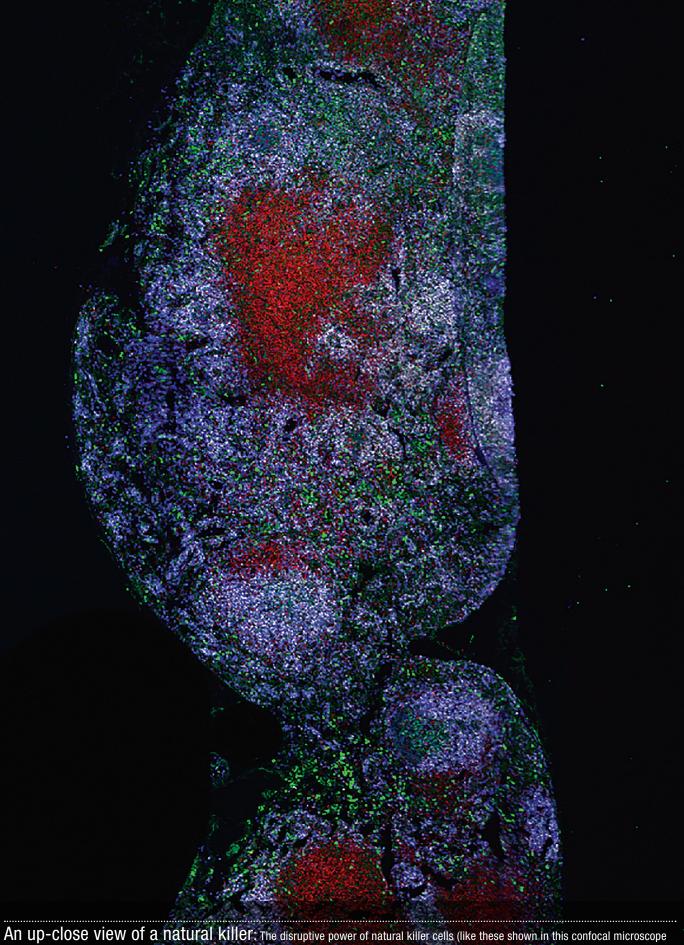
Research Horizons

A PUBLICATION OF THE CINCINNATI CHILDREN'S RESEARCH FOUNDATION





An up-close view of a natural killer: The disruptive power of natural killer cells (like these shown in this confocal microscope image) may explain why some deadly viruses have eluded vaccine attempts for decades, according to new research from scientists at Cincinnati Children's and collaborating medical centers.

Research Horizons

SUMMER 2015

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Cover: These confocal microscope images reflect insights recently published by emerging scientists at Cincinnati Children's that advance our basic understanding of topics including muscle cell development, how intestinal bacteria influence our immune systems, and why vaccines remain elusive for a number of deadly viruses.

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New approaches to stubborn challenges

A growing cadre of investigators brings fresh perspectives and bold ideas to a wide range of research dilemmas

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Ensuring the future of pediatric research

Key programs support scholars who seek to combine careers in medicine and science

HONORS

Theresa Alenghat, VMD, PhD, Division of Immunobiology, and Douglas Millay, PhD,

Division of Molecular Cardiovascular Biology, have been named 2015 Pew Scholars in the Biomedical Sciences. This prestigious honor is awarded to approximately 20 young scientists each year by the Pew Charitable Trusts. Each scholar in this year's class will receive a four-year grant totaling \$240,000 to build upon their research.

Robert Frenck Jr, MD,

Interim Director and Medical
Director, Division of Infectious
Diseases, received the 2014
Elizabeth Spencer Ruppert, MD, FAAP,
Outstanding Pediatrician of the Year
Award, the highest honor given by the
Ohio Chapter of American Academy of
Pediatrics. Frenck leads two statewide
programs that provided physicians with
strategies to improve immunization rates
among Ohio's children and teens.

Bryan Goldstein, MD,

Heart Institute, was named one of 12 National Fellows for the inaugural Society for Cardiovascular Angiography and Interventions Emerging Leader Mentorship Program.

Shanna Guilfovle, PhD

Division of Behavioral Medicine and Clinical Psychology, received the Carolyn S. Schroeder Award for Outstanding Clinical Practice from the Society of Pediatric Psychology. This award recognizes outstanding commitment and significant contributions to pediatric psychology by a full-time provider of direct clinical services.

Thomas Boat, MD.

Retired Dean of the University of Cincinnati College of Medicine and Vice President for Health Affairs, received the William Cooper Procter Medallion, the highest honor given by Cincinnati Children's. The award recognizes a career of contributions since 1993, including serving as Director of the Research Foundation and Physician-in-Chief at Cincinnati Children's as well as Chairman of the UC Department of Pediatrics. Boat retired in November from his UC roles and rejoined Cincinnati Children's as part of the Division of Pulmonary Medicine.



