still finalizing what cell type to become, and are easily influenced by "wrong" genetic or biologic conditions. In the context of brain cancer, they can become tumor-initiating cells (or cancer seeds), prompted by mutations in genetic pathways. During the disease process, these cancer seeds can be a source of resistance to therapy, making certain cancers harder to treat.

To thrive, glioma cells depend on what scientists call the "permissive micro-environment" of the brain, which exists in an area separated by the blood-brain barrier. Designed to protect the brain, the barrier also makes delivering therapeutic agents to diseased parts of the brain more challenging. Researchers are developing new technologies that can cross the barrier to deliver targeted treatments, such as lipid (fat)-based nanoparticles capable of toting molecular-based therapeutics.

HARD TO MAKE, HARDER TO KILL

Even in this micro-environment, it is not easy to become a brain cancer cell, says Biplab Dasgupta, PhD, whose office and laboratory are within steps of Chow's and Drissi's. Unlike cancers that require fewer gene mutations, cancer-initiating cells may require a larger number of mutations to form glioblastoma.

"Normal cells have a built-in mechanism to commit suicide when things go wrong," Dasgupta says. "It is essentially a chance factor for a mutated cell to dodge the suicide mechanism. The changing environment and our changing lifestyle – including diet – likely allow mutated cells to survive long enough to acquire additional mutations and become full-blown cancer."

As a result, brain cancer cells are smart survivors. If you block one of their mechanisms of survival, they can harness their heterogeneous nature and use genetic/molecular cross-talks to work around treatments.

"They adapt and evolve in response to therapy," Dasgupta explains. "Glioblastoma cells are different than other cancers – they are extremely aggressive, metabolically different, and hard to grow on the petri dish."

DIFFERENT ANGLES

Chow, Drissi and Dasgupta study high-grade gliomas like enthusiasts piecing together a scientific jigsaw puzzle, each working from a different angle.

Two of those angles target the abilities of brain cancer cells to use energy and to cheat nature's rules of cell division. A third involves blocking a central molecular signaling axis that enhances the resourcefulness of cancers to adapt and work around targeted therapies.

BREAKING NATURE'S RULES

Normal cells abide by the mitotic clock and nature's rule that cells should divide only a limited number of times. In the cell nucleus is the chromosome, which carries the genetic code and DNA that control a cell's fate.

At the end of every chromosome is the telomere, a series of DNA sequences that, like the plastic caps on the ends of shoelaces, keep the whole works from unraveling. These "caps" help preserve the genetic stability of cells. Each time a cell divides, the telomere gets shorter. After so many divisions, the telomere gets short enough it tells the cells to stop dividing.

Not so with cancer cells, explains Drissi. In brain cancer cells, there are two molecular processes that let the cells ignore nature's stop signs. One is a protein complex called telomerase. The second is a process called ALT (Alternative Lengthening of Telomeres). Normal cells do not produce telomerase or have ALT, but brain cancer cells do.

When telomerase or ALT kicks in, prompted by genetic mutation, telomeres preserve their length and brain cancer cells grow, spread and kill.

Drissi and his team are testing ways to block the activity of telomerase, to prevent cancer cell telomeres from preserving length. Lab data show that blocking telomerase kills brain cancer cells. The real plus is that it also makes brain cancer cells more sensitive to radiation.

"Radiation treatment causes devastating side effects for children, so being able to make cancer cells more sensitive to radiation and lowering radiation doses would be very beneficial," he explains.

Drissi had been testing a molecular inhibitor that successfully blocked telomerase activity in cancer cells. It led to a multi-institutional Phase II clinical trial, although the death of a patient already very sick with brain cancer ended the study and the testing of that drug. He is now working on a new inhibitor to stop telomerase, and testing a molecular inhibitor that appears to block the establishment of ALT.

FOSTERING NEGATIVE ENERGY

Dasgupta takes aim at glioblastoma cells by messing with their energy. One tactic involves a study he led that helped answer a controversy over how the popular diabetes drug metformin - and its analog phenformin – slow the growth of glioblastoma cells. Another tactic focuses on the ultimate goal of being able to use lipid-based nanoparticles to deliver a molecular inhibitor of AMPK, an enzyme that helps control glioblastoma cells' energy.

The metformin controversy centered on the widely accepted notion that it slowed glioblastoma by activating AMPK, then blocked the protein mTOR. Gene mutations in the mTOR molecular pathway are a key driver of many cancers. Clinical trials testing metformin for cancer were built on this premise. Dasgupta and his colleagues proved the theory wrong in a study published in *PNAS: Proceedings of the National Academy of Sciences*. Their study showed that metformin directly inhibited mTOR to cause tumor regression without involvement from AMPK.

Another observation in the study, Dasgupta says, is that while metformin slowed glioblastoma growth, the tumors managed to survive in a diminished state. Metformin shut down the cells' ability to use oxygen as energy, but they immediately switched to a different energy source – sugar – through a process called glycolysis. So although tumors regressed, they survived. And the longer they survived, the less effective metformin became – helping illustrate the importance of targeted and combined treatments for glioblastoma.

