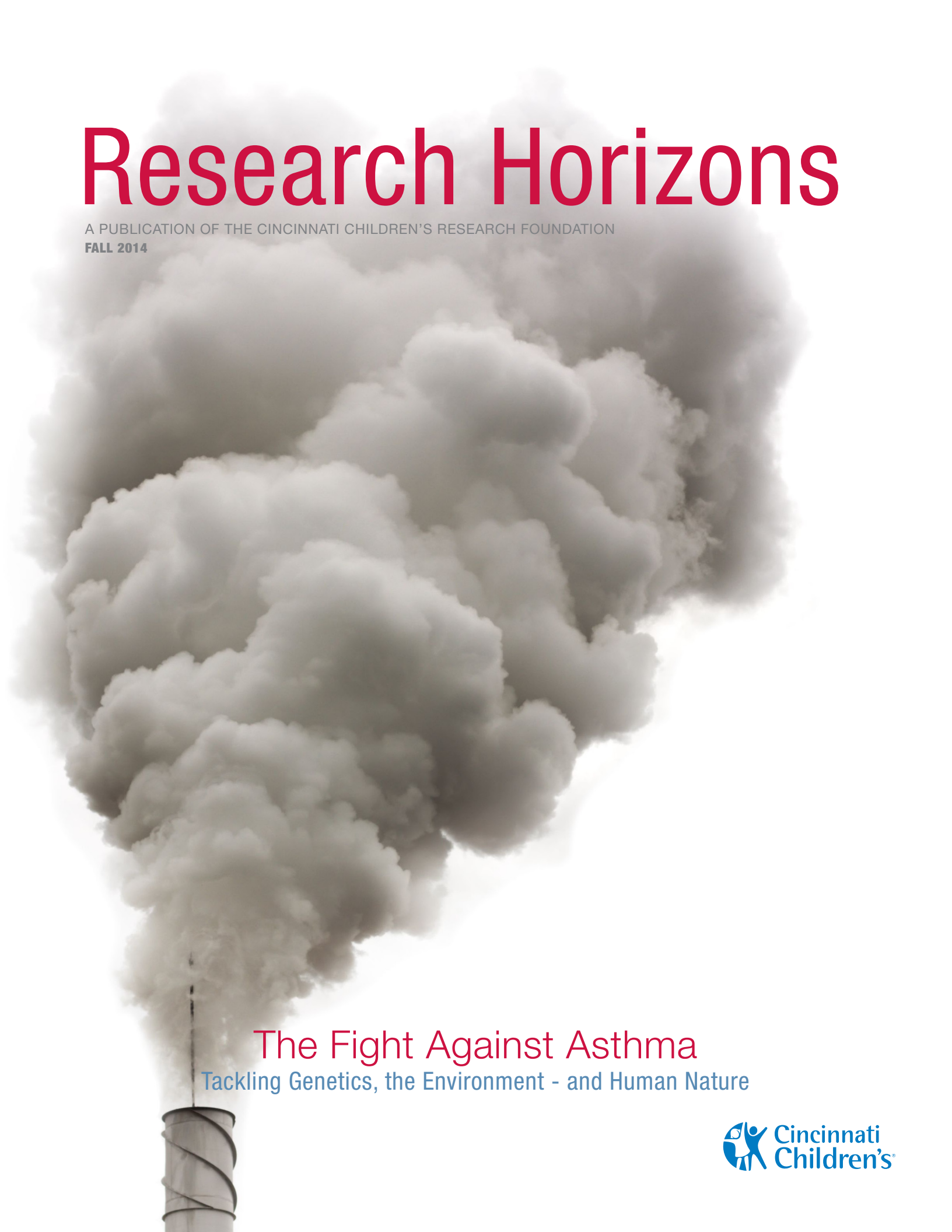
Research Horizons

A PUBLICATION OF THE CINCINNATI CHILDREN'S RESEARCH FOUNDATION
FALL 2014



The Fight Against Asthma

Tackling Genetics, the Environment - and Human Nature

Cincinnati Children's®

SOURCES FOR THESE AND ALL STATISTICS THROUGHOUT:
AMERICAN LUNG ASSOCIATION AND NATIONAL CENTER FOR HEALTH STATISTICS

Research Horizons

FALL 2014

Front Cover: Cincinnati Children's is leading the way in asthma research and clinical practice. Much of our work examines how environmental factors contribute to the disease. In Cincinnati, air pollutants, climate factors and old housing stock play significant roles in our region's higher-than-average asthma incidence.

Research Horizons

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HONORS

Robin Cotton, MD,

Division of Otolaryngology, received the 2014 Jacobson Innovation Award of the American College of Surgeons. Cotton was recognized for his seminal work in the care and reconstruction of the stenotic pediatric airway.

Robert Frenck,Jr., MD,

Division of Infectious Diseases, was named "Pediatrician of the Year" for 2014 by the Ohio chapter of the American Academy of Pediatrics.

James Heubi, MD,

Division of Gastroenterology, Hepatology and Nutrition, Director of the Clinical Translational Research Center, has been named President Elect of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

Kasper Hoebe, PhD,

Division of Immunobiology, was listed in the 2014 Thomson Reuters publication, The World's Most Influential Scientific Minds. The publication lists researchers in a variety of fields who published the greatest number of highly cited papers over the past 11 years.

Brad Kurowski, MD, MS,

Division of Rehabilitation Medicine, received the 2014 Early Career Award from the American Congress of Rehabilitation Medicine, for his significant contributions to rehabilitation research. Kurowski's investigations have focused on the long term effects of early childhood traumatic brain injury.

Punam Malik, MD,

Division of Experimental Hematology and Cancer Biology, was named the Marjory J. Johnson Endowed Chair of Gene and Cell Therapy. Malik is Director of the Comprehensive Sickle Cell Program and the Translational Trials Development and Support Laboratory.

Janeen Meinzen-Derr, PhD, MPH,

Division of Epidemiology and Biostatistics, received the Charlotte R. Schmidlapp award for 2014 in support of her research with children who have hearing loss complicated by other disabilities. The Schmidlapp Award is given to young women investigators who show leadership promise. The award grants $50,000 per year for up to two years.

Monica Mitchell, PhD,

Division of Behavioral Medicine and Clinical Psychology, was one of eight Cincinnati women distinguished as a YWCA Career Woman of Achievement for 2014. Mitchell is Senior Director of Community Relations at Cincinnati Children's and an associate professor in the Division of Behavioral Medicine and Clinical Psychology.

Nancy Ratner, PhD,

Division of Experimental Hematology and Cancer Biology, received the Jacob Javits Investigator Award for 2014. The award is given to scientists who demonstrate excellence and productivity in neurological research supported by the NINDS. Ratner's investigations focus on understanding the genetics of neurofibromatoses (NF1 and NF2).

Jeffrey Robbins, PhD,

Division of Cardiovascular Molecular Biology, has been awarded the Lucian Award by McGill University in Montreal, Canada, for his pioneering work in cardiovascular diseases. As part of the award, Robbins is invited to spend a week as visiting professor at McGill University in May 2015.

Amy Shah, PhD,

Division of Endocrinology

Shah received the Young Investigator Award from the International Society for Pediatric and Adolescent Diabetes. Each year, the award is given to an investigator under the age of 40 who makes significant contributions to the field of pediatric diabetes research. Shah refers to an article published in Diabetes in August 2013, "The effects of type 2 diabetes on lipoprotein composition and arterial stiffness in male youth," as her most significant to date.

Arnold Strauss, MD,

received the 2014 Daniel Drake Medal from the University of Cincinnati (UC) College of Medicine. The Medal is the highest honor bestowed by the College of Medicine and is given annually to living faculty or alumni for outstanding contributions to medical education, scholarship and research. A cardiologist and cardiology researcher, Strauss recently stepped down from his post as Rachford Professor and Chair of Pediatrics at UC, Director of the Cincinnati Children's Research Foundation and Chief Medical Officer of Cincinnati Children's Hospital Medical Center.

Stephen Waggoner, PhD,

Division of Immunobiology

Waggoner was one of three scientists chosen to receive the 2014 Avant-Garde Award for HIV/AIDS Research from the National Institute on Drug Abuse. Each scientist receives $500,000 per year for five years to support research into the prevention and treatment of HIV/AIDS in drug users. Waggoner's project will focus on preventing natural killer cells from destroying activated helper CD4 cells, to strengthen vaccine effectiveness.

GRANTS

Steve Danzer, PhD,

Anesthesia, will study "Identification and Reversal of Primary and Secondary Epileptogenic Changes" with a five-year, $1.6 million grant from the National Institute of Neurological Disorders and Stroke.

Rashmi Hegde, PhD,

Developmental Biology, will use a four-year, $1.3 million grant from the National Eye Institute to study "Mechanism of Action of Retinal Determination Proteins."

FuKun Guo, PhD,

Experimental Hematology and Cancer Biology, will use a four-year, $1 million grant from the National Institute of General Medicine Sciences to pursue "Novel Signaling Function of Cdc42 GTPase In Vivo."

Michael Jordan, MD,

Immunobiology, will use a $1 million, four-year grant from the National Institute of Allergy and Infectious Diseases to examine "Exploiting the DNA damage response to selectively sculpt the TCR repertoire."

Ian Lewkowich, PhD,

Immunobiology, will pursue the study of "Mechanisms of IL-17A-mediated Enhancement of Asthma Severity" with the help of a $1.8 million award over five years from the National Heart, Lung and Blood Institute.

Qing Richard Lu, PhD,

Brain Tumor Center, will study "A Novel Model of Medulloblastoma to Define Cancer Pathways and Molecular Targets" with a $1.2 million grant over four years from the National Institute of Neurological Disorders and Stroke.

Peter Margolis, MD,

James Anderson Center for Health Systems Excellence, will use a one-year, $1 million grant from the Patient-Centered Outcomes Research Institute for the "Improve Care Now" network.

Sean Moore, MD,

Gastroenterology, Hepatology and Nutrition, will use a two-year, $1 million grant from the Bill & Melinda Gates Foundation to explore "Epigenetic Modeling of Environmental Enteropathy in Mice."

Nancy Ratner, PhD,

Experimental Hematology and Cancer Biology, will study "Ras Proteins in Nerve Tumorigenesis" with the help of a five-year, $1.6 million grant from the National Institute of Neurological Disorders and Stroke.

Michael Rosen, MD, MS,

Gastroenterology, Hepatology and Nutrition, will examine "Th2 Cytokines and signaling in Pediatric Inflammatory Bowel Disease," aided by a five-year, $1.1 million award from the National Institute of Diabetes and Digestive and Kidney Diseases.

Amy Shah, MD,

Endocrinology, will use a $1 million grant from the National Heart, Lung and Blood Institute over five years to pursue "Understanding the Role of HDL Subspecies in Adolescents."

Samir Shah, MD,

Hospital Medicine, will study "Improving Post-Discharge Outcomes by Facilitating Family-Centered Transitions from Hospital to Home" with the help of a $2 million grant over three years from the Patient-Centered Outcomes Research Institute.

Earl Siegel, PhD,

Drug and Poison Information Center, will continue work on a "Poison Control Stabilization and Enhancement Program," with supplemental funding of a five-year, $1.4 million grant, now in its final year, from the Health Resources and Services Administration.

Bruce Trapnell, MD,

Neonatology and Pulmonary Biology, will use a four-year, $2.5 million grant from the National Heart, Lung and Blood Institute to study "Macrophage Based Gene Therapy for Hereditary Pulmonary Alveolar Proteinosis."

Jeff Whitsett, MD,

Neonatology and Pulmonary Biology, will use a five-year, $1.2 million grant from the National Heart, Lung and Blood Institute to study "Lung and Cardiovascular Development and Disease Pathogens."

Hector Wong, MD,

Critical Care Medicine, will use a four-year, $1.9 million award from the National Institute of General Medicine Sciences to examine "Novel Diagnostic and Stratification Tools for Septic Shock."