Kara Shah, MD, PhD

Director, Division of Dermatology, was one of five experts elected to the National Psoriasis Foundation Medical Board. Shah has been instrumental in building clinical and research programs at Cincinnati Children's in atopic dermatitis, pigmented lesions, cutaneous lymphoma, genodermatoses and wound care.

Research Horizons

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Samir Shah, MD, MSCE,

Director, Division of Hospital
Medicine, received the 2015 MillerSarkin Mentoring Award from the
American Pediatric Association (APA).
The award recognizes the contributions
of an APA member who has provided
outstanding mentorship to learners or
colleagues, both locally and nationally,
and serves as a model to others who
aspire to mentor others as they mature.

Lori Stark, PhD, ABPF

Director, Division of Behavioral Medicine and Clinical Psychology, and Arnold Strauss Chair for Mentorship, has won the Award for Outstanding Mentorship from the Society of Pediatric Psychology. Formerly known as the Martin P. Levin Mentorship Award, this honor recognizes faculty in pediatric psychology who mentor students in an exemplary way, providing professional advice and guidance through various training phases.

Jeffrey Whitsett, MD

Chief, Neonatology, Perinatal and Pulmonary Biology, and Co-Director, Perinatal Institute, received the 2015 Mary Ellen Avery Neonatal Research Award from the American Pediatric Society (APS) and the Society for Pediatric Research (SPR). Whitsett's pioneering work includes clarifying the roles surfactant proteins play in lung development and leading the way in making surfactant protein replacement a routine treatment for immature lungs and respiratory distress syndrome.

Brenda Wong, MD, MBBS,

Division of Neurology, and Director, Comprehensive Neuromuscular Center, was honored in February, 2015, by CureDuchenne, a national non-profit organization that supports research, for her outstanding leadership in treating boys with Duchenne muscular dystrophy and her work leading clinical trials of promising therapies.

Uma Kotagal, MBBS, MSc.

Senior Vice President, Quality, Safety and Transformation and **Executive Director, James M.** Anderson Center for Health Systems Excellence, received the Daniel Drake Medal, the highest honor given by the University of Cincinnati College of Medicine. The medal recognizes her career of outstanding contributions to medical education, scholarship and research. Kotagal was born in Bombay, India. She joined Cincinnati Children's as a fellow in 1975. After devoting much of her early career to neonatal intensive care, Kotagal became the Anderson Center's first director and a widelyrecognized leader in health services research and system transformation.



GRANTS

Theresa Alenghat, VMD, PhD,

Immunobiology, will use a five-year, \$1 million grant from the Burroughs Wellcome Foundation to study the epigenomic regulation of host-microbiota interactions in the gastrointestinal tract.

Bruce Aronow, PhD,

Biomedical Informatics, will use a five-year, \$1.1 million grant from the National Institute of Mental Health to study the multimodal analysis of high-risk psychosis mutations in induced neuronal cells.

Steve Danzer, PhD,

Anesthesia, received a five-year, \$2 million grant from the National Institute of Neurological Disorders and Stroke to study the mTOR regulation of aberrant neuronal integration.

Sudhansu K. Dey, PhD,

Reproductive Sciences, received a five-year, \$2.4 million grant from the National Institute on Drug Abuse to study "Endocannabinoid Signaling during Early Pregnancy."

Stuart Goldstein, MD,

Nephrology, will use a three-year, \$1.5 million grant from the Agency for Healthcare Research and Quality to study the "Reduction of Nephrotoxic Medication-Associated Acute Kidney Injury."

Gang Huang, PhD,

Experimental Hematology and Cancer Biology, will study the role of "Hypoxia-Inducible Factor-1alpha in Myelodysplasia" using a five-year, \$1.8 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

Xi Jason Jiang, PhD,

Infectious Diseases, will use a fiveyear, \$1.3 million grant from the National Institute of Allergy and Infectious Diseases to study the HBGA receptors in host cell entry and infection of <u>norovirus</u>.

Mi-Ok Kim, PhD,

Biostatistics and Epidemiology, will study "Propensity Score-based Methods for Comparative Effectiveness Research using Multilevel Data" with the help of a two-year, \$1.1 million grant from the Patient-Centered Outcomes Research Institute.

Rohit Kohli, MBBS, MS,

Gastroenterology, Hepatology and Nutrition, will study the improvement rates of non-alcoholic fatty liver disease following bariatric surgery, using a fiveyear, \$2.4 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

Jeffery Molkentin, PhD.