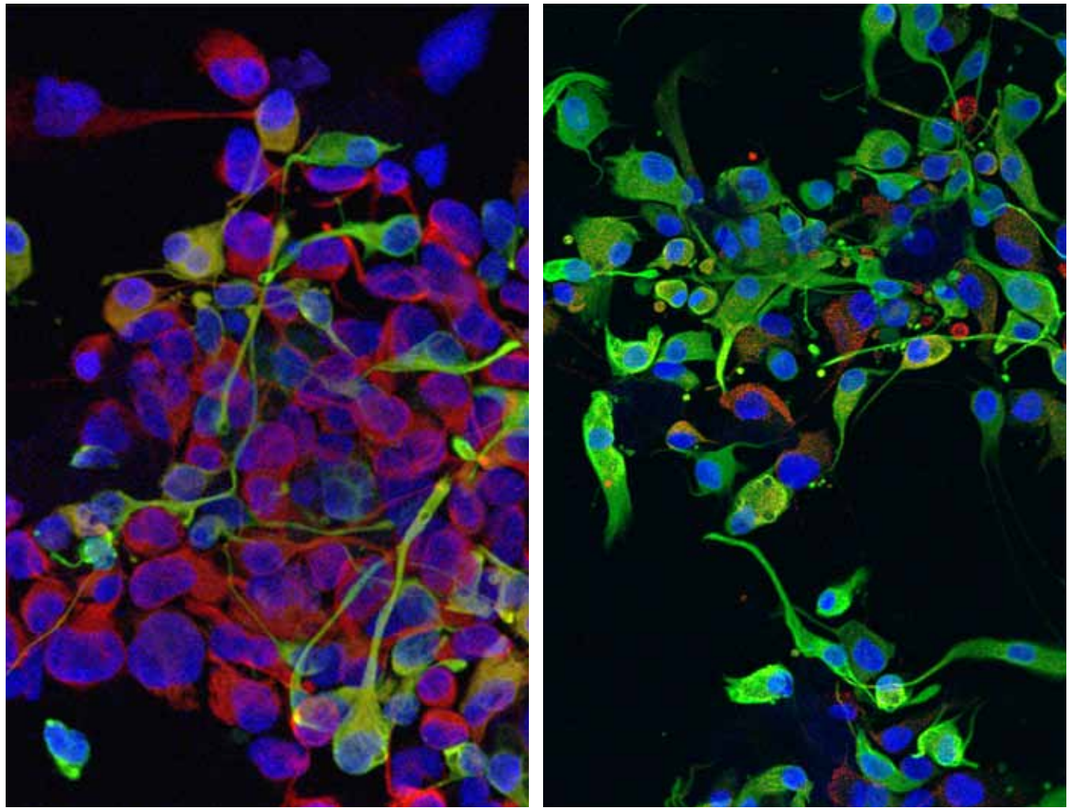
Dasgupta and colleagues recommended that clinical trials of metformin consider these newly discovered mechanisms.

Although AMPK is not part of metformin's anti-cancer properties, Dasgupta and Chow have found that the enzyme remains important to the survival of cancer cells under severe metabolic stress, like glioblastoma cells. In other less-stressed cancer cells, AMPK works in reverse as part of the Lkb1-AMPK tumor suppressor pathway.

Using glioblastoma cells taken directly from human surgical biopsies, Dasgupta is now testing the use of "silencing RNA" that turns off AMPK. The silencing RNA is delivered directly to the glioblastoma cells via an engineered virus delivered *in vitro*. If the model is successful, scientists will test the inhibitor in mouse models.

"It is essentially a chance factor for a mutated cell to dodge the suicide mechanism. The changing environment and our changing lifestyle – including diet – likely allow mutated cells to survive long enough to acquire additional mutations and become full-blown cancer."

– Biplab Dasgupta



The panel on the left shows a confocal microscopic image of undifferentiated brain cells. The panel on the right shows differentiated DIPG cells. Both differentiated and undifferentiated cells have the potential to form tumors. Color coding in the images helps researchers compare the genetic makeup of normal brain cells to those with cancer. Their goal is to isolate, characterize and ultimately target these cells to eradicate brain cancer.

CHOKING OFF CANCER'S ROOT SYSTEM

Chow studies a core molecular signaling axis for adult and pediatric glioblastoma known as the PI3K/AKT/mTOR pathway. His laboratory developed a mouse model that revs up this pathway to mimic human glioblastoma.

He compares PI3K/AKT/mTOR in glioblastoma to plants that appear to be freestanding, but have an underground network of complex roots. Although PI3K/AKT/mTOR may be at the core, its components can activate a number of downstream molecules and pathways. This gives glioblastoma plenty of escape routes from therapeutic agents.

Using the mouse model, Chow's team tests combinations of molecular inhibitors of PI3K/AKT/mTOR's components to see how effectively they slow tumor growth and block escape routes. Hitting critical bottlenecks or junctions for molecular signaling could inhibit tumor growth enough to be a key component of combination treatments. One tactic involves using two agents: rapamycin, which blocks the well-established mTOR pathway, and an inhibitor of PI3K, an enzyme that triggers the disease process. The combined agents have had a dramatic effect on cell death in the mouse model.

These results are important to keep in mind, says Chow, as the PBTC is preparing to initiate a Phase 1 clinical trial to test a PI3K inhibitor.

He emphasizes that success with a drug or combination of treatments does not mean the search ends – it's just a promising beginning. Given the genetic diversity and complexity of glioblastomas, and how the cancers differ in each patient, the hunt for additional targeting inhibitors to block brain cancer pathways must continue.

"We have to take an unbiased approach and say 'it could be anything, so let's look at everything,'" he says. ■






Eyes on the Prize

DOCTORS STAKE CAREERS ON STOPPING A DEADLY TUMOR
THAT HAS STUMPED SCIENCE FOR DECADES

by Mary Silva



"We have a huge spirit of collaboration between basic scientists, translational scientists and clinicians in our division and throughout the medical center. It's the perfect blend of bench to bedside and back again."

– Maryam Fouladi

Among the list of unwelcome, invasive, aberrant growths that can take up residence in a child's brain, a few rise to the top for their ability to do harm.

Doctors call them "high-grade" tumors, so named because in the numbering scheme assigned to such growths, 1 or 2 means a tumor is treatable and chances of survival, quite good. One labeled 3 or 4 is high-grade, with a far poorer prognosis.