Aaron Zorn, PhD,

Developmental Biology, will study the "Molecular Basis of Digestive System Development in Xenopus" with the help of a four-year, $1.4 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

Arnold W. Strauss Fellow Award

Six Cincinnati Children's fellows were named Arnold W. Strauss Fellows in this inaugural year for the fellowship program. The Strauss Fellow Award program was instituted in 2014 in honor of Arnold Strauss, MD, who stepped down July 1 from directing the Cincinnati Children's Research Foundation.

Each award is a one-year, $10,000 funding opportunity; three are awarded to clinical fellows (MDs) and three to postdoctoral fellows (PhDs).

THE 2014 RECIPIENTS ARE

Nihal Bakeer, MD
Cancer and Blood Diseases Institute

Yoshinobu Odaka, PhD
Ophthalmology

Amanda Schondelmeyer, MD
Hospital Medicine

Nicole M. Sheanon, MD
Endocrinology

Fuli Xiang, PhD
Molecular Cardiovascular Biology

Changwen Zhang, PhD
Gastroenterology, Hepatology & Nutrition

Heart Repair with Stem Cells Needs Further Exploration

A researcher at Cincinnati Children's Hospital Medical Center advises caution in treating heart attack patients with cardiac stem cells to regenerate damaged tissue.

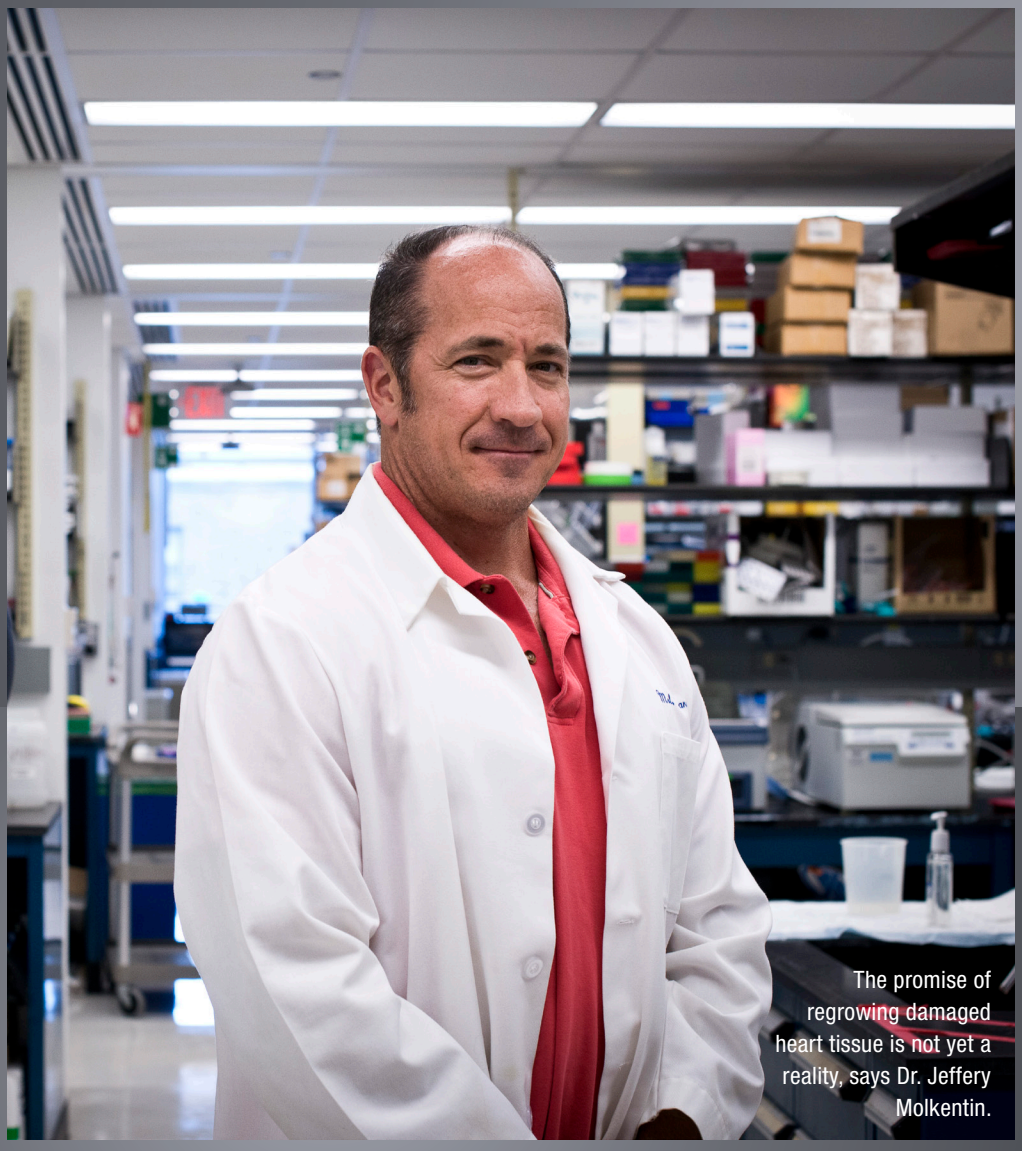
A study of ongoing clinical trials that use the stem cells suggests that they do not regenerate contractile heart muscle cells at high enough rates to justify the treatment, says its principal investigator Jeffery Molkentin, PhD.

In a May 7 report in the journal *Nature*, Molkentin, a cardiovascular molecular biologist and Howard Hughes Medical Institute investigator at Cincinnati Children's, uncovered new evidence in what has become a contentious debate in the field of cardiac regeneration.

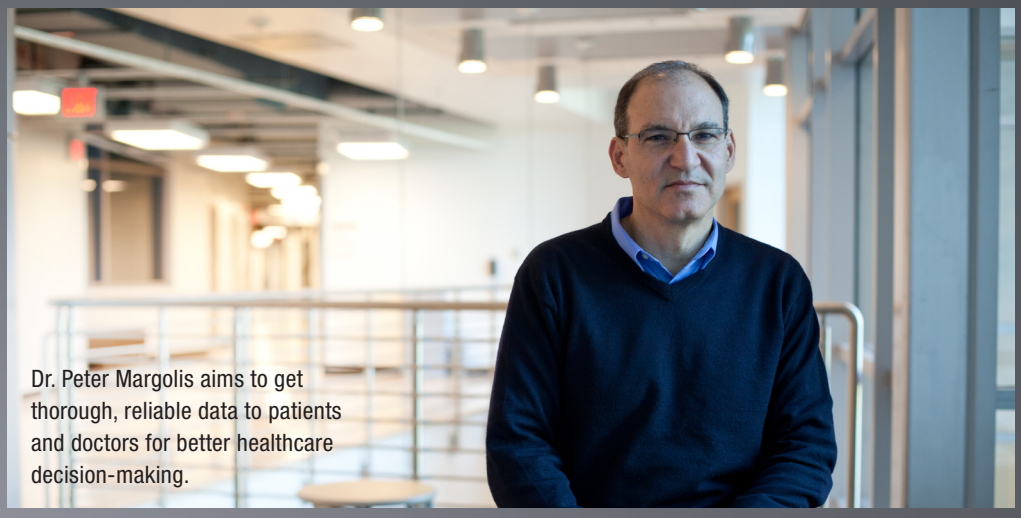
"The stem cells will produce cardiomyocytes, but at rates so low – roughly one in every 3,000 cells – it becomes meaningless," says Molkentin. The stem cells are removed from healthy regions of a damaged heart, then processed in a laboratory before being re-injected into the heart.

The experimental treatment is based largely on preclinical studies in rats and mice, which suggested that the stem cells completely regenerate myocardial cells and heart muscle. The preclinical studies involving rodents don't reflect what really occurs within the heart after injury, where internal regenerative capacity is almost non-existent, according to the report by Molkentin and his colleagues.

"Caution is warranted until the mechanisms in play are better defined or we are able to dramatically enhance the potential of these cells to generate cardiomyocytes," Molkentin says.



The promise of regrowing damaged heart tissue is not yet a reality, says Dr. Jeffery Molkentin.



Dr. Peter Margolis aims to get thorough, reliable data to patients and doctors for better healthcare decision-making.

Creating a National Network for Clinical Research

Having a comprehensive national compendium of data about which tests and treatments work best for specific conditions would provide an inestimable advantage to care for doctors and patients alike.

It is why PCORnet, the National Patient-Centered Clinical Research Network, was developed. And Peter Margolis, MD, PhD, James Anderson Center for Health Systems Excellence, will help make it a reality. Margolis was recently chosen to chair the PCORnet Steering Committee.

PCORnet (www.pcornet.org) is a $100 million initiative of the Patient-Centered Outcomes Research Institute (PCORI). Its goal is to improve the nation's capacity and efficiency in conducting comparative effectiveness research – research that helps determine what works best for patients with specific conditions. PCORnet will do this by creating a large, representative network for conducting clinical outcomes research.

PCORI was authorized by Congress to conduct research to provide information about the best available evidence to help patients and their healthcare providers make more informed decisions. PCORI's research is intended to give patients a better understanding of available prevention, treatment and care options, and the science that supports those options.

Margolis is also principal investigator of the ImproveCareNow Network (www.improvecarenow.org) and co-principal investigator of PEDSnet.

Cincinnati Children's Inventions get Third Frontier Boost

An additional $3 million grant from Ohio's Third Frontier technology development initiative will help ideas and technology conceived in Cincinnati Children's laboratories move into the marketplace.

The grant is the third given to Cincinnati Children's from the Third Frontier; in the first two rounds, the medical center received a total of $4.2 million. Those funds were invested in seven start-up companies based on Cincinnati Children's technologies. To date, those companies have attracted additional investment of more than $50 million and created some 200 biotech jobs with average annual salaries exceeding $100,000.

The medical center will match the latest grant with our own $3 million investment; the combined $6 million "Tomorrow Fund" will help finance promising initiatives and startups.

Cincinnati Children's has a number of research and development initiatives in place to identify new technologies for unmet medical needs, especially those involving rare pediatric conditions.

Record Year for Kidney Transplants

Problems caused by obesity could be one reason for an increase in pediatric kidney transplants, says Dr. Jens Goebel.

Surgeons at Cincinnati Children's performed 34 kidney transplants in 2013 – more than any other pediatric medical center in the United States.

In past years, no more than 30 children had received kidney transplants in a single year, says Jens Goebel, MD, Medical Director of kidney transplantation. Goebel says the latest increase was driven by two factors. One is fetal treatments that allow more infants to survive bladder outlet obstructions. Many of these children later need kidney transplants.

The second cause was a steady increase in focal segmental glumerosclerosis (FSGS), a disease that attacks the kidneys' filtering system and causes scarring. In children, FSGS is the most common cause of end-stage kidney disease. "Nobody really knows why FSGS is on the rise, but the obesity epidemic may be one of the explanations," Goebel says. He adds that more children with advanced FSGS are being referred to Cincinnati Children's because we are an NIH Center of Excellence for FSGS research.

Bacteria, Genes Linked to Severe Crohn's Disease

The discovery of specific bacterial populations and a core gene signature associated with Crohn's disease could lead to new diagnostic testing and improved treatment, according to a study by Cincinnati Children's researchers and published July 8 in the online *Journal of Clinical Investigation*. Yael Haberman Ziv, MD, was the study's first author.

"This study identifies a set of bacteria that are associated with symptoms, and a group of anti-inflammatory genes that are associated with intestinal damage in children with Crohn's disease," says Lee (Ted) Denson, MD, Medical Director of the Inflammatory Bowel Disease Center and one of the study's authors.

Investigators studied tissue samples from the ileum, the lowermost portion of the small intestine, in a large number of children with Crohn's disease. They found specific types of bacteria and a "core" gene expression signature, both of which appear to affect inflammatory changes in the gut. In addition, certain genes in the core signature appeared to be specifically associated with intestinal damage from deep ulcers.

The presence of these bacterial and gene expression factors could improve accuracy in predicting the outcomes of treatment, compared to conventional clinical diagnosis. This information might help doctors target patients who can benefit from more intensive treatment for Crohn's disease—particularly as newer biological therapies become available.