Molecular Cardiovascular Biology, will examine how "Thrombospondin 4 Regulates Adaptive ER Stress Response" with a three-year, \$1.8 million grant from the National Heart, Lung and Blood Institute.

Louis Muglia, MD, PhD,

Perinatal Institute, received a oneyear, \$2 million grant from the March of Dimes to help establish its Prematurity Research Center Ohio Collaborative, a multi-year research program aimed exclusively at finding the unknown causes of premature birth.

Masato Nakafuku, MD, PhD,

Developmental Biology, will use a fiveyear, \$2.5 million grant from the National Institute of Neurological Disorders and Stroke to study the molecular control of neurogenesis in the adult subventricular

Nancy Ratner, PhD,

Experimental Hematology and Cancer Biology, will study "Brain Dysfunction in Neurofibromatosis" using a five-year, \$1.6 million grant from the National Institute of Neurological Disorders and Stroke.

Marc Rothenberg, MD, PhD

Allergy and Immunobiology, will use a two-year, \$2.8 million grant from the Patient-Centered Outcomes Research Institute to study the "Comparative Efficacy of Therapies for Eosinophilic Esophagitis."

Patrick Ryan, PhD, MS,

Biostatistics and Epidemiology, will use a two-year \$1.6 million grant from the National Institute of Environmental Health Sciences to study personal exposure to ultra-fine particulate matter and respiratory health.

Rolf Stottmann, PhD

Human Genetics, will use a four-year, \$1.2 million grant from the National Institute of General Medicine Sciences to study a genetic approach to defining the Ttc21b interactome in mammalian ciliopathies.

Nikolai Timchenko, PhD.

Surgery, will pursue "NAFLD: Mechanisms and Treatments" with a \$1.2 million, three-year grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

Stronger Research, Together

The 15-story Clinical Sciences Pavilion at Cincinnati Children's opened in June after three years of construction, adding more than 445,000 square feet of laboratories, offices and support space for one of the largest pediatric research centers in the U.S.

Features include:

- Exam rooms and other patient spaces dedicated to clinical research
- Research imaging center
- Metabolic kitchen for training families of children with special dietary needs
- Multiple floors of "wet" laboratory space
- Extensive collection of patient-inspired art



How Mothers Shape Their Offspring Long Before Birth

Researchers at Cincinnati Children's are shedding new light on one of nature's biggest mysteries – how our bodies attain their forms.

A study published in March 2015 in *Nature Communications* reports that the size and patterning accuracy of fruit fly embryos depend on the reproductive resources invested by the mother, even before the egg leaves the ovary.

"One of the most intriguing questions in animal development is something called scaling, or the proportionality of different body parts," says Jun Ma, PhD, senior author and a scientist in the Divisions of Biomedical Informatics and Developmental Biology. "Whether you have an elephant or a mouse, their organ and tissue sizes are generally proportional to the overall size of the body. We want to understand how you get this proportionality."

By studying fruit flies, one of the simplest forms of animal life, Ma and his colleagues are producing mathematical models that will allow them to explore similar questions in more advanced life forms, including humans. Ultimately, such research could help explain the root causes of certain birth defects.

The scientists start in the ovary of the mother fruit fly, where the genetic and biological resources to form the eggs of her future brood

are harnessed. Researchers follow development through to the growth of her embryos, and combine mathematical modeling with laboratory testing to get a complete picture. The process requires a large number of experimental measurements and a well-stocked fly room.

In the latest study, funded by the National Institutes of Health and National Science Foundation, Ma and colleagues report developing a mathematical model called TEMS (Tissue Expansion-Modulated Maternal Morphogen Scaling). A morphogen is a protein that instructs genes to make products that control the formation of body parts. The TEMS model lets researchers quantify the mother fly's biological investment in this process. The larger the investment, the bigger the return in terms of well-proportioned body parts.

The new TEMS model will help Ma and colleagues develop a systems-level understanding of how fruit flies attain their forms - knowledge that ultimately could benefit people of all shapes and sizes.

Jun Ma, PhD





Vocal Research Could Unlock Mystery of 'The Change'

A research partnership between Cincinnati Children's and the Cincinnati Boychoir could help better explain how boys' voices change in adolescence and if those changes can be steered to ensure that boys keep singing.

It is a research project so unusual as to garner coverage in the *Washington Post, USA Today* and other media outlets.

The Cincinnati Children's team is led by Alessandro de Alarcon, MD, MPH, of the Division of Otolaryngology. As an ear, nose and throat physician and director of the Center of Pediatric Voice Disorders, his typical focus is airway reconstruction, voice disorders, sinonasal conditions and eosinophilic esophagitis.