Maryam Fouladi, MD, came to Cincinnati Children's in 2008 to lead the Brain Tumor Program in our Cancer and Blood Diseases Institute. The program cares for and cures many children with brain tumors. Fouladi and her team are especially interested, however, in the tumors labeled 3 and 4.

"My objective in coming here was to develop treatments for the worst and highest-risk brain tumors — high-grade gliomas and diffuse intrinsic pontine glioma, both of which have a terrible prognosis," Fouladi says.

Terrible seems an understatement. These gliomas arise in the brain stem, the part of the brain that controls life-giving functions like breathing and circulation. Because of where they grow, they cannot be removed. And they grow rapidly. Nearly all patients with diffuse intrinsic pontine glioma (DIPG) die within two years of diagnosis.

MANY PEOPLE, A SINGLE PURPOSE

Working to save the children whose lives these tumors destroy is a team of more than 40 people - basic and translational scientists, neurosurgeons, neuroradiologists, pathologists, neuro-oncologists, nurses, social workers – the list goes on.

"We have a comprehensive program with every subspecialty you could imagine for a child with a brain tumor," Fouladi says. "In one sentence, our mission statement is to cure DIPGs in 10 years. And in the meantime, to increase survival and decrease toxicities for these kids with the poorest prognosis."

Brain stem tumors are what drew Fouladi to becoming a neuro-oncologist. She remembers as a pediatric resident hearing her mentor tell a family that their child with a DIPG was going to die no matter what the doctors did.

"I was shocked," she recalls. "It was 1993, and I couldn't believe that was all we could do. It became my goal to be part of a generation that helps find a cure."

Yet despite steady effort, science has remained largely confounded by the tumors. "We have made no strides in literally 40 years," Fouladi says.

Recently, however, there has been progress in understanding the biology of brain stem tumors, fueled largely by families who have lost children to the disease.

Dr. Maryam Fouladi heads the Brain Tumor Program. Although they can cure many brain tumors, the team is particularly focused on high-grade gliomas and diffuse intrinsic pontine gliomas, for which there are currently no cures.

FAMILIES STEP FORWARD

As with most rare pediatric diseases, public research funding for study of these tumors has been difficult to come by. So organizations begun by families of DIPG patients, such as The Cure Starts Now Foundation and the DIPG Collaborative, have stepped up.

"We are enormously lucky that the DIPG Collaborative and the Cure Starts Now have funded our work to the tune of $600,000 in the past 2½ years," Fouladi says, "and have pledged their continuing support."

That funding helped create an international DIPG registry, a database of information about DIPG patients. Participants include an international who's who of experts in DIPG who share data, imaging, pathology, and research findings. The resulting wealth of information is opening new windows of discovery.

"In the two years since the registry was created, we have enrolled 400 patients, with 900 more committed to enroll, from over 30 institutions in the U.S., Canada and Australia," says Fouladi, who leads the effort. "And we are now working to link with a European registry."

A GAME-CHANGING PROGRAM

The registry will connect to another remarkable resource developed by Mariko DeWire, MD, who joined Cincinnati Children's just over two years ago. The program collects donated brain and tumor tissue from children who die from DIPG and other high-grade brain tumors.

Called simply "the autopsy study," it is modeled on a program DeWire was involved with during her fellowship at St. Jude's Hospital. In the Cincinnati Children's program, the brain is removed within 24 hours of death and goes directly to the laboratory, where it is imaged for extent of invasiveness. The tumor tissue is removed, sequenced for genomic analysis and used to grow additional tumor cells for research.

FIGHTING BACK – AND GIVING BACK

The push for the study came primarily from parents, who see it as a way to fight back against a disease that shows no mercy. Although most children stricken with DIPG are between the ages of 5 and 7, DeWire also has teenage and young adult patients who ask to donate their brains. "They want to see some good come from their situation," she says. "Doing this is their way of helping those who come after them."

Some parents stay in touch with the project even after their child dies. "They have told me they feel as though their child is still living, and it gives them great comfort," says DeWire.

Dr. Mariko DeWire developed a brain donation program for patients who die from high-grade brain tumors. Tissue from those donations has helped researchers take giant steps in understanding and treating the tumors.

In just over a year, our doctors have performed 18 autopsies, and already the program is proving its scientific value. Information from the autopsies is helping our scientists make giant steps forward in understanding the tumors and identifying potential treatments. (More about their research, page 20).

THE POWER OF MANY

Moving from potential treatments to actual remedies is a process riddled with regulatory obstacles. Fouladi works to ease the process as Chair of the Pediatric Brain Tumor Consortium, an NIH-funded group of 11 of the country's top brain tumor programs. Members use their scientific clout to get promising treatments into clinical trials as quickly as possible.

In April 2014, the group received a five-year renewal grant of $13 million, funding they will put toward their research activities.

Fouladi is heartened by what scientists here and elsewhere have learned in just the few years since tumor donation programs and the DIPG registry began.

"Our researchers are developing a comprehensive understanding of the biology of these tumors, and are translating what they find into the clinic.

"We have learned that these tumors are different from adult tumors. They have changes that could be targeted by some of the drugs we are developing now," she says. "For the first time in 40 years, we are focusing on real possibilities for treating these children." ■

'A JOY AND A PRIVILEGE'

The social work team in the Brain Tumor Program finds they are the students; their families, the teachers

Beyond the researchers looking for answers and the physicians and nurses who provide expert care, the Brain Tumor Program includes dozens of clinical support staff. They include child life specialists, psychologists, school intervention specialists, and social workers.

They are part of the Patient and Family Wellness Center within the Cancer and Blood Diseases Institute. From the moment a child is diagnosed, these individuals play an integral part in the patient's and family's experience.

Social workers Mandy Bley, LISW-S, Bridget Kikta, LSW, and Maureen Donnelly, LISW-S, work specifically with families in the Brain Tumor Program. "Our relationship with the child and the family is key. We see them every time they come to clinic," Bley says. "It's an opportunity to validate the experiences they are having in their journey."