Nearly 1.4 million American adults and children suffer from Crohn's disease or ulcerative colitis. Symptoms include abdominal pain, persistent diarrhea, rectal bleeding, fever, fatigue and weight loss. The illnesses can cause severe complications, including colon cancer in patients with long-term disease. There is no known cure.

The study was sponsored by the Crohn's & Colitis Foundation of America.

Hermine Brunner, Md, Will Lead Division of Rheumatology

Hermine Brunner, MD, has been appointed Director of the Division of Rheumatology. Brunner joined Cincinnati Children's in 2001, where she has focused on clinical treatment and outcomes in lupus erythematosus. Brunner has published more than 125 peer-reviewed manuscripts, reviews and book chapters and is active in the Lupus Foundation of America and the Arthritis Foundation. She received her medical degree from Ludwig Maximillians University in Munich, conducted her pediatric residency at the University of Chicago and her pediatric rheumatology fellowship at the Hospital for Sick Children in Toronto.

Steroids Ineffective, Possibly Harmful In Treating Biliary Atresia

Steroid treatment after surgery for biliary atresia can cause more harm than good, says gastroenterologist Dr. Jorge Bezerra.

Treating infants with high doses of steroids after surgical treatment fails to improve outcomes in children with biliary atresia and can lead to earlier onset of serious adverse events, according to data from a new study.

Biliary atresia is the leading reason for pediatric liver transplantation. Some physicians contend that steroid treatments improve outcomes from hepatoportoenterostomy, also known as the Kasai procedure. This study indicates otherwise.

"Although we cannot exclude some small potential benefit from steroid treatment, we observed no statistical differences in two-year survival between patients receiving steroid treatment after surgery and those receiving placebo," says Jorge Bezerra, MD, in the Division of Gastroenterology, Hepatology and Nutrition at Cincinnati Children's.

Results from a 14-center clinical trial involving 140 infants were published May 7, 2014, in the *Journal of the American Medical Association (JAMA)*.

Studies Show Promise for Treating Troublesome Food Allergy

Two recently published findings might clear a path to better treatment for a difficult-to-manage food allergy.

Research reported online July in *Nature Genetics* identifies a new genetic and molecular pathway in the esophagus that causes eosinophilic esophagitis (EoE).

A chronic inflammatory disorder of the esophagus, EoE is triggered by allergic hypersensitivity to certain foods and an accumulation of eosinophils (white blood cells) in the esophagus. It causes gastrointestinal distress, difficulty swallowing, tissue scarring, fibrosis, strictures and other medical complications.

A team of researchers, led by Marc Rothenberg, MD, PhD, Director of the Division of Allergy and Immunology and the Center for Eosinophilic Disorders, and John Harley, MD, PhD, of the Center for Autoimmune Genomic Etiology, identified a molecular pathway specific to epithelial tissue in the esophagus that involves a gene called calpain14 (CAPN14). The gene becomes dramatically up-regulated in the disease process. The researchers attribute the up-regulation to the immune hormone Interleukin 13 (IL-13), a well-known molecular activator of EoE. Because CAPN14 can be inhibited by drugs, the study opens up new therapeutic possibilities, say the researchers.

In another finding for EoE, the results of a clinical trial led by Rothenberg published in the July 2014 *Gastroenterology* showed that high doses of the corticosteroid fluticasone propionate halted the inflammation of eosinophilic esophagitis (EoE) in a number of people. Some trial participants did not respond to fluticasone, however, even after six months of high-dose treatments, providing evidence that certain people with EoE are steroid-resistant. By analyzing gene expression in esophageal tissues, the scientists identified a cluster of genes that may help predict steroid responsiveness. The study was funded by the National Institute of Allergy and Infectious Diseases.

Treatments targeting the molecular underpinnings of eosinophilic esophagitis could be key to managing the disease, says Dr. Marc Rothenberg.

A Molecular Key to a Healthy Pregnancy

A team led by Dr. Sudhansu K. Dey has identified a signaling gene crucial to healthy embryo implantation in the uterus.

Researchers have identified a crucial molecular key to healthy embryo implantation and pregnancy, in a study led by Cincinnati Children's that could improve treatment of infertility and abnormal development of the placenta.

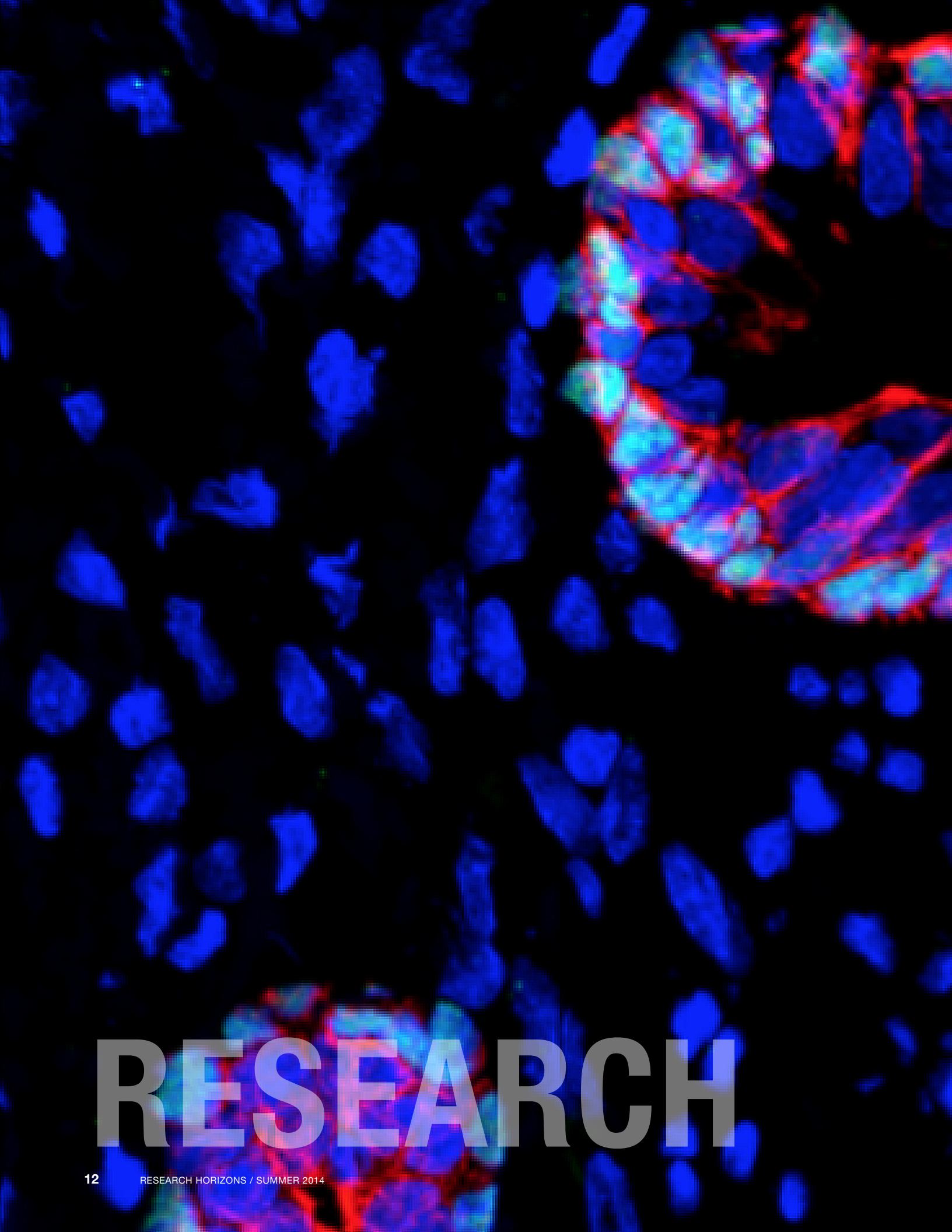
The scientists found that uterine expression of a gene called Wnt5a – a major signaling molecule in cell growth and disease – is also critical to healthy embryo implantation in the uterus. The study was published in *Cell Reports* on July 17.

Research on mice showed that molecular signaling from Wnt5a, working with its co-receptors in the uterus, causes uterine implantation chambers – or crypts - to form at regular intervals. The signaling also helps direct embryos as they settle into the womb. The authors say disruption of appropriate uterine signaling leads to abnormal formation of the crypt and spacing of embryos.

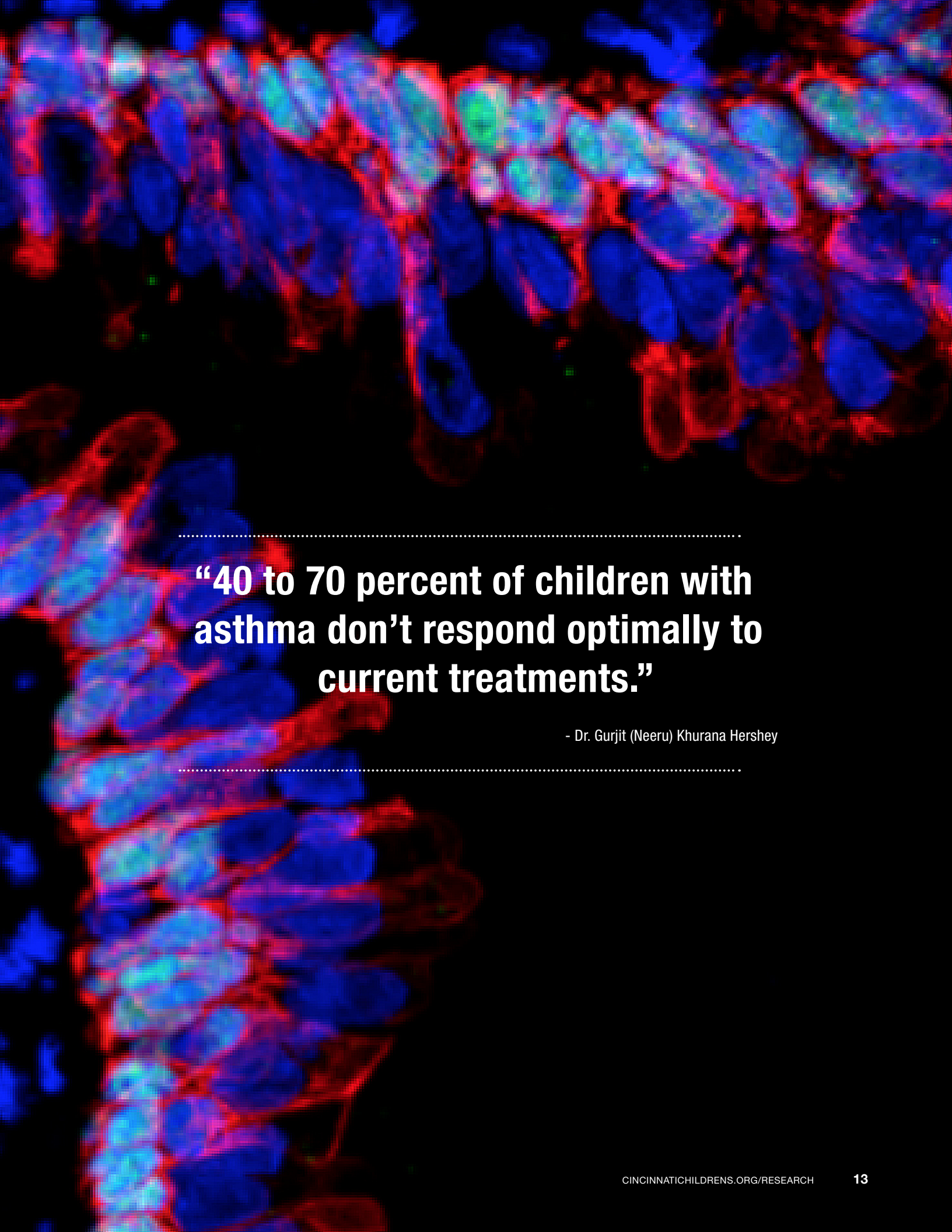
"Proper implantation is important to healthy pregnancy, and it is not clearly understood what prompts embryos to move and implant within a uterine crypt with regular spacing," says Sudhansu K. Dey, PhD, senior investigator and Director of Division of Reproductive Sciences at Cincinnati Children's. "If something goes wrong at this stage, there could be adverse effects throughout the course of pregnancy – whether it is subfertility, infertility, restricted growth, miscarriage or preterm birth."