This multi-year study will involve recording voices, measuring vocal cord thickness and gathering other data to learn more about how voices change as boys pass through puberty. The study also will evaluate methods of teaching boys how to "steer" their voices during the change. About two dozen choir members ages 5 to 11 will participate.

Boychoir leaders proposed the project with the hope of reversing the trend of boys giving up choral singing during the change. Some never return with their "adult" voice.

"All the pieces of this really haven't been explored in a way that could give us some answers," de Alarcon told the *Cincinnati Enquirer*.

Breast Milk May Not Prevent Obesity



Human milk is the optimal first food for babies, but its power to prevent obesity later in life is not so clear.

A study led by scientists at Cincinnati Children's, published in April in *Current Obesity Reports*, reviewed more than 80 breastfeeding studies spanning more than 20 years. The review indicates that obesity prevalence was 10 to 20 percent lower among breastfed infants than those raised with formula. However, the components of breast milk can vary from woman to woman, which suggests that other factors beyond breastfeeding also play important roles in whether a child grows up obese.

"By understanding the mechanisms of how breastfeeding and the composition of human milk affect infant development, we may be able to generate a more nuanced view of the connection between breastfeeding and obesity risk," says Jessica Woo, PhD, MHSA, Division of Biostatistics and Epidemiology, a co-author of the study.

Woo and her colleague at Cincinnati Children's, Lisa Martin, PhD, Division of Human Genetics, suggest three potential biological factors related to breastfeeding that may influence obesity later in life: the role of maternal obesity, the effect of breastfeeding on how the digestive system processes food, and how breastfeeding may influence the risk of child-

hood obesity through alterations in taste preferences and diet.

"The complex nature of the relationship between breastfeeding and obesity, including the fact that human milk and milk production vary among women, suggests that the medical literature does not promote breastfeeding as a frontline strategy to prevent obesity," Martin says.

Above: Jessica Woo, PhD, MHSA Below: Lisa Martin, PhD



Scientists at Cincinnati Children's are leading a multinational effort to improve the cardiovascular risk assessment of children by comparing the health of middle-aged adults to the results of studies they participated in decades ago.

The study, "Childhood Cardiovascular Risk and Adult Cardiovascular Disease Outcomes: An International Long-term Follow-up," recently earned a five-year, \$13.5 million award from the National Heart, Lung and Blood Institute. The goal is to better understand risk factors in children and reassess when interventions should begin.

"Back in the '70s, people felt children could not get hypertension," says Elaine Urbina, MD, MS, Director of Preventive Cardiology at Cincinnati Children's. "So the first step is to define what is normal in healthy children in terms of blood pressure and glucose and determine where those cut-points should be."

She and Jessica Woo, PhD, MHSA, from the Division of Biostatistics and Epidemiology, are co-principal investigators on the project.

The project plans to follow up with as many as 40,000 people who participated as children

in seven studies that began in the 1970s, including five U.S. studies and one each in Australia and Finland. Each of these studies measured cardiac risk factors in childhood and tracked the participants' health into adulthood.

The first challenge for researchers is locating participants. "We hope to find 20,000," Urbina says. "These kids are now entering their 50s and likely to begin experiencing cardiovascular disease."

One of the seven studies involved children at Princeton City School District near Cincinnati who were as young as 6 when the study was conducted from 1973-76. They were well into adulthood when a follow-up study was done from 2000-2004. That study detected 17 cases of cardiovascular disease in the initial follow-up period. Researchers at the time reported that "pediatric metabolic syndrome and age at follow-up assessment were significant predictors of cardiovascular disease."

The new project seeks to confirm those findings across a much larger population.

Elaine Urbina, MD, MS



How Soon Does Heart Disease Risk Begin?

Heart Disease Risk Among Obese Teens More Common Than Expected

Not only do severely obese adolescents carry excess weight, they also have much higher risk for heart disease than previously realized, according to findings published in March in *JAMA Pediatrics*.

Of the 242 participants in the "Teen Longitudinal Assessment of Bariatric Surgery" (Teen-LABS) study, 95 percent had at least one cardiovascular disease risk factor. This includes 75 percent who had elevated blood pressure (including hypertension and pre-hypertension) and nearly 75 percent who were insulin resistant. Meanwhile, 50 percent had unhealthy cholesterol levels.

Centers participating in the Teen-LABS project include Cincinnati Children's, Nationwide Children's Hospital, Texas Children's Hospital, the University of Alabama at Birmingham, and the University of Pittsburgh Medical Center.