That journey is life-changing, says Kikta, even when a child's tumor can be treated or cured.

"Life is different in many ways for these families," she says, "Children often suffer deficits, and that comes with a new set of challenges."

The team walks a fine line between acknowledging the experience of cancer and helping children live as normally as possible.

Bley paraphrases a line from the book, The Fault in our Stars. "These kids are not their disease. They are bigger than that. There is a joy and privilege in getting to know who they are, what's important to them, and how they interact with the world."

Because of this, the social workers say, children of every age want to find meaning in their experience. A young adult or teenager might choose to donate their brain for research, write a poetry book or become a champion for research. Younger children, says Bley, "Have their own way to make their mark. They might have a lemonade stand to raise money or create a picture book about their experience." The Program has developed special outings and groups for families to meet and share their experiences.

"Often, the families stay in touch after a child passes away," Donnelly says. "They want to hear about the research being done that is going to further knowledge and lead to a cure – they find that comforting. Families who have donated their child's brain for research often share their decision publicly, to encourage other families."

When asked about the value of their work, the team's response is unanimous.

"This job has shown me how much good is in the world," says Kikta. "In the face of the most horrible things, there are families who will walk through fire for their children. There are foundations started by people who have lost someone they care deeply about, and they choose to pay it forward by contributing to research."

Adds Bley, "I am forever inspired how in hard moments, families find a way to take the next step and keep going. To be able to witness that is a privilege."

Social workers (from left) Mandy Bley, Bridget Kikta, and Maureen Donnelly work with children in the Brain Tumor Program, and their families.

What follows are excerpts from a paper written by Lauren Hill for an English class in her senior year of high school, April 2014. Lauren was diagnosed with the fatal DIPG tumor in November 2013. Throughout the course of her cancer, she has been an outspoken proponent of research funding for childhood cancers in general, and for DIPG in particular, raising more than $1 million for DIPG research.

"Being diagnosed with DIPG is like giving someone a best-if-used-by date. Children affected with this disease are given a few months to two years at best to live, deprived the luxury of having a long and healthy life. Parents of the diagnosed are in absolute shock and devastated at the terribly short amount of time their child has been predicted to live. What makes the situation worse is that there is nothing anyone can do to stop it from happening. It is like being tied to train tracks, looking down the dark path like a deer frozen in front of the oncoming headlights, the DIPG freight train is always moving and stops for no one. This terminal pediatric brain cancer is perhaps the most baffling to researchers because virtually no progress has been made in thirty years.

DIPG research is in short supply of tumor samples because this disease is inoperable and only affects less than 200 people a year in the United States alone. Many parents are asked to donate their child's tumor after they succumb to this terrible disease and this provides researchers the tissue samples they need to develop more knowledge and better strategies for combating DIPG. However for many children diagnosed with DIPG, these treatments will not come quick enough.

It is sad to think that drug companies are willing to shell out research money for cancer treatments that give seventy-five year olds a few more years to live but overlook the causes of those who will not even reach double digits in their lifetime.

Children are the future of the world. What happens to them is far more important than what happens to an aging elderly. The impact of DIPG has not reached enough people and the knowledge of this disease needs to be spread. Researching this disease should be of the upmost (sic) importance in the world of cancer research because if DIPG can be cured, all cancers can be cured. It is now time that the stories of tragedy turn into stories of triumph... It is time for a change in research, a change in the methods of cancer treatment, and a change in the heartbreaking prognosis of DIPG."

One-Two Punch Could Knock Out Cancer Relapse

New research suggests combination therapy to battle aggressive brain tumors

by Tim Bonfield

The thing about treating brain tumors is that too many of them fail to stay treated. Medical literature is riddled with examples of promising chemotherapies that initially shrink tumors, but then the cancer adapts and comes roaring back.

Now an international research team, led by scientists at Cincinnati Children's, may have found a way to overcome the problem of rapid drug resistance. The latest findings specifically address an aggressive form of medulloblastoma, one of the most common forms of brain cancer in children. However, the work suggests an approach that may have wider impact.

The team discovered a novel tumor suppressor gene in medulloblastoma, and showed that Rolipram, a cellular cAMP-elevating agent and antidepressant approved for use in Europe and Japan, also has the ability to suppress brain tumor formation in mice. Detailed findings were published online Aug. 24, 2014, in *Nature Medicine*.

Qing Richard Lu, PhD, scientific director of the recently formed Brain Tumor Center at Cincinnati Children's, was the lead investigator. The study included collaborators from nine medical centers in four countries.

"Although current treatments improve survival rates, many patients develop relapse tumors carrying mutations that resist treatment," Lu says. "This underscores an urgent need for alternative targeted therapies."

A PATHWAY TO A CURE?

With the rapid growth of whole-genome sequencing techniques, scientists are learning more about how and why the body's normal defenses against cancer break down. One line of defense begins with the gene GNAS. In healthy people, this gene encodes the Gαs protein, which in turn kicks off a molecular signaling cascade that suppresses tumor growth. Mutations disrupting this pathway can lead to rapid cancer cell growth.

Lu and his colleagues uncovered the GNAS connection to medulloblastomas by finding a mutation in a sample from a child's tumor. Existing medical literature revealed that the gene's function could be influenced by the antidepressant medication Rolipram.

Lu and colleagues studied this pathway using a line of mice that do not express the GNAS gene. These mice developed brain tumors, as expected, but when given the drug Rolipram, the tumors shrank. The researchers believe the drug restores the Gαs pathway's tumor suppressing power by elevating levels of a signaling molecule called cAMP. Better still, the treatment appears to help against even the toughest tumors.