Despite some differences in mouse and human implantation, signaling in embryo spacing could be clinically relevant, Dey says, because the embryo sometimes implants close to or on the cervix. That causes extensive bleeding that could endanger both mother and fetus.

The study is a continuation of research Dey and his team published in 2011 in *Developmental Cell*. It was funded in part by the National Institutes of Health and the March of Dimes. Collaborators included researchers from the National Institute of Genetics in Japan, the University of California at Davis and the National Cancer Institute.



RESEARCH



“40 to 70 percent of children with asthma don’t respond optimally to current treatments.”

- Dr. Gurjit (Neeru) Khurana Hershey

Asthma ATTACK

Fighting asthma on many fronts reflects the realities of a disease with confoundingly complicated causes.

by Mary Silva

Cincinnati often makes the list of worst cities in the nation for asthma sufferers. The rate of asthma here, particularly among African American, city-dwelling children, is consistently higher than in other regions of the country. And it has risen steadily, here and nationally, since 2001.

So, too, has the rate of research in asthma at Cincinnati Children's. Gurjit (Neeru) Khurana Hershey, MD, PhD, Director of the Division of Asthma Research since 2008, has assembled an A-list team of scientists within her division and throughout the medical center who are helping unlock asthma's secrets.

WHY STEROID RESPONSE VARIES

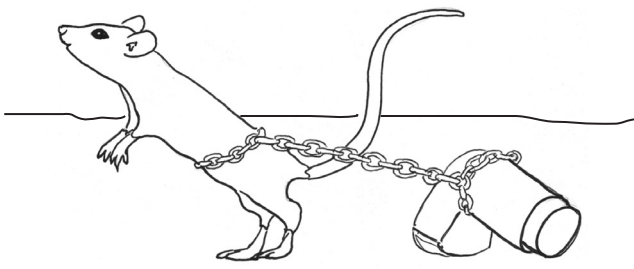
Khurana Hershey's own research focuses on finding better treatment. Steroids are often used to decrease inflammation in the lungs. But the drugs work better for some kids than others, even when dosing is exactly the same.

"Forty to 70 percent of children with asthma don't respond optimally to current treatments," Khurana Hershey says. "Why is that and what can we do for these kids?"

In one study just completed, Khurana Hershey examined children who were hospitalized for their asthma. After taking a sample of airway cells on admission, doctors followed up 24 hours later, after steroid treatment.

"Most of the kids get better and leave the hospital within 24 hours," Khurana Hershey says. "But some need to stay significantly longer. It's not because they have worse asthma. We think it's because they don't respond well to the medication."

She believes the lack of response is due to biologic differences. In animal studies, Khurana



Hershey and her team isolated a gene that appears to separate mice that respond to steroids from those that do not. Mice without the gene do not respond well to steroids.

RESTORING RESPONSE

The finding could help identify children who would not be helped by steroids, even before treatment begins. Khurana Hershey is testing a compound derived from the gene that may restore steroid responsiveness. She says the compound, "is produced naturally by the body, we can replace it, and we believe it will make kids more responsive to steroids." She has written a grant to conduct a trial of the compound and predicts it will have a major impact on the health of children who do not respond to steroids, and on the cost of caring for them.

BLOCKING INFLAMMATORY RESPONSE

In another treatment-related study, Khurana Hershey teamed with Eric Brandt, PhD, Division of Asthma Research, and epidemiologist Patrick Ryan, PhD, of the Division of Biostatistics and Epidemiology, to explore the impact of diesel exhaust particles (DEP) on children's asthma.

They published findings last November in the *Journal of Allergy and Clinical Immunology* that when kids with allergic asthma are exposed to high levels of diesel exhaust, they develop more severe asthma and have elevated levels of IL-17 (Interleukin 17), a molecule that feeds inflammatory response. These kids also do not respond well to steroids.

Khurana Hershey is now exploring the use of a drug already on the market for another use that, she says, "completely blocks the increase of IL-17 and the harmful effects of DEP in animal models." She is awaiting approval by the FDA to test the drug in this new way.

MEMORY OF EXPOSURES PAST

Finally, Khurana Hershey is studying the influence of DEP exposure on memory cells in the lungs and the severity of asthma upon re-exposure to an allergen such as house dust mite. Memory cells are marvels of the immune system, responding to antigens we have been exposed to previously. In the case of a vaccine, memory cells serve us well – with asthma, not so much.

Khurana Hershey's mouse studies show that early DEP exposure appears to have a major impact on memory cells. "The cells persist and are just sitting there in the lungs, waiting to react," she says. "Every time you have another allergen exposure, they go into overdrive and cause inflammation."

Her findings could lead to new approaches to treatment.

"We know now we have to prevent the exposure. We have to think about the memory cells and not just treat the acute event. It changes the whole focus about how you think about the disease."

Dr. Gurjit Khurana Hershey

GENE DISCOVERY RAISES QUESTIONS ABOUT A TRUSTED BIOMARKER

Just by breathing secondhand tobacco smoke, we take in more than 7,000 chemicals. Hundreds of them are harmful, and many are known to cause cancer.

For children whose lungs are already compromised by asthma, the effects can be particularly devastating. Jocelyn Biagini Myers, PhD, an epidemiologist in the Division of Asthma Research, studies these effects.

THE IMPACT OF SECONDHAND SMOKE

There is plenty of evidence that secondhand smoke poses special problems for kids with asthma. The latest surgeon general's report on the effects of secondhand smoke states that children with asthma who are exposed to secondhand smoke have more frequent and more severe asthma attacks.

"The literature supports that children whose parents smoke are more likely to develop asthma and have more severe asthma," Biagini Myers says.

But some children with asthma are more susceptible than others to secondhand smoke. Biagini Myers and her team suspected that genetics played a part.

THE GENETIC DIFFERENCE

In a study recently accepted for publication in *Pharmacogenomics,* the researchers identified a novel gene, NAT1, that could be partially responsible for differences in cotinine level. A child who has a mutation in the NAT1 gene shows much higher hair cotinine levels than someone who does not have the mutation, even for the same amount of smoke exposure. Since the NAT1 gene is involved in the breakdown of many harmful compounds present in secondhand smoke, this could mean that children with the mutation are more susceptible to smoke exposure.

Doctors have relied on the biomarker cotinine to determine smoke exposure. A child's cotinine level should correspond to his nicotine exposure. This recent discovery could change that thinking.

"Variation in the genes that metabolize nicotine to cotinine can shut the process down or cause it to happen more rapidly," Biagini Myers says. "So two children living in the same house with the same exposure can have different levels of cotinine because of their genetic makeup."

The NAT1 mutation might offer a major clue. Understanding the variation is critical to characterizing children's exposures to secondhand smoke, says Biagini Myers, particularly kids with asthma.

"Our gold standard biomarker of exposure isn't without shortcomings. The biomarkers don't always correlate well with parental reports of exposure, and this might be one of the reasons why."

Dr. Jocelyn Biagini Myers

SHEDDING LIGHT ON A COMPLEX IMMUNE RESPONSE

A researcher in the Division of Immunobiology and Center for Systems Immunology hopes to expand the understanding of immune response in asthma with the help of his first R01 grant.

Ian Lewkowich, PhD, will use the five-year, $1.8 million grant from the National Heart, Lung and Blood Institute to examine immune response in severe asthma.

Scientists now realize that severe asthma is driven by different biological mechanisms than those underlying its milder forms. Lewkowich studies a more recently recognized immune cell in asthma that he believes plays a role in regulating severity, the Th17 cell.

In milder disease, asthma-inflamed lungs contain many eosinophils but few neutrophils, white blood cells that respond to infection. But in the more severe asthma that Lewkowich studies, neutrophils dominate. The Th17 cell, a relative newcomer to the helper T cell compendium, triggers this neutrophil-dominant immune response.

"Th17 cells, recruited to the inflamed lung on allergen exposure, produce factors that recruit neutrophils," Lewkowich says.

Those factors are cytokines, proteins crucial to immune response. Th2 cells, long associated with asthma, produce IL (Interleukin)-13; Th17 cells produce IL-17. Lewkowich suspects that the interplay of these two cytokines in the lungs increases asthma severity. "With this grant, I hope to tease out in detail the mechanism behind how these two cytokines interact."

HOW THEY GOT THERE

The presence of the two cytokines in the lung starts with an allergic individual's first exposure to an allergen. "For some reason the individual has a mixed Th2 and Th17 response," Lewkowich says, "and it develops into a situation where both cells are in the lungs, and both produce factors that cause more severe asthma."

He has observed this interaction in mouse studies.

"If we give IL-13, we induce airway hyperactivity and inflammation. If we give IL-17, we don't induce airway hyperactivity or mucus production. But when we give both, IL-17 enhances what IL-13 is doing. We get worse disease. This was a starting point to find out how IL-17 was driving more severe asthma."

Th17 cells could also play a role in milder forms of disease as well, Lewkowich says, as they constitute a normal response to infection in the lung. Th17 cells are drawn in to fight the infection, and they produce IL-17.

"The immune cells react as they should, producing IL-17. But the IL-17 mixes with IL-13 that is already present because of the asthma, and results in an asthma exacerbation - a period of uncontrolled disease."

Lewkowich will use his grant to explore other aspects of this cytokine mix, including what he terms "transcriptional cooperation between the two cytokines." He has also teamed with Melinda Butsch Kovacic, PhD, and Gurjit "Neeru" Hershey, MD, PhD, to look at response to and production of IL-17 in individuals with varying degrees of asthma severity.

He hopes his research will result in better treatments for severe asthma.

"My grant won't solve asthma, but if we can get a better understanding of the mechanisms that drive severe asthma and use that understanding to help make treatments more effective, that would be great."

Dr. Ian Lewkowich

THE POWER OF THE EPIGENOME

It might be time to reconsider the notion that our DNA is our destiny. There is mounting evidence that the epigenome wields an equally powerful influence over our health. Hong Ji, PhD, is a believer, and interested in epigenetic influences on asthma.

Ji "came across the idea of the epigenome" while looking to take her postdoctoral studies in a new direction. She was excited by the possibility of changing one's biological fate. "You can't really change your genome, but you can alter your epigenome."

She now studies the effects of environmental assaults on the epigenome, and their impact on asthma.

Ji describes epigenetics as "the place between the environment and the genome." Genes need instructions for what to do and when. Those instructions lie in the chemical markers and switches that make up the epigenome; these switches turn the expression of genes on and off.

Toxins such as air pollution or secondhand smoke "can have a powerful effect on the epigenome and can alter gene expression," Ji says. She believes this occurs by affecting DNA methylation, a type of epigenetic signaling.

TOXINS AND DNA

"DNA methylation changes the way a gene is packaged and how it is expressed," Ji says. DNA is tightly wound around proteins within each cell; changes to this packaging can determine whether the genes in that cell are expressed or not.

In one recently completed study, Ji and her colleagues measured the extent of DNA methylation from secondhand smoke exposure in children with asthma.

"We found that secondhand smoke exposure modifies a gene that regulates IL-17 production and T helper 17 cells' differentiation through methylation," says Ji.

IL-17 plays a significant role in inflammation in asthma; its expression level ties to disease severity. The researchers found that greater exposure to secondhand smoke seems to increase the methylation of this gene, possibly resulting in increased inflammation.

"We need more research to prove this," says Ji, "but it would speak to why secondhand smoke could increase asthma severity."

In another study of DNA methylation, Ji is working with colleagues at Cincinnati Children's to study African-American sibling pairs who live in the same household, but one has asthma and one does not. The researchers divided their study between children who live in areas of high air pollution and those who do not.