Thomas Inge, MD, PhD, Surgical Director, Surgical Weight Loss Program for Teens at Cincinnati Children's, is the study's chair. Marc Michalsky, MD, Surgical Director of the Center for Healthy Weight and Nutrition at Nationwide Children's, was the lead author for the latest findings. In addition to Inge, three other Cincinnati Children's and University of Cincinnati scientists contributed: Todd Jenkins, PhD, MPH; Elaine Urbina, MD, MS; and Ralph Buncher, ScD, MS.

Inge says the new findings add to research already demonstrating disturbing links between teen obesity and heart disease risk. Other studies have found signs of early atherosclerosis, poor pulmonary function, arterial stiffness, increased carotid artery thickness, left ventricular hypertrophy and elevated levels of inflammation.

"All of these other research findings tell us that parents and healthcare providers have to take note when kids are climbing the BMI (body mass index) ladder," Inge says. "They should follow accepted guidelines for staged intervention, including consideration of surgery for severe pediatric obesity, and attempt to get ahead of the problem."

Thomas Inge, MD, PhD



Young women with severe lupus need higher doses than expected of a medication that can protect their ovaries during chemotherapy, according to research led by a scientist at Cincinnati Children's.

Physicians often prescribe cyclophosphamide to patients with childhood-onset systemic lupus erythematosus (cSLE) once the disease becomes severe enough to threaten the kidneys or other organs. However, chemotherapy can lead to infertility among some women if steps are not taken to protect their ovaries.

The drug triptorelin is used to protect ovaries among older adult women of reproductive age. Hermine Brunner, MD, Director of the Division of Rheumatology at Cincinnati Children's, led a team of researchers who worked to establish an ideal dosage of triptorelin for adolescents and young adults less than 21 years old. Their work was published online in February 2015 in *Arthritis & Rheumatology*.

Triptorelin dosed at 120 mg per kilo of body weight led to sustained ovarian suppression, which prevents the ovaries from making

estrogen, in 90 percent of study participants. On average, it required 22 days to achieve suppression, the researchers found. This dosage level is higher than that used for older adults, but the medication was well tolerated.



Hermine Brunner, MD

Finding the
Right Dose
to Protect
Ovaries
During Lupus
Treatment

Researchers at Cincinnati Children's have identified a gene that appears to explain why a significant percentage of children with asthma fail to respond to corticosteroid treatment.

The findings, published April 21, 2015, in the *Journal of Allergy and Clinical Immunology,* indicate that testing for the gene VNN-1 could help identify children who need an alternative to the most common treatment for chronic asthma and acute asthma attacks.

"Difficult-to-treat patients account for over 50 percent of health care costs associated with asthma," says Gurjit Khurana Hershey, MD, PhD, senior author of the study and Director of the Division of Asthma Research at Cincinnati Children's. "This study provides the basis for a biomarker to determine which patients might be best to target with new treatments."

The Cincinnati Children's team found VNN-1 by performing genome-wide analysis of nasal epithelial cells collected from 57 children admitted to the hospital with acute asthma exacerbations. The search started with a candidate list of 20,000 genes, which was quickly whittled down to eight strong possibilities.

The team, which included first author, Chang Xiao, MD, PhD, and colleagues from five

other divisions at Cincinnati Children's, used a series of tests to determine that VNN-1 was the one gene on the list that is required for inhaled steroids to work during an asthma attack.

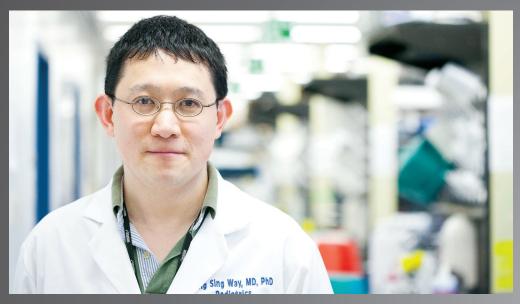
Now the search has begun to evaluate drugs that target the VNN-1 pathway as potential asthma treatments.



Gurjit Khurana Hershey, MD, PhD

Gene
Discovery
Sheds Light
on 'Difficultto-Treat'
Asthma

Mother's Own Immune System May Cause Pregnancy Complications



Preclinical research demonstrates that refocusing an expectant mother's immune cells to prevent them from attacking the fetus may help prevent some premature births and stillbirths.

Findings were published March 9, 2015, in *The Journal of Clinical Investigation*. The study suggests that preventing pregnancy complications may be a delicate balancing act between sustaining the maternal-fetal immune system while reducing risk of causing harm to the fetus.