"Many chemotherapies become ineffective as soon as the surface receptors they target change, but this drug may help to get inside the cells targeting a signaling juncture downstream to overcome the drug resistance," Lu says.

The Rolipram findings reflect only one drug affecting one part of the Gαs signaling pathway. Lu and colleagues are working to identify all of the other genes and related markers along the pathway. It may be that other drugs acting at other points will prove even more effective.

CHILDREN NEED KID-FOCUSED DRUGS

The medulloblastoma study is one of the first important findings from a growing team of brain tumor researchers at Cincinnati Children's. Lu arrived in Cincinnati about a year ago from the University of Texas Southwestern Medical Center in Dallas. As scientific director of the Brain Tumor Center, he works with a loosely affiliated group of more than 15 scientists here who are using whole-genome sequencing and other methods to reveal why brain tumors form and how they can be stopped.

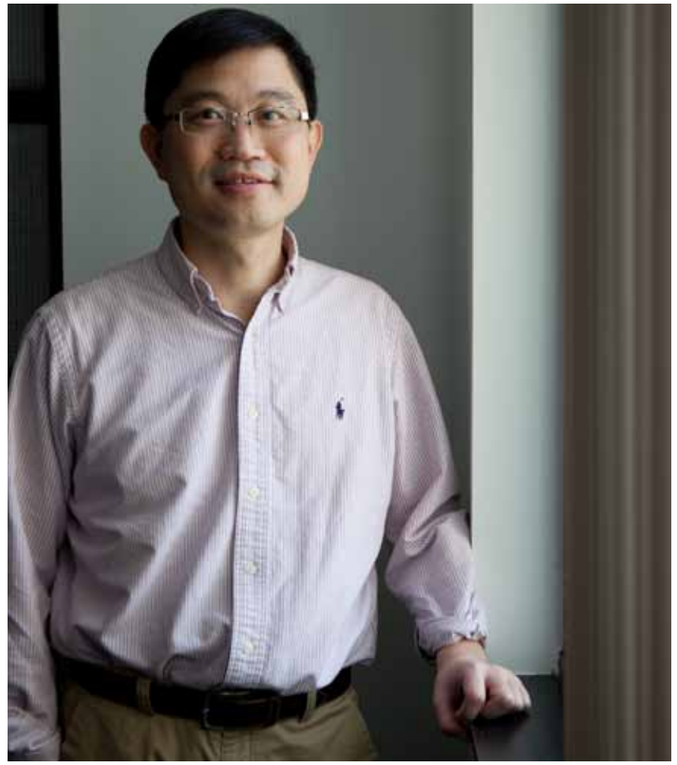
Finding precise ways to target cancer cells is especially important for treating children with brain cancer, Lu says. Several adult chemotherapies are designed to target rapidly dividing cells, which stand out as tumor markers once the adult brain is fully formed. In children with brain tumors, healthy brain cells are dividing and multiplying right alongside the cancerous ones. Simply targeting dividing cells can harm a child's developing brain.

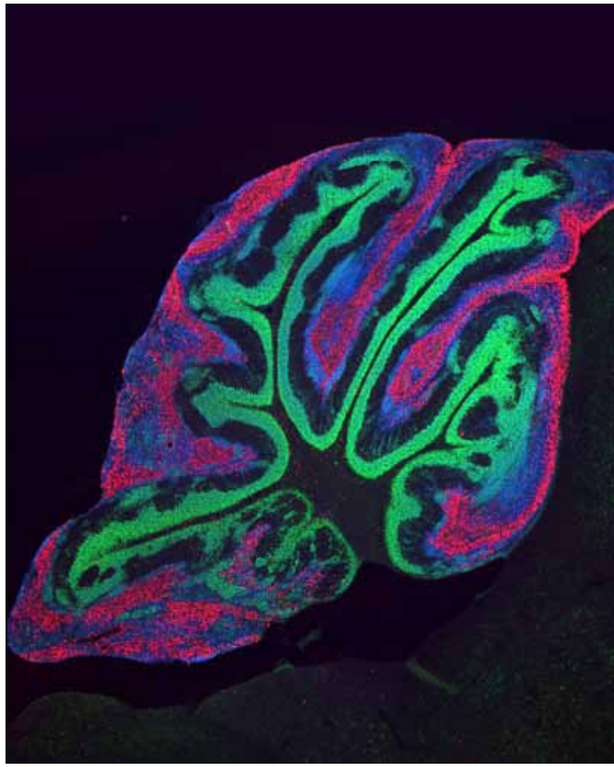
"Pediatric brain tumors are quite different than adults. Genome sequencing shows that they use different mechanisms to initiate tumor formation," Lu says. "So pediatric cancers need to be targeted in different ways."

The next step for the follow-up study will be to prepare for a clinical trial with different cAMP-raising agents. Findings that look hopeful in mice often do not work as well in humans, so it remains too early to tell how many children, if any, could be helped by a Rolipram-chemo combination therapy. Regardless, Lu sees the findings as a proof of concept. Even if Rolipram, or analogs thereof, do not work, other promising treatments will emerge by following a similar gene-disease-drug search process.

"By studying brain tumors in children with whole-genome sequencing, we will have a better chance of finding the mutations that really cause the cancer," Lu says. "In adults, we can find many mutations, but it is unclear which ones are crucial for initiating tumor formation. It will still take a few more years, but as we identify more tumor-causing factors, this will lead to more effective treatments with fewer risks of side effects." ■

Dr. Qing Richard Lu says the antidepressant Rolipram has potentially strong tumor suppressing power, especially against an aggressive form of medulloblastoma. In the image of a mouse brain below, actively dividing cancer cells appear in red.





Imaging Changes the Game for Brain Tumor Surgery

Doctors use precise technology, unmatched skill - and a strong sense of what makes us human

by Tom O'Neill

The deeper neurosurgeons navigate into the human brain to remove complex tumors, the more a simple truth emerges: image is everything.