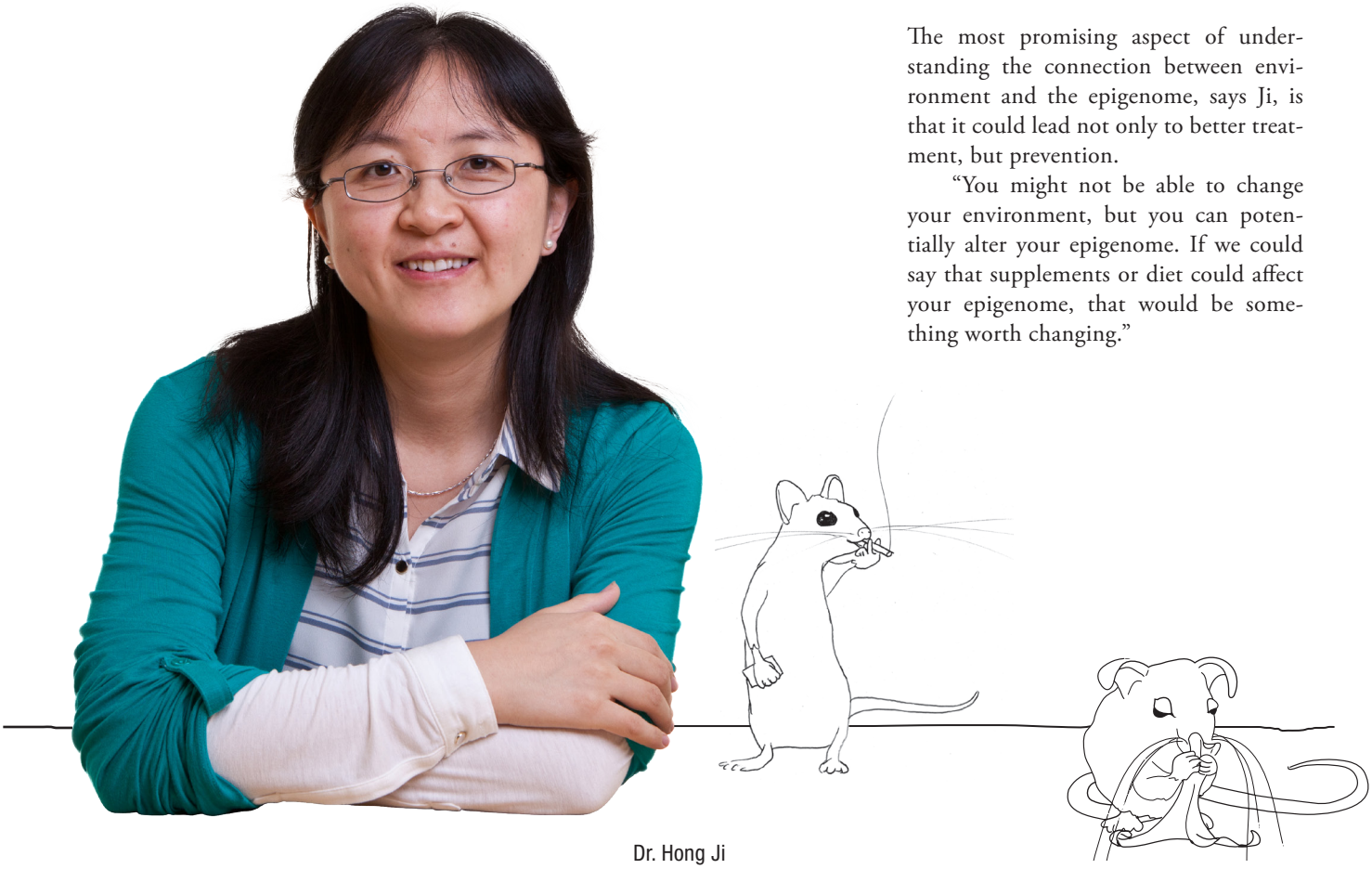
When Ji compared their DNA methylation profiles, one factor stood out.

"Their methylation levels were modified by how much air pollution they were exposed to," she says. "No matter if you have asthma or not, your epigenome appears to be modified by air pollution."

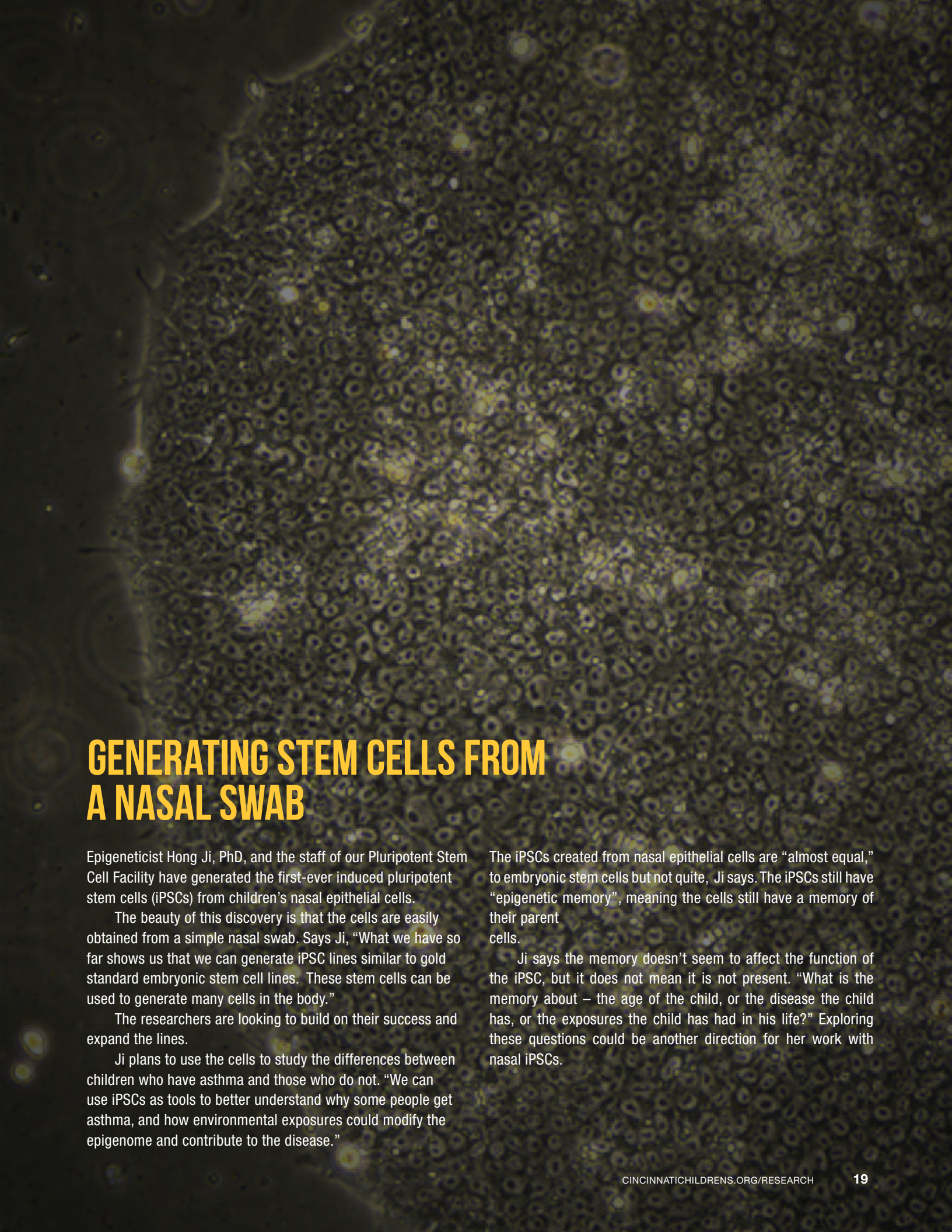
THE POSSIBILITIES

The most promising aspect of understanding the connection between environment and the epigenome, says Ji, is that it could lead not only to better treatment, but prevention.

"You might not be able to change your environment, but you can potentially alter your epigenome. If we could say that supplements or diet could affect your epigenome, that would be something worth changing."



Dr. Hong Ji



GENERATING STEM CELLS FROM A NASAL SWAB

Epigeneticist Hong Ji, PhD, and the staff of our Pluripotent Stem Cell Facility have generated the first-ever induced pluripotent stem cells (iPSCs) from children's nasal epithelial cells.

The beauty of this discovery is that the cells are easily obtained from a simple nasal swab. Says Ji, "What we have so far shows us that we can generate iPSC lines similar to gold standard embryonic stem cell lines. These stem cells can be used to generate many cells in the body."

The researchers are looking to build on their success and expand the lines.

Ji plans to use the cells to study the differences between children who have asthma and those who do not. "We can use iPSCs as tools to better understand why some people get asthma, and how environmental exposures could modify the epigenome and contribute to the disease."

The iPSCs created from nasal epithelial cells are "almost equal," to embryonic stem cells but not quite, Ji says. The iPSCs still have "epigenetic memory", meaning the cells still have a memory of their parent
cells.

Ji says the memory doesn't seem to affect the function of the iPSC, but it does not mean it is not present. "What is the memory about – the age of the child, or the disease the child has, or the exposures the child has had in his life?" Exploring these questions could be another direction for her work with nasal iPSCs.

STOPPING INFLAMMATION BEFORE IT STARTS

For the many children with asthma who are not helped by steroids, demand runs high for a more precise inflammation blocker.

Patricia Fulkerson, MD, PhD, a researcher in the Division of Allergy and Immunology, targets the progenitor cells that develop into eosinophils, white blood cells that can cause havoc in the lungs of asthmatic children.

Eosinophils have long been known to play a tissue-damaging role in the late stages of asthma-related inflammation. But in the past decade, they also have they been found to play a significant role in the earliest stages of immune response.

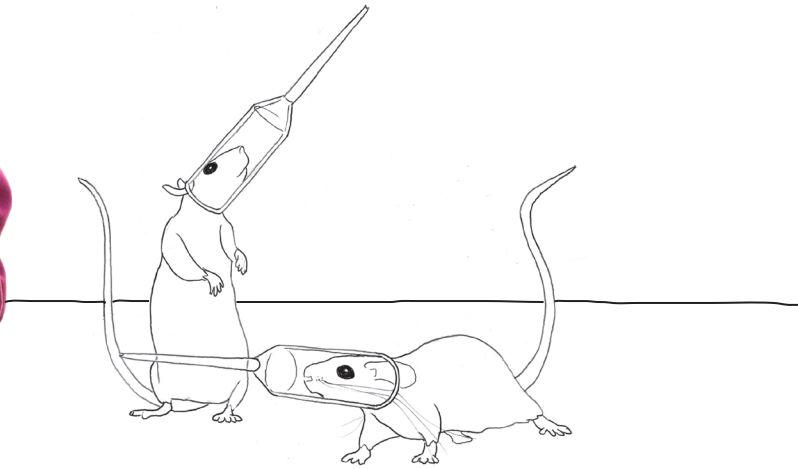
LYING IN WAIT

Scientists were surprised to learn that eosinophil progenitor cells (EoPs) can be found in the lung itself, not just in the bone marrow. Recent studies have revealed that EoPs lie in wait in the lung, poised to produce full-fledged eosinophils when the lung is exposed to allergens. These cell factories are part of what makes the lungs hypersensitive in children with asthma.

Fulkerson and her lab team have developed methods to isolate EoPs from the bone marrow and to culture systems to differentiate them for further study. They are using these cells to isolate the signals involved in producing EoPs and to identify the molecular pathways that progenitors need to survive.

STOPPING PROGENITORS IN THEIR TRACKS

"Very little is known about the progenitors. They are a rare cell in the bone marrow and we are still learning about their basic biology," Fulkerson says. "However, I think that they are an ideal target for new therapies. Instead of blocking eosinophils after they have already formed, my research is focused on preventing them from being made."