"Pregnant women are especially susceptible to infection, so it might seem counterintuitive to prevent their immune cells from properly penetrating placental tissues," says senior study author Sing Sing Way, MD, PhD, a researcher in the Division of Infectious Diseases at Cincinnati Children's. "However, we found that pregnancy complications largely stem from harmful maternal immune cells that recognize and attack the placenta and other immunologically foreign tissues derived from the fetus. Restricting the access of harmful immune cells to developmentally delicate fetal tissue represents a highly innovative therapeutic strategy."

A team led by Way and first author Vandana Chaturvedi, PhD, used mouse models to evaluate pregnancy outcomes after causing infections with *Listeria monocytogenes*. When infections began, researchers noted that early responding neutrophils and macrophages produced high levels of the CXCL9 protein, which in turn attracted harmful T cells that attacked the fetus. This finding is significant because placental cells are normally programmed not to express chemoattractant proteins like CXCL9.

neutralize CXCL9 activity by blocking its receptor on T cells. Both methods prevented *Listeria* infections from causing stillbirths in treated mice. Importantly, the team found that neutralizing CXCL9 also helped prevent some pregnancy complications that were not caused by infections.

These findings indicate that preventing harmful immune cells from entering the placenta may have broad applications. As a next step, Way and colleagues plan to evaluate the pregnancy protecting ability of a class of small molecule inhibitors that already are being tested as treatments for human autoimmune and inflammatory disorders.

Sing Sing Way, MD, PhD

Tweddell Named Heart Institute Executive Co-Director

One of the leading cardiac surgeons and thinkers in the field, James Tweddell, MD, has joined our Heart Institute as an executive co-director and professor of surgery.

Tweddell will lead the Heart Institute's surgical team together with David Morales, MD.

Tweddell built a premier pediatric cardiothoracic surgery program at the Medical College of Wisconsin, where he had served since 1994. In that time, he rose to become medical director of pediatric cardiothoracic surgery at Children's Hospital of Wisconsin and chief for the Division of Cardiothoracic Surgery.

Tweddell has authored more than 125 peer-reviewed articles along with numerous

books, chapters, invited reviews and editorials. He also has served on multiple editorial boards and national committees.

Cincinnati is a homecoming for Tweddell, who grew up in the suburb of Indian Hill, graduated from Miami University in nearby Oxford, Ohio, and earned his medical degree at the University of Cincinnati College of Medicine. He completed post-graduate training at New York University Medical Center and Washington University Medical Center in St. Louis.

James Tweddell, MD



'Microscope in a Needle' Helps Study of Newborn Muscle Development

Rather than removing tissue to study cells under a microscope, imagine placing a microscope inside living tissue – with no more trauma than getting a flu shot. That is precisely the type of new research tool that Roger Cornwall, MD, is using at Cincinnati Children's to launch a novel clinical study of children with cerebral palsy and brachial plexus injuries.

Cornwall is the first scientist in the world to employ a device called the Zebrascope, an improved form of microendoscope with resolution powerful enough to capture images of sarcomeres – the key building block of muscle fibers – without removing tissue samples.

The device, created by researchers at Stanford University, derives its name from how images of sarcomeres appear as a series of black and white stripes. The device is so tiny that its light-emitting and light-sensing fibers can fit inside a pair of needles.

"This is the first device of its kind that allows looking inside a muscle cell, in vivo, in real time," says Cornwall, who also serves as Co-Director of the Hand and Upper Extremity Center at Cincinnati Children's. "This will allow us to confirm findings from research in the mouse about why permanent limitations to arm movement often occur when newborns sustain brachial plexus nerve damage during difficult deliveries. This also will allow new studies of muscle function in cerebral palsy, for which no animal model has been developed."

The device will help Cornwall conduct a clinical trial examining muscle development in children with elbow flexion contractures caused by brachial plexus or cerebral palsy. The first patient to join the study was tested with the new device in January.

Roger Cornwall, MD



We want your feedback!

Complete a survey about our *Research Horizons* and *Pediatric Insights* publications and be entered to win an Apple Watch. Go to this website to begin: www.cincinnatichildrens.org/reader-survey

Two Databases Launched to Study Rare Disorders

Cincinnati Children's will use a \$2.2 million award to create a database that scientists worldwide can use to learn more about the long-term health outcomes of children with a wide variety of rare genetic disorders.

The Longitudinal Pediatric Data Resource (LPDR) is funded through the Newborn Screening Translational Research Network, an ongoing project of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The database will be built by members of the Cincinnati Children's Division of Biomedical Informatics.

The resource will allow researchers to search for patterns between clinical patient data and libraries of molecular, genetic and genomic information. Diseases to be tracked include lysosomal storage disorders, inborn errors of metabolism, and severe combined immunode-ficiency disorders.