Advancements in imaging technology have transformed not only what neurosurgeons can do once they reach a tumor, but also how they negotiate the delicate pathways to get there. The slightest deviation in a "safe corridor" through brain tissue can forever change a child's ability to move her eyes, move her toes, or move her parents to tears with a word or a smile.

Surgeons call these areas of the brain "eloquent" – one of medicine's great understatements given that they control everything from movement to emotion.

The overlapping use of functional MRI, stereotactic navigation and intraoperative neuromonitoring allows brain tumor surgeons and neuroradiologists to see the impact of each surgical decision in real time.

Research at Cincinnati Children's is driving a wide range of improvements in neurosurgery, including advanced diffusion tensor imaging (DTI) – a more detailed form of MRI – and surgical management of brain tumors and epilepsy.

"There's no question that imaging technology and new surgical tools have given us a level of safety the pioneers of neurosurgery would have thought unfathomable," says Francesco Mangano, DO, chief of neurosurgery at Cincinnati Children's. "We are able to see slight gradations of gray, and tell if we are in an eloquent area we need to avoid. From that standpoint, I think imaging has revolutionized how we do things."

Tumors in the deepest and most delicate areas of the brain, such as the thalamus and the brain stem, were once routinely considered inoperable. The brain stem is a neurosurgeon's mine field. It provides sensory and motor stimulation to the face and neck. It controls heart rate, breathing, the central nervous system, pain sensitivity, sleeping and eating.

Approximately one in five brain tumors in children are gliomas in the brain stem.

'AMAZING MOMENTS'

"When Francesco resects a tumor near the bottom of the brain stem, near those critical areas, he'll ask everyone to be quiet," says James Leach, MD, a neuroradiologist at Cincinnati Children's. "At that point he's relying on many simultaneous cues. He's listening to the patient's heart rate monitor, seeing the neuromonitoring responses, and carefully assessing the 'feel' of the tumor and surrounding tissues. Those are amazing moments."

The stakes are high. Within those eloquent regions lies the mind, which is invisible. No MRI can show a child's sense of humor or creativity.

"There are ramifications for not only a child's ability to walk or talk, but also his capacity to feel certain types of emotions," says Charles Stevenson, MD, who leads Cincinnati Children's brain tumor neurosurgery team. "Who they are. Their humanity.

"It's hard to conceptualize but it's critical to talk about that potential risk with families," he says. "That's the problem with the brain. None of our studies or scans tells us much about a person's mind. So I think about that a lot when planning these surgeries."

THE PATH OF TECHNOLOGY

Cincinnati Children's became in 2007 the first pediatric hospital in the world to employ the BrainSUITE ™ concept in the operating room, with an integrated neurosurgical microscope, high-definition screens and a specialized bed with complete, multimodality MRI capabilities. Data from pre-operative tests is automatically and precisely aligned with the position of the patient's head during surgery.

Technology is crucial, but the success of brain tumor surgery relies heavily on the team's intuitive skills, say Drs. Charles Stevenson, left, and James Leach.

The three cornerstones of surgical imaging are layered: MRI, functional MRI and tractography are the map; stereotactic imaging reveals the safest routes to a tumor; and neuro-monitoring gives immediate results of every movement.

"The deeper you go," Mangano points out, "the more difficult it is to remain oriented to where you are."

Success between surgeon and radiologist is a function of teamwork and trust. Stevenson likens surgical navigation to a military laser-guided missile.

"You want to minimize the opening in the skull, come right down on that tumor, then get out like you were never there," he says. "These tools allow us to do that."

Mangano led a research team showing how DTI reveals the neural tracts in white matter by measuring the *in vivo* diffusion of water in tissue. It was published in July 2013 in the *American Journal of Neuroradiology*. He and his team have published several articles on these advanced imaging techniques. DTI is becoming increasingly important because it provides surrogate markers – like traffic cones – within the microstructure of white matter.

Dr. Francesco Mangano is chief of the Division of Neurosurgery at Cincinnati Children's.

A LOOK AT THE FUTURE

The future of neurosurgery will bring less cutting. MRI-guided laser thermal ablation requires only a keyhole incision in the skull, through which surgeons thread a laser stylet and attack tumor tissue with light energy. It has been used primarily on adults since FDA approval for non-experimental use in 2007.

"We're starting to see studies and my gut feeling is that it's a good technique," Mangano says. "We have the technology, we just need to identify the right patient. We could be doing it here within months."

Patients will also get younger. Cincinnati Children's now performs brain surgery, including tumor resection, in children as young as several months. Swelling is a particular concern because a baby's system hasn't fully developed the ability to regulate itself. Blood transfusions are often required.

"You have to have your exit strategy," Stevenson says, "and you have to manage it in an expeditious and safe way."

THE UNBEARABLE LIGHTNESS OF SPEAKING

Leach says research at Cincinnati Children's will lead to more detailed imaging and a deeper knowledge of anesthesia's impact on brain activity in children. Language localization is elusive.

Words are, in a sense, invisible stop signs for neurosurgeons. And it's hard to avoid what you cannot see.

"That's a challenge," Leach says. "It's important to better understand how and where language is organized in children."

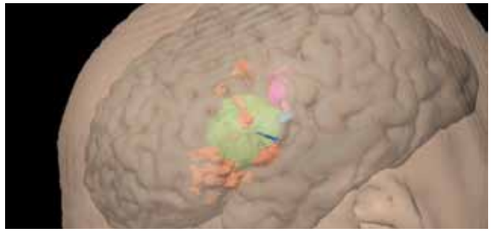
Traditionally, language was thought to concentrate in two major areas in the dominant hemisphere called Wernicke's and Broca's areas. But it's far more complex and affects children differently than adults.