Dr. Patricia Fulkerson

LUNG ATLAS WILL SPEED REVOLUTION IN PERSONALIZED MEDICINE

Cincinnati Children's is one of seven research centers collaborating on the world's first molecular atlas of the developing lung, a project expected to have far-reaching impact on asthma, cystic fibrosis, lung cancer and other lung diseases. Jeffrey Whitsett, MD, of the Perinatal Institute, and Steven Potter, PhD, in the Division of Developmental Biology, are co-principal investigators for Cincinnati Children's on the project.

The National Heart, Lung, and Blood Institute is funding the Molecular Atlas of Lung Development Program to build an open-access resource for scientists studying the final stage of lung development, which includes the formation of alveoli, the tiny air sacs that allow for the exchange of oxygen and carbon dioxide.

MAPPING THE LUNG'S TERRAIN

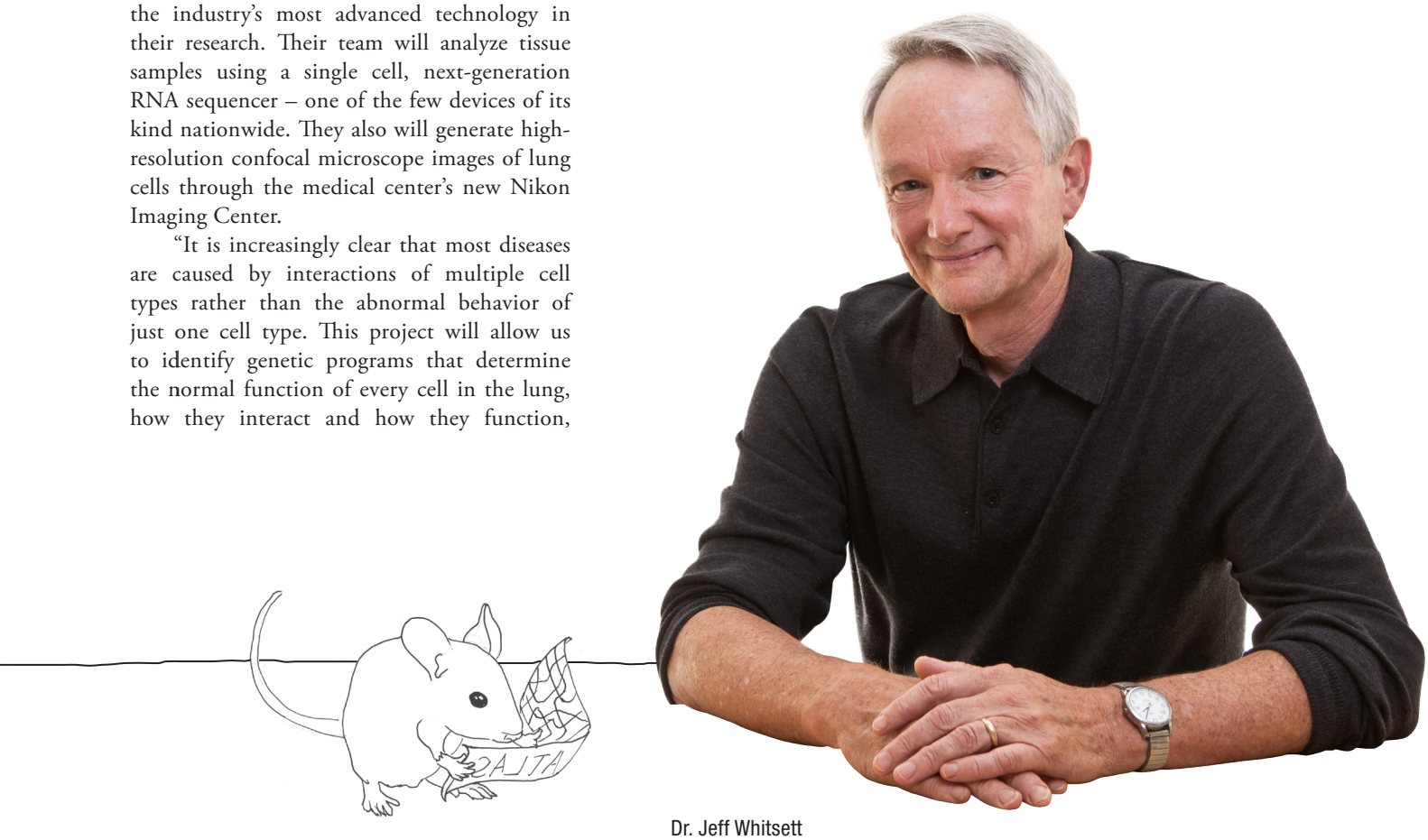
The atlas will produce a molecular profile of every cell type in the developing lung in human and mouse models. Whitsett and Potter will use a five-year, $4 million grant and some of the industry's most advanced technology in their research. Their team will analyze tissue samples using a single cell, next-generation RNA sequencer – one of the few devices of its kind nationwide. They also will generate high-resolution confocal microscope images of lung cells through the medical center's new Nikon Imaging Center.

"It is increasingly clear that most diseases are caused by interactions of multiple cell types rather than the abnormal behavior of just one cell type. This project will allow us to identify genetic programs that determine the normal function of every cell in the lung, how they interact and how they function, both before birth and after," Whitsett says. "By understanding how normal cells function, we'll be able to disentangle and reconstruct the abnormalities that lead to disease."

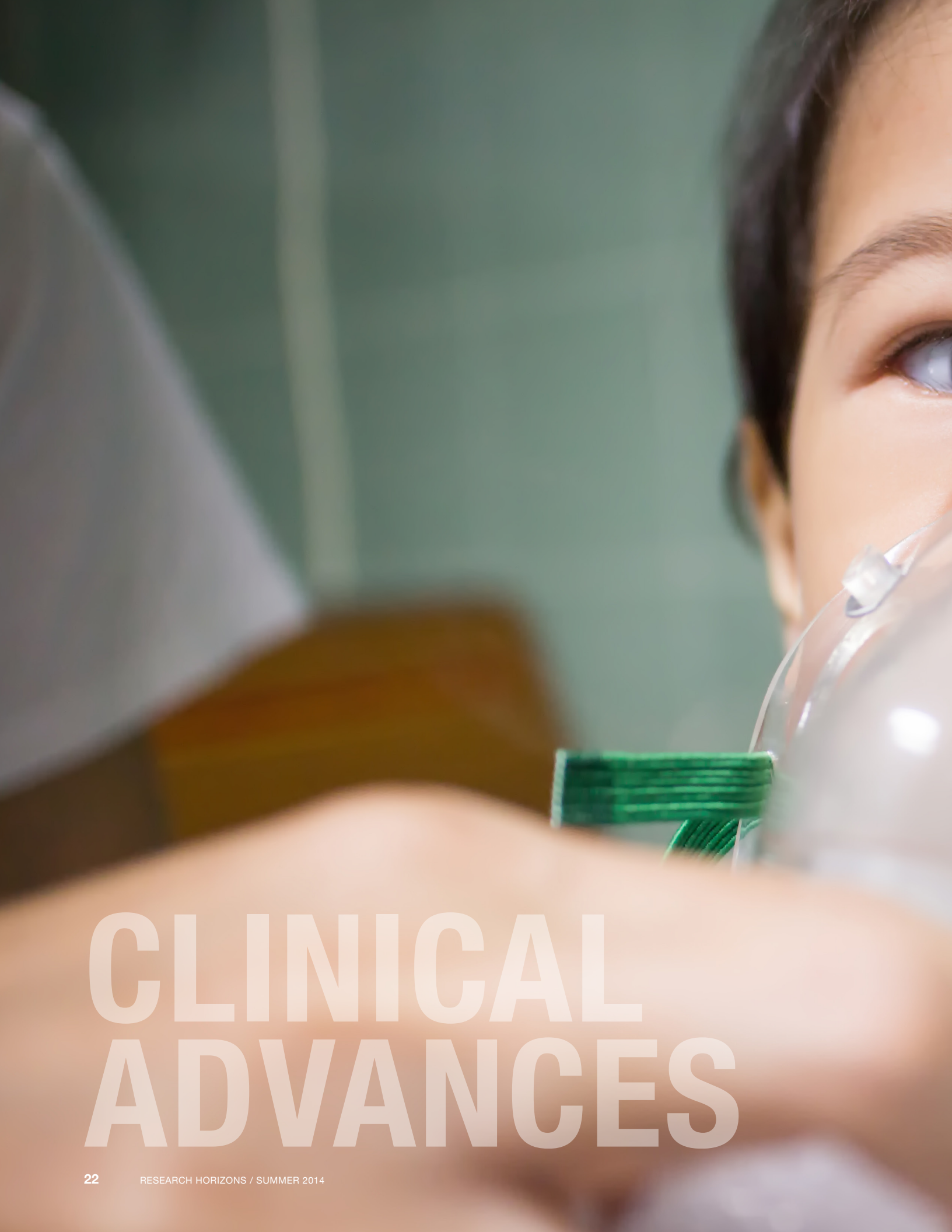
Other participating centers include Children's Hospital Los Angeles, University of Alabama at Birmingham, and Pacific Northwest National Laboratory. Duke University and RTI (Research Triangle Institute) International will serve as data coordinators; the University of Rochester will house a related human tissue repository.

The lung atlas will be valuable for studying and treating many lung diseases. For asthma, Whitsett says, the atlas could open a universe of therapeutic targets and accelerate the evolution of personalized medicine.

"We are progressing rapidly toward the ability to perform patient-specific evaluations at a single-cell level," he says. "This will help us identify which treatments are most likely to be effective for a particular individual. For example, we have new medications that target IL-13 (a protein involved in inflammation). But they only work for a small subset of patients. RNA sequencing could become a tool for finding those patients."



Dr. Jeff Whitsett



CLINICAL ADVANCES

“Our goal was to get everybody on the same page when treating asthma.”

- Dr. Carolyn Kercsmar

Overhauling Care from Hospital to Home

IMPROVING OUTCOMES FOR CHILDREN WITH ASTHMA IS A JOURNEY OF SMALL STEPS

by Tim Bonfield

The asthma clinical care success story at Cincinnati Children's begins with two numbers: 7.2 and 20.9

In July 2008, children covered by Medicaid who had poorly controlled asthma were being admitted to the hospital at the rate of 7.2 per 10,000 population. Asthma-related emergency visits were even higher at 20.9 per 10,000 population.

By March 2014 the new numbers were: 5.0 and 13.7.

These remarkable changes did not reflect a breakthrough medication, nor any changes in Cincinnati's asthma-aggravating climate. Instead, teams of physicians, nurses, respiratory therapists and other professionals at Cincinnati Children's applied the science of quality improvement, making a series of small changes that ultimately produced dramatic results.

"We've been working at this for several years. Most of our work has been about 'How do we change systems to deliver the interventions that we already know work?'" says Mona Mansour, MD, MS, Director of Primary Care at Cincinnati Children's. "How do we make sure that children who need specialty consultations get them? Are we consistently developing asthma action plans? Are we making sure children go home with medications in hand? Are we systematic in how we provide education?"

The following stories illustrate the changes Cincinnati Children's made that are helping transform outcomes for kids with asthma.

SEEKING THE WHOLE STORY

Transforming asthma care at Cincinnati Children's started in 2008 with a look in the mirror.

"Our goal was to get everybody on the same page when treating asthma," says Carolyn Kercsmar, MD, Director of the Asthma Center. "I was recruited here to develop an interdisciplinary asthma program and a plan for improving asthma outcomes and to get all groups working towards collaborative improvement projects."

To this end, she assembled a task force of leaders in Emergency Medicine, General and Community Pediatrics, Adolescent and Transition Medicine, Hospital Medicine, Pulmonology, Allergy/Immunology, Asthma Research, and the James M. Anderson Center for Health Systems Excellence. Their goal: to analyze a long-running problem involving a group of "frequent flyers," children who returned to the hospital more often than most kids with asthma.