"A large number of serious diseases of newborns can potentially be identified through existing newborn screening programs," says project leader Peter White, PhD, Director of Biomedical Informatics at Cincinnati Children's. "In a growing number of these disorders, early detection provides the opportunity for improving



Marc Rothenberg, MD, PhD



Peter White, PhD

the lives of these children. The LPDR will fast-track research on these diseases by collecting much larger sets of patients, and following patient outcomes over time."

Meanwhile, the Consortium of Eosino-philic Gastrointestinal Disease Researchers (CEGIR) has launched a patient contact registry for people with eosinophilic gastrointestinal diseases (EGID). Establishing the database will make it easier for investigators to identify and recruit patients for new research studies. For enrolled patients and caregivers, the registry will provide direct notification of research studies, periodic research updates, patient advocacy information, and more.

"This registry will transform our ability to develop the best diagnostics and treatments for EGIDs by improving the way in which patients and their families can contribute and be involved in the efforts to understand these diseases," says Marc Rothenberg, MD, PhD, Director of Allergy and Immunology and the Cincinnati Center for Eosinophilic Disorders at Cincinnati Children's.

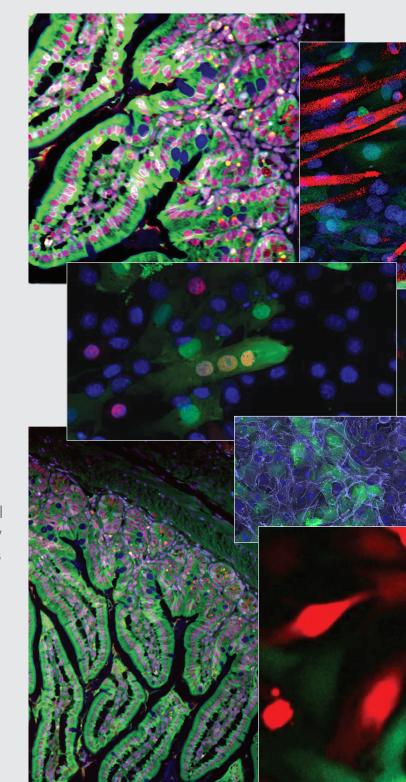
New Approaches to

s many grateful families can attest, strong progress has been made on many fronts against childhood disease. Yet the mission remains far from accomplished. For cancer, diabetes, muscular dystrophy and so many more conditions, the thirst for innovation, the need for more discovery, only grows.

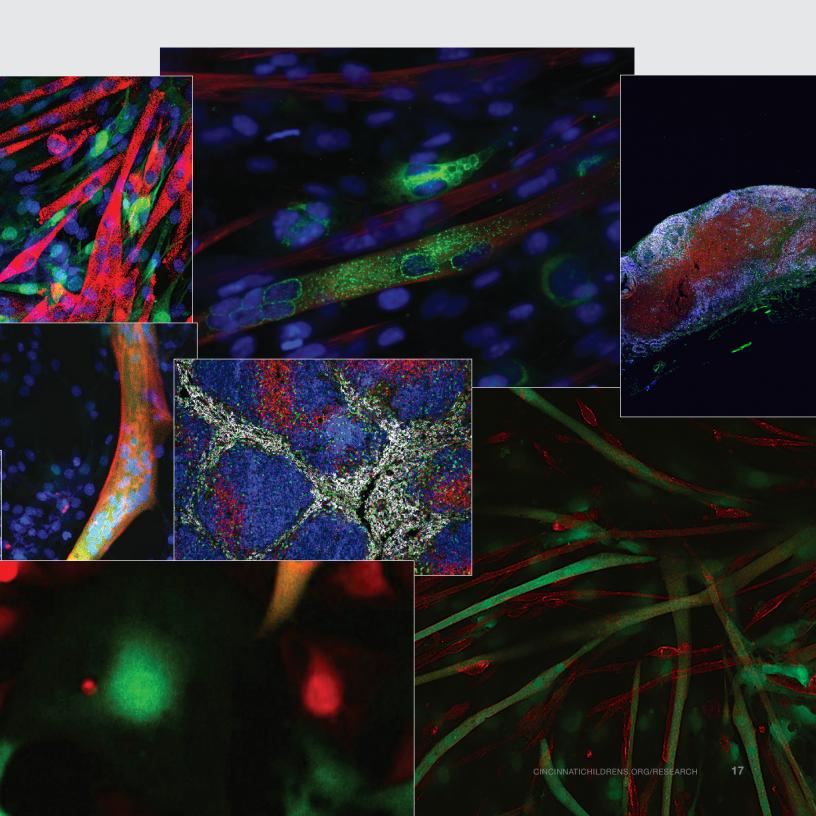
In this issue of Research Horizons, we are excited to report about a growing cadre of investigators at Cincinnati Children's who are bringing fresh perspectives and bold ideas to a wide range of long-troublesome research challenges.