One recent moment left Stevenson a bit speechless himself. He just happened to catch a TV news segment on a local cancer fund-raiser, and recognized the young woman being interviewed.

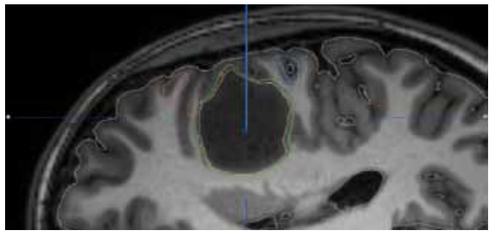
"I operated on her when she was in high school," Stevenson says. "She was a dancer, but one side of her body had grown weak, and in her class photo, half her face wasn't smiling. It was a very large tumor. And now there she was, a bright college student, a young lady with enormous potential, giving an interview beautifully – with a perfect smile. I love that." ■

THE THREE PILLARS OF IMAGING TECHNOLOGY

Functional Magnetic Resonance Imaging (fMRI) uses a magnetic field and pulses of radio wave energy to capture images of the brain "in action." Standard MRI shows the anatomy of the brain, functional MRI captures brain activity, and tractography outlines connections.



Stereotactic Navigation provides computer guidance for surgical procedures using magnetic resonance (MRI) or computerized tomography (CT) images. With it, neurosurgeons use imaging obtained prior to surgery to plan their opening and guide tumor removal.



Intraoperative Neuromonitoring captures circuitries in the brain by essentially intercepting the signal to various muscle groups, using electrodes. Any disruption, however slight, shows immediate reflexive responses that can indicate a potential functional disruption.

The Extraction of the Stone of Madness by Hieronymus Bosch, depicting trepanation (c. 1488-1516).

A BRIEF HISTORY OF BRAIN SURGERY

People have been drilling holes in skulls for a long time, to relieve everything from seizures to real or perceived mental illness.

- At one burial site in France from 6,500 BC, archaeologists found 40 prehistoric skulls with trepanation holes. A trephine is an instrument that cuts a round hole, typically near the top of the skull. Remarkably, skull growth showed that many patients survived.
- A thousand years ago, Peruvians treated head injuries with a series of holes. Patients depicted in European paintings from the Middle Ages look dire amid religious imagery.
- In 1879, Scottish physician William Macewen performed the first documented brain tumor removal. "What a leap of faith that was," Stevenson says. The teenage patient lived eight years tumor-free.
- American Harvey Cushing is considered the "father of modern neurosurgery" for the many advances he led in brain surgery. After his death from a heart attack in 1939, an autopsy revealed a potentially fatal cyst in his brain.

A Better Way to Blast Tumors

Proton therapy will revolutionize treatment and research

by Tim Bonfield

Most of the massive structure required to support the machinery within the Proton Therapy Center will never be seen by the patients treated there. More than 31,000 yards of concrete and 600 miles of rebar will be almost entirely underground once the center opens in winter 2016-17.

Enough concrete to pave a sidewalk from Cincinnati to Louisville. A machine that weighs as much as three passenger jetliners, and accelerates subatomic particles to over 100,000 miles per second. An investment exceeding $120 million.

All of it to provide the best radiotherapy treatment available for children and young adults with brain tumors, lymphoma, sarcomas and other cancers.

These are just some elements of the new Proton Therapy Center under construction at Cincinnati Children's Liberty Campus. The facility reflects the latest evolution in pediatric cancer care, and when it opens in winter 2016-17, it will be one of only two such centers in the country owned by a pediatric medical center.

"For the rising numbers of children who survive their cancers, this form of therapy will help them live much healthier lives for their next 50 years," says John Breneman, MD, radiation oncology medical director of the new center. "We expect proton therapy to become a new option for previously untreatable tumors, and to sharply reduce the long-term side effects that often occur with conventional radiotherapy."

For many children with cancer, proton therapy is the most precise and advanced forms of radiation treatment available, according to the American Brain Tumor Association. It can significantly reduce the risks of learning disabilities, heart damage and secondary cancers that can be triggered years later by exposure to conventional radiotherapy.

The Proton Therapy Center will replace conventional radiation treatments for more than 80 percent of children with cancer treated here, says Breneman, one of the nation's leaders in pediatric radiation therapy. This approach will be especially valuable for treating medulloblastomas and other brain tumors that can be difficult to treat with surgery and chemotherapy. It will also avoid damaging the heart, blood vessels and lungs when treating lymphomas in the chest.

Although more than 200 medical centers in North America provide pediatric cancer care, to date, only 13 facilities provide proton therapy. The Cincinnati facility will serve families from Cincinnati and the surrounding region as well as patients referred here from other parts of the U.S. and the world.

HOW PROTON THERAPY WORKS

Traditional radiotherapy delivers beams of X-ray energy (photons) that kill cancer cells, but also strike healthy tissues on the way into the tumor and on the way out, significantly limiting the safe maximum intensity of the treatment.

Proton therapy involves pencil-thin beams of particles (protons) that are generated by accelerating hydrogen ions in a cyclotron to two-thirds the speed of light. Accurately aimed particles stop inside the tumor, where they release all their energy, a phenomenon known as the Bragg peak. This virtually eliminates exit damage, which means proton beams can carry higher doses of cancer-killing energy and can target tumors located closer to critical structures.

Patients typically receive proton therapy five times a week for two to eight weeks. Using varying intensities of the proton beam, therapists "airbrush" tumors layer by layer, constantly adjusting to the tumor's irregular shape. The most challenging aspect is to precisely aim the particles as tumors move inside growing, breathing, restless patients. Much of the expense involved in building the Proton Therapy Center goes into the massive, computer-controlled gantries, the equipment that aims the particles as they rotate around the patient. Each gantry is about the size of a house.