Children from Hamilton County, in which Cincinnati Children's is located, and who are covered by Medicaid represented a fraction of the region's overall asthma population. Yet they accounted for a majority of our asthma hospitalizations.

The solutions the task force developed would take several years to implement. And their project – initially to produce more consis-

Drs. Kercsmar (left) and Britto meet regularly with the asthma care team to discuss plans for patient care.

tent, more reliable hospital care – would soon evolve into a quest to improve outcomes in ways that extend far beyond the hospital's walls.

COLLECTING DEEPER PATIENT HISTORIES

One of the first goals was to get hospital staff to be more consistent in using a Childhood Asthma Risk Assessment Tool (CARAT) whenever children with asthma were admitted. The result was a widespread shift in thinking.

"Before these improvements, we tended to focus almost exclusively on addressing the immediate symptoms that brought the child to our doors," says Jeffrey Simmons, MD, MS, a hospitalist at Cincinnati Children's. "But we learned that whatever happened in the past 24 hours isn't the whole story. All the other things going on in a child's life can be just as important."

Physicians, nurses and respiratory therapists are empowered to ask the CARAT questions – and to make referrals to support services as needed. The interviews help expose many factors that can lead to repeated hospital visits: lack of medication compliance; exposure to secondhand smoke and air pollution; indoor exposures to mold, cockroaches, and pet dander and other allergens; lack of transportation; even the mental health of a child's caregiver.

MEDICATIONS-IN-HAND

Difficulty obtaining and taking medications was a leading difficulty confirmed by the task force. Seven years ago, only 40 to 50 percent of Medicaid-covered families were filling prescriptions for the short-term steroids and longer-term controller medications their kids needed after leaving the hospital.

Now, the hospital pharmacy fills the first 30 days' worth of medications for every child on Medicaid before families go home, and offers the service to all other families. Two local pharmacies make deliveries to Medicaid families in nearby Butler County, where the hospital's satellite campus lacks an in-house pharmacy.

CLEARING THE SMOKE

Every day, physicians see the connection between cigarette smoke exposure and asthma attacks.

"It's apparent because the room just reeks of cigarette smoke when I go in to care for the child," says Melinda Mahabee-Gittens, MD, an emergency medicine physician and researcher at Cincinnati Children's. "Yet when we ask caregivers if they smoke, they almost always say, 'Yes, but I don't smoke around my child.'"

The smoke exposure problem is so common among families with children who have asthma that Cincinnati Children's will begin offering a smoking cessation clinic this fall. And now, physicians are able to order tests for cotinine, a common biomarker for smoke exposure, through the hospital's electronic medical records system. Unlike vague recollections, these tests provide strong confirmation of the child's recent secondhand smoke exposure.

"We will be able to let parents see the level of exposure," Mahabee-Gittens says. "Then we will offer them the opportunity to participate in the smoking cessation clinic. And when we retest the child, they will see that they've actually done something good for the health of their child."

ASTHMA COMPLEX CARE CENTER

Even more progress will be made with the opening of a new Asthma Complex Care Center this fall. The Center will consolidate diagnosis and care for the toughest-to-manage children.

Currently, for complicated asthma cases, families can spend months arranging a string of specialty tests and consultations. Some families never complete this journey, which makes their child more likely to need repeated emergency care.

The complex care center is a "day hospital" approach that allows children to stay for several hours at a time to receive multiple services in one trip. "Within a span of two short stays, we can accomplish tasks that would have taken a year," Kercsmar says.

THE POWER OF COORDINATED CARE

As children with asthma spend less time in hospitals, the need to reduce gaps and inconsistencies in outpatient care takes on even more urgency.

Cincinnati Children's has worked for several years to improve data sharing between area hospitals and physician practices. Experts in asthma treatment here have developed "care bundles" that help community pediatricians provide the latest in evidence-based care.

Providing effective care to asthma patients means understanding their life outside the hospital, says Dr. Jeffrey Simmons.

COMMUNICATION MAKES A DIFFERENCE

Many children with poorly controlled asthma come from families that move frequently. Caregivers change. Contact information goes bad. As a result, the ideal goal of children having a consistent medical home can shatter into a disconnected jumble of encounters with widely scattered clinics, urgent care centers and other hospitals.

In an effort to keep better track of children with asthma, an expanded regional ED Admit Alert System went live in Greater Cincinnati in May 2012. The alert system was created as part of a larger data-sharing project led by the Greater Cincinnati Beacon Collaboration (GCBC). The system allows 21 hospitals to send messages to more than 85 physician practices whenever an inpatient admission or ED visit involves one of their patients with diabetes or asthma.

For children with asthma, the alerts allow care providers to schedule follow up visits with families to adjust medications, address adherence problems, update asthma action plans and more. For leaders at Cincinnati Children's, it was surprising to see how many organizations were involved in treating a single child with asthma.

"After the program began, we began receiving information from a number of other providers that we did not anticipate would have any significant volume for our patient population," says Mansour.

By detecting more of these scattered encounters, the hospital was able to enroll more kids into another unique program.

CARE COORDINATION ACCOMPLISHES EVEN MORE

More than 400 children covered by Medicaid have participated in a care coordination program led by Cincinnati Children's. The program focuses on children who have had one or more asthma-related hospital admissions or two or more emergency department visits in a year.

Participating children are assigned to care coordinators who make sure the children re-

ceive a bundle of interventions. These can include frequent phone reminders about keeping appointments and refilling prescriptions, home nursing visits to educate families and patients, and helping families find transportation, legal assistance and other support.

"If a family cannot get to a pharmacy, we can arrange for home delivery," Mansour says. "But these are labor-intensive activities, so we are constantly evaluating which interventions add value."

USING TECHNOLOGY FOR CHANGE

Cincinnati Children's has recently launched an expanded telemedicine center. The center provides a large space for multidisciplinary groups to discuss complex cases and several smaller spaces for individual physicians to conduct long-distance consultations.

The center is likely to be useful for managing children with asthma. Last year, Cincinnati Children's was part of a small pilot in-home telemedicine project conducted with device maker Cisco. A recently presented abstract detailing the results reports that brief video visits were better than phone calls for certain purposes.

"It definitely has some potential, not so much to take the place of an office visit but to be a 'booster' in between," says Kercsmar.

THE ULTIMATE GOAL: SELF-MANAGEMENT

Care coordination is starting to show results, particularly among hard-to-manage teens. By bundling a set of chronic care interventions and making sure nearly every patient receives that care, treatment adherence rates and outcomes have sharply improved, according to a Cincinnati Children's study published online Jan. 27, 2014, in *Pediatrics*.

The interventions included using evidence-based algorithms and decision support tools to provide more consistent treatment; incorporating databases and tracking tools to record symptoms and set triggers for medication adjustments; linking teens to community resources; and following up with patients whose asthma is not well-controlled.

"We have made good progress at achieving consistency with hospital services, but those improvements reach only one segment of children with asthma," says Maria Britto, MD, Director of the Center for Innovation in Chronic Disease Care and senior author of the study. "The vast majority of kids with poorly controlled asthma are not being admitted and are not going to the ED. Instead, they are coughing every night, not participating in sports, and enduring other limitations on their lives."

Reaching these children requires innovative approaches. Britto and colleagues are studying several ways to help teens do a better job of managing their asthma, exploring questions such as:

Will teens take their medications more consistently if providers make it easy for them to text reminders to themselves? To track the teens' behavior, researchers have provided participants with "smart-halers" that electronically monitor medication use.

Can motivational approaches be matched to a teen's personality type? Cincinnati Children's is testing an assessment tool that mimics popular personality quiz formats found on Facebook and other social media. Knowing whether a teen is outgoing or shy, driven to please or not, can suggest which motivational approaches have the best chance of success.

"For example, peer-to-peer support might be good for a highly social person, but not for someone who is highly concerned about privacy," Britto says.

Dr. Maria Britto says consistent outpatient care is important because many children with poorly controlled asthma never visit the hospital.


774,000
EMERGENCY VISITS IN THIS COUNTRY EACH YEAR ARE ASTHMA-RELATED

EXTENDING THE REACH OF INNOVATION

Keeping asthma-related hospital visits to a minimum cannot be achieved without helping children get the care they need in other ways.

Cincinnati Children's is translating lessons it learned while streamlining hospital-based asthma care to help improve outcomes in other settings. The medical center is expanding a program that involves school nurses in care management. We are studying ways to help kids take more control over their own disease. And it is sharing the lessons learned with a network of pediatric hospitals across Ohio.

CONNECTING WITH SCHOOL NURSES

Cincinnati Children's recently completed a pilot project that helped improve detection of children with poorly controlled asthma by working much more closely with school nurses in the Cincinnati Public School District, the region's largest and most urban school system.

The project involves more training for school nurses about asthma care and providing them with limited access to the hospital's electronic medical records system. Nurses can see when a student is discharged from the hospital, and they are able to see changes in a student's asthma action plan and stay up-to-date on medications prescribed. The nurses also participate in telephone "huddles" to discuss patient issues with the hospital's asthma care coordinators, pulmonary nurses and others.

After reporting successes with eight Cincinnati public schools, Cincinnati Children's plans to expand the program this fall to the entire school district, says Mansour.

Another project – still in early discussion – would designate one or two "asthma-friendly" schools. This program would leverage advances in technology while connecting families to community resources to improve conditions for children with asthma. Eventually, such schools could serve as demonstration projects for educators who want to reduce asthma-related absenteeism, Mansour says.

BETTER WAYS TO EDUCATE

Melinda Butsch-Kovacic, PhD, a researcher in the Division of Asthma Research, is using community-based research to help families learn to manage asthma. She and Carolyn Kercsmar, MD, of the Asthma Center at Cincinnati Children's, work with kids to develop customized educational videos following hospitalization for asthma.

"The kids personalize the video, using their name and adding an avatar that they choose that looks like them," Butsch Kovacic says. The video includes a taped segment of the child using his medications properly while he receives discharge instructions, contains the child's individual asthma action plan, a list of his asthma triggers and specific medications.

The video is emailed or mailed to the child's home a few days after she leaves the hospital. Children report watching the video multiple times; they also share the video with parents, siblings, grandparents, teachers and coaches so others learn how to manage their condition.

SHARING THE LESSONS

Cincinnati Children's progress in asthma care is being shared widely with scientists, pediatric specialists and policy makers.

Among several publications, the medical center is featured in a Robert Wood Johnson Foundation white paper exploring the business case for improving pediatric asthma care. A case study on the Cincinnati asthma alert system is detailed in the journal *eGEMs*. A study exploring the connection between medical home quality and asthma readmission risk was published in the January 2013 issue of *Pediatrics*.

Cincinnati Children's also is one of six hospitals in Ohio participating in the Ohio Pediatric Asthma Repository (OPAR), which is gathering data about thousands of asthma patients statewide.

The project seeks to quantify demographic, environmental and other factors that contribute to asthma exacerbations in Ohio. And by sharing best practices, the group hopes to reduce the wide variations that currently exist in clinical care across the state.

COMMUNITY & ENVIRONMENTAL OUTREACH

“Diesel particulates are especially worse than other pollutants because near the source, such as trucks and buses, most are ultra-fine, about 100 nanometers or less.”

- Dr. Patrick Ryan

THE CINCINNATI REGION'S RATE OF PEDIATRIC ASTHMA IS MORE THAN TWICE THE NATIONAL AVERAGE. IN SOME URBAN-CORE NEIGHBORHOODS, IT IS NEARLY 10 TIMES AS HIGH.

Cincinnati's Lockland High School is situated right on I-75, one of the country's most heavily travelled interstates. Research by the University of Cincinnati has found that more than 30 percent of American public schools are within a quarter mile of highways that are primary truck and traffic routes.

Asthma's Problems, and Solutions, are All Around Us

Repairing what causes and worsens asthma truly takes a village, and more

By Tom O'Neill

Diesel particulates have an elemental carbon core surrounded by thousands of harmful chemicals, including polycyclic aromatic hydrocarbons, and metals such as iron, nickel and lead. They are so tiny that hundreds of thousands could fit comfortably on the dot of an "i."

These products of the transportation industry are fueling a wide range of asthma research projects at Cincinnati Children's.

"They are small, nasty particles," says Patrick Ryan, PhD, an environmental epidemiologist. "They are especially worse than other pollutants because near the source, such as trucks and buses, most are ultra-fine, about 100 nanometers or less."

These diesel particulates, smaller than pollen and bacteria, are readily breathed deep into the lungs, where they settle. They are common in Cincinnati's urban core, with its environmentally tricky confluence of three major interstates, low-lying areas, hills, industry and traffic.

Diesel exhaust is an increasingly worrisome contributor to the many environmental and behavioral factors feeding our growing asthma problem. The Cincinnati region's rate of pediatric asthma is more than twice the national average. In some urban-core neighborhoods, it is nearly 10 times as high.

To better understand these concerns, teams of researchers at Cincinnati Children's are taking an interlocking approach to analyzing the risk factors and behaviors causing heightened rates of admission – and readmission – for children with asthma.

TRAP'D

The TRAP (Traffic-Related Air Pollution) study, published in the March 2014 edition of *The Journal of Pediatrics*, examined asthma risk factors and the disparity in readmission rates among different groups of children. Ryan, of the Division of Biostatistics and Epidemiology, was among six researchers, led by Nicholas Newman, DO, MS, and Robert Kahn, MD, who studied a cohort of 758 Cincinnati children ages 1 to 16.

They looked at sensitization to environmental allergens, tobacco smoke exposure, traffic pollutants such as diesel, and social factors shared by families. Diesel exhaust particles "compose a substantial portion of particulate matter in urban areas," the study noted.

White children with high TRAP exposure were readmitted for asthma treatment at a rate three times higher than white children with low TRAP exposures. But African American children were readmitted at a much higher rate than their white counterparts, regardless of TRAP exposure. This suggests that

"Sometimes, the answer isn't just a prescription, but a system. I cannot write a prescription for a new home or clean air."

— Nicholas Newman, DO, MS

there are other factors influencing the high readmission rate among the African American children.

Nineteen percent of children who were readmitted within 12 months also lived in families with lower reported household incomes, had mothers with a high school education or less, and were receiving an asthma controller medication.

"We were trying to understand how chronic vehicle exhaust exposure impacts asthma and what other factors may also contribute to asthma readmission," says Newman, a pediatrician at Cincinnati Children's and lead author of the study. "Sometimes, the answer isn't just a prescription, but a system. I cannot write a prescription for a new home or clean air."

Physicians and researchers closely examined home conditions that worsened asthma, and how to address those issues directly with families. Some solutions are as simple as using an air conditioner. Some problems, such as mold or cockroach infestation, might require involving the landlord or local health department.

CONNECTIONS WITH SCHOOLS AND MORE

Efforts to tackle the community's high asthma rates extend far beyond the confines of hospital labs, data systems and computer screens. Cincinnati Children's has established strong relationships with community organizations that have direct impact on children's lives.

One such program works with nurses in the Cincinnati Public Schools (CPS). With parents' consent, the schools can access information about the medication schedules of children with asthma, including more in-depth screening. The program was expanded earlier this year to include all schools in CPS, having started with just a handful.

Cincinnati Children's has also arranged for local pharmacies to be notified automatically when a prescription is written for a student who takes asthma medication. If the parent does not fill the prescription, he is contacted by hospital personnel and receives assistance in getting the prescription filled. Cincinnati Children's also typically provides a one-month supply of medication when the patient is discharged.

IDENTIFYING 'HOT SPOTS'

Studies by Cincinnati Children's researchers have identified "hot spot" neighborhoods with the highest risk factors for asthma. Children in these neighborhoods are many times more likely to live in poverty and in housing with allergens that exacerbate their asthma.

"We expected to see disparities, but the breadth of the disparity was startling," says Andrew Beck, MD, MPH, who works in the Divisions of General and Community Pediatrics and Hospital Medicine.

By identifying where children who are treated repeatedly for asthma live, and by overlaying U.S. Census data, Beck is able to characterize a child's address and the socio-economic condition of the neighborhood. "We looked at census variables, aggregated the 25 percent worst neighborhoods, and found there was a strong relationship with every measure of poverty," he says.

GETTING 'CLEAR'

Several years ago, Beck formed a partnership with the Cincinnati Health Department called the Collaboration to Lessen Environmental Asthma Risks, or CLEAR, to support an environmental health intervention directly from the inpatient unit, linking households to health code enforcement.

Doctors from Cincinnati Children's and the health department created a more nuanced series of questions for parents and caregivers when a child arrived at the inpatient unit with an asthma-related problem. These screenings allowed doctors to better understand risks that potentially contributed to the child's admission.

If housing issues were reported by the family, families were offered a referral to the Cincinnati Health Department. Health department inspectors would visit the home and issue code violations to landlords, helping to abate conditions known to affect asthma morbidity.

"In an ideal world they would work with the tenant and landlord to remediate those conditions," Beck says. In one instance, a series of complaints from a multi-family housing unit led to the formation of a tenants' association.

IMPROVE HOUSING, IMPROVE HEALTH

Providing this sort of help to families who live in housing conditions that worsen their children's asthma is crucial to reducing exacerbations in the community, doctors believe.

Most of the city's poorest young asthma sufferers live in rental units. In 2008, Robert Kahn, MD, MPH, of the Division of General and Community Pediatrics, was instrumental in creating the Cincinnati Child Health-Law Partnership, or Child HeLP. The partnership connects Cincinnati Children's and the Legal Aid Society of Greater Cincinnati to assist patient families with a variety of issues, including health-related housing problems.

In one instance recounted in the July 17 edition of the *New York Times*, Child HeLP intervened on behalf of a Cincinnati Children's patient whose family was battling its landlord over housing conditions. Child HeLP intervened and repairs were made to address mold and rodent problems – both of which have even more serious effects on asthmatic children – not just in the one unit, but in all 16 buildings the landlord owned.

HOMES AWAY FROM HOME

Adherence also is a key factor in asthma readmission rates.

A study published in the May 2014 edition of the *Journal of Community Health*, co-led by Kahn, linked asthma readmissions to children routinely staying overnight at another caregiver's house.

They studied 774 children ages 1 to 16 who were admitted for asthma problems. Nineteen percent of the children were readmitted within 12 months, but the figure jumped to 33 percent among children who spent at least one night away from home per week.

Typically, the study found that these children were staying with a grandparent, a parent, or a friend's family, and their medication did not always go with them. With these factors in mind, the study recommends that practitioners "… consider asking about spending nights away from home, and work with families to craft discharge plans, follow up plans and asthma care plans that place minimal strain on existing family structures."

Many children spend one night or more each week away from home, without their asthma medications. A recent study recommends that practitioners consider this when developing care plans.

Melinda Butsch Kovacic, PhD, MPH, found that face-to-face research provides the most reliable data.

Going to the Source

In community-based research, science meets real life.

Reality can often be a smack upside the head of a scientist. It certainly was for Melinda Butsch Kovacic, PhD, MPH, when she wanted to understand the hurdles faced by many kids with asthma.

"I'm a quantitative researcher," says Butsch Kovacic. "But in this case, numbers didn't get at what we needed to know."

Butsch Kovacic studies the impact of environment on chronic disease in children. Much of her work in the Division of Asthma Research focuses on children who are economically vulnerable. As principal investigator of a National Institute of Environmental Health Sciences (NIEHS)-funded Pediatric Environmental Exposure Study, she examines risk factors for asthma that include exposure to diesel exhaust particles and secondhand smoke, obesity, and socioeconomics, to name a few.

MAKING THE COMMUNITY CONNECTION

When the study revealed strong connections between the risk of severe asthma and socioeconomic status, Butsch Kovacic decided it was time to team up with an organiza-

tion that understood the children at highest risk. She partnered with Findlay Street Center (formerly Seven Hills Neighborhood Houses), a social service agency and community center in one of Cincinnati's most impoverished neighborhoods. And she discovered the limits of traditional scientific research.

"The questions we were asking didn't get at the real problems. There was much more to it than science."

The Center serves mostly single parent African-American families in the city's urban core, where the incidence of asthma should be relatively high. But when Butsch Kovacic asked about it, the agency reported that only eight of the nearly 300 children they serve had asthma.

"As the neighborhood lies along I-75, these are kids who are highly exposed to vehicle-related air pollutants," she says. "There should be many more asthmatics. Were families just not reporting their asthma?"

So she changed her researching ways. She learned about community-based participatory research, which enlists community members not merely as research subjects, but as partners in the research process.

She put together a community health council of people, many of whom were parents of children with asthma at the Center. She learned that many thought asthma was a condition that kids would outgrow. Few kids were taking prescribed medications .

She also learned that many asthmatic children were not signing up for the Center's sports and activity programs. "Instead of dealing with their asthma, they just limited their physical activity," Butsch Kovacic says. "If you can't breathe, you're not going to do karate or basketball."

UNDERSTANDING FAMILIES

Talking with kids and families provided real insights. "I realized that to help with health issues, we first needed to understand the underlying issues or root causes."

When probed just slightly, for example, a "no" answer to the question of whether asthma limited a child's activity revealed that the child simply chose inactivity to avoid triggering his asthma. An answer about excessive "screen time" revealed that watching hours of TV was a way to keep a child indoors – and safe – in a high-crime neighborhood.

Butsch Kovacic believes that the future in managing asthma lies in community-based research and using both quantitative and qualitative approaches. She hopes to obtain grant funding using the work she has begun at Findlay Street Center as a model for how to improve community health. She is building collaborations across the community to focus on health, education and opportunity at the Center. "I want to create and sustain a collaborative community learning laboratory that will help people better understand, prevent and manage not just asthma, but a variety of conditions."

Photos to the right were taken by kids for the PhotoVoice project, a community-based research project aimed at getting a kid's-eye view of the challenges in their lives.

Tracking Toxic Exposure

Diesel sensor measures exposure to harmful, ultrafine exhaust particles

An 8-year-old boy with an unusual-looking monitor hooked to the strap of his backpack walks home from school.

His journey on the residential, less-industrial west side of Cincinnati is a test. His companion is a device called a "Personal Ultrafine Particle Counter." Taking air-quality "snapshots" in one-second intervals, it detects diesel and other ultrafine particulates up to 100,000 per cubic centimeter of air. It has a GPS locator to "tag" the location of the child when he is exposed.

Patrick Ryan, PhD, MS, an environmental epidemiologist at Cincinnati Children's, hopes refining the device to make it smaller and more energy-efficient will it play an important role in future asthma studies on the short- and long-term effects of exposure to diesel fumes.

Another child does a similar walk, closer to Cincinnati's urban center. Her test shows more consistent levels of diesel particulates at street-level and a high level in her home. Ultrafine particulate matter inside a home could be generated by such things as cooking, smoking, gas stoves and furnaces.

"I think they're both very telling about the different environments," says Ryan. "One shows the importance of personal monitoring because diesel particles and other pollutants vary substantially depending on where you are and when you are exposed. The other one shows that in highly polluted areas, there's a near-constant exposure, but that could be reduced indoors."

Ryan has applied for a federal grant that he hopes will expand on research he began with collaborators at the University of Cincinnati Department of Environmental Health and College of Engineering in 2012, in which 20 children ages 9 to 13 wore the device while walking around their neighborhoods. His goal is to conduct another field study involving 10 children, then a full study with 100 children, half of whom will have asthma.

The monitor has a rechargeable lithium-polymer battery, operates on water condensation and can operate up to six hours on a charge. Ryan and the device's developer, Ohio-based Enmont, believe if they can produce a smaller, inexpensive device, it will quantify asthmatic childrens' exposure to diesel particulates and help find paths to new asthma treatments.

Patrick Ryan, PhD, MS, with small particulate sensor.

THE ROAD MORE TRAVELLED

This graph shows the output from the particle sensor device worn by a child as he walked to school. Red shows areas of greatest exposure to vehicle exhaust.

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