"You want all of the radiation on the tumor, and if possible, none of it reaching beyond the tumor," says Breneman, who also serves as vice-chair of radiation oncology at University of Cincinnati (UC) Health. "Proton therapy comes much closer than conventional radiotherapy to achieving this."

CENTER TO PLAY LEADING ROLE IN RESEARCH

Research will play an integral role in the new facility. One of the gantries will be dedicated exclusively to research and development – making it the only fully dedicated proton research gantry in the world, says John Perentesis, MD, Executive Co-Director of the Cancer and Blood Diseases Institute. This gives a cross-campus team of scientists from Cincinnati Children's and five colleges of the University of Cincinnati unprecedented access to an emerging technology.

Experts in cancer biology, genomics, particle physics, and engineering have already begun studying ways to refine and expand the use of proton therapy. Projects include studying the biological effects of proton radiation across differing types of tumors and tissues, cancer stem cell research, and developing new therapies. Other projects will evaluate and sharpen imaging technology and computer tracking systems. Longer-term clinical studies will track outcomes and identify ideal dose levels for various cancers and age ranges, Perentesis says.

The Proton Therapy Center also will anchor a new inpatient and outpatient oncology treatment center at the Liberty Campus, developed in conjunction with the UC College of Design, Art, Architecture and Planning and its Live Well Collaborative.

"Our objective is to use 21st century technology to transform and extend the compassionate and supportive environment that families and patients already experience when receiving cancer care here, from initial diagnosis all the way through to survivorship," Perentesis says.

10 YEARS IN THE MAKING

Planning for the Proton Therapy Center reaches back a decade and will intensify in the coming months. As the project moves into final construction, Abram Gordon, the Center's executive director, will manage a flurry of details – including the mid-2015 shipment of a 90-ton cyclotron from Germany to Cincinnati.

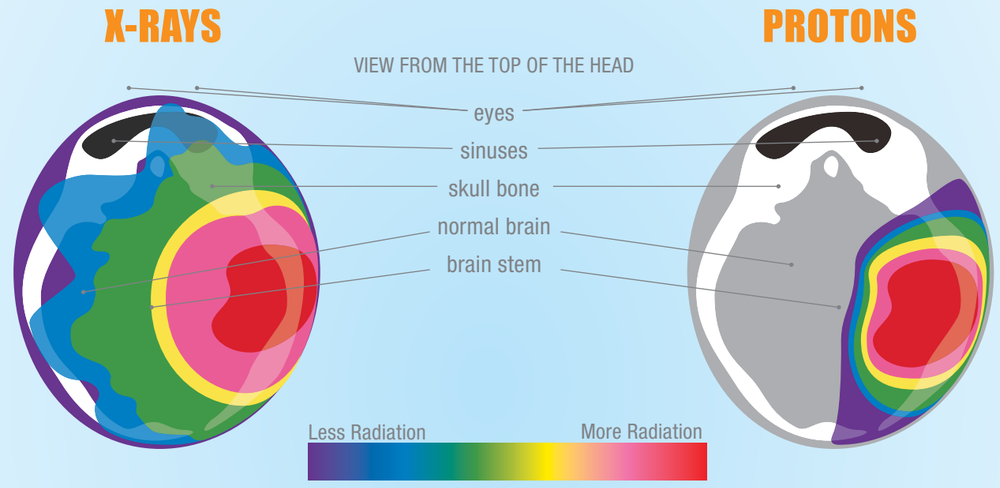
The cyclotron is so large it requires a special, multi-axle trailer to move. Roads will be closed at certain points along the route. A powerful crane will be needed to hoist the equipment into place once it arrives. The trip will take several weeks.

It will take another year to 18 months to complete the assembly, calibrate the device and obtain required inspections and approvals.

"It is a complex and expensive project," Gordon says. "Not every medical center has the resources to build something like this. But once it's ready, it will significantly improve the outcome for children with cancer." ■

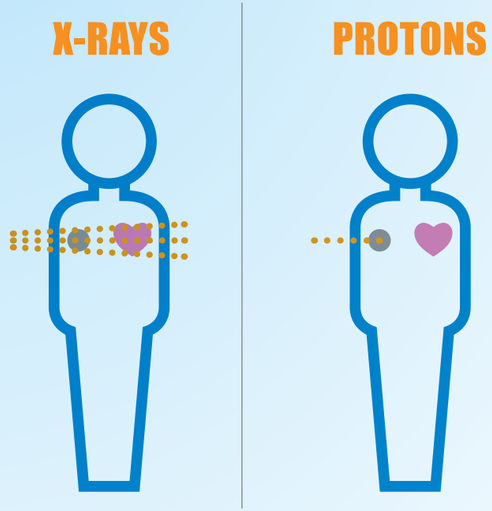
In the space currently filled with scaffolding (top), the Proton Therapy Center's massive gantries will aim proton beams at tumors. The protons will be generated by a 90-ton cyclotron (middle), then accelerated along an underground track (bottom).

PROTON THERAPY VS. CONVENTIONAL RADIATION



Proton Therapy Center at a Glance:

- Treatment to begin in winter 2016-17
- Treatment indicated for up to 85 percent of pediatric tumors
- Location: Cincinnati Children's Liberty Campus
- Cost: $120 million
- Features: Varian ProBeam® Proton Therapy system, including two clinical gantries and one gantry dedicated to research. The building includes space to add another gantry.
- Cyclotron, the heart of the system, weighs 90 tons, equivalent to three empty 737 jetliners
- Housing the particle accelerator track and gantries requires 31,000 yards of concrete, enough to pave a 120-mile sidewalk from the therapy center to Louisville, Ky.
- Materials include 155 miles of wiring and 600 miles of rebar.



Proton beams stop within the tumor rather than passing through the body, which limits radiation exposure of surrounding tissue.

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