Their work shines new light on how children grow, how muscle cells function, how intestinal bacteria interact with our immune systems, even how providers communicate with families. New discoveries about high-density lipoprotein (HDL) particles could have far-reaching impact on preventing heart disease. Fresh information about natural killer (NK) cells could reverse years of difficulty developing vaccines against malaria, hepatitis C and other deadly viruses.

Many of these new avenues of exploration have been opened only because Cincinnati Children's invests and reinvests in building a pipeline of talented scientists. Read on to learn more about their work and what it takes to support it.



Stubborn Challenges





Size Matters

by Tim Bonfield

any people know that HDL cholesterol is supposed to be the "good" cholesterol.

While low density lipoproteins (LDL) – the "bad" cholesterol – collect in cardiac artery walls, high-density lipoproteins (HDL) help to transport them away. Thus, if people want to avoid heart attacks and strokes, they should boost their HDL cholesterol levels while reducing their LDL cholesterol levels.

If only preventing heart disease could be so straightforward.

In the clinic at Cincinnati Children's, Amy Sanghavi Shah, MD, MS, works closely with obese teens who have developed Type 2 diabetes and have already begun to show early signs of heart disease risk. In the laboratory, she works to find better ways to reduce those risks. In the process, she has learned that the relationship between heart disease and HDL is much more complicated than previously believed.

"It's not just the HDL cholesterol number," Shah says. "Cardiovascular risk also appears to be influenced by the types of HDL a person has."

NEW LOOK AT HEAVILY STUDIED PARTICLE

Scientists have known for many years that HDL is not just cholesterol. These complex particles have a core packed with triglycerides and cholesteryl esters surrounded by a coating of phospholipids and apolipoproteins. In fact, cholesterol comprises less than 20 percent of an HDL particle.

Less well known, until recently, has been that HDL particles can vary significantly in size and composition. Run a blood sample through a standard lipid panel and the results will reveal simple levels of HDL and LDL cholesterol and triglycerides. Put that same sample through a gel filtration column and the

results will reveal one or more of 10 subspecies of HDL.

"These different-sized particles appear to have differing actions," Shah says. "The larger ones that are richer in phospholipids may have a beneficial effect, while the smaller ones are more cholesterol rich and appear more likely to have negative effects."

But why do some people have larger HDL particles floating in their blood while others have smaller ones? Are these size differences a possible cause of increased heart disease risk, or a symptom of the disease process? That is what Shah and colleagues hope to find out.

"There's a lot more to know inside the world of HDL," she says.

PROFILING HDL PARTICLES

In addition to size differences, Shah and colleagues are using the latest in proteomics technology to learn more about the apolipoproteins on these HDL particles.

This line of research built upon work from scientists at the University of Washington who found that HDL particles carry some 90 different proteins. Shah and colleagues applied similar mass spectrometry technology to HDL subspecies collected from teens with Type 2 diabetes, with results published in July 2013 in the journal *Diabetes*.

"We found proteins that confirm HDL has a role in lipid transport and identified proteins that point to roles in antioxidation, immunity and glucose metabolism," Shah says.

The complicated roles played by HDL may help explain why a number of other studies have produced head-shaking findings:

- Several large clinical trials of HDL cholesterol-boosting drugs have shown disappointing results at reducing heart disease risk.
- People with Type 2 diabetes have

- shown residual cardiac risk even when LDL has been reduced to the lowest possible levels.
- Even people born with unusually high, natural HDL cholesterol levels (a small percentage of the population) do not consistently escape heart disease risk.

FUTURE POSSIBILITIES

So if controlling HDL levels has such inconsistent effects on heart disease risk, should people bother with cholesterol testing? Well, yes.

Shah predicts cholesterol testing will become much more sophisticated as understanding of HDL particles grows, so staying in the testing habit has value. If nothing else, the findings of simple cholesterol testing serve to remind people of the undisputed need to battle obesity and preventing Type 2 diabetes by eating well and getting plenty of regular exercise.

In the meantime, the search has begun to identify and understand the most beneficial subspecies of HDL.

"We need to understand what these different subspecies are doing," Shah says. "Eventually, we hope new therapies may be developed that can help boost the right kinds of HDL."

Having one foot in the lab and another in the clinic gives Shah a special perspective on the urgency of the work ahead.

Only now are the children who started developing Type 2 diabetes as part of the obesity wave that struck America in the 1990s beginning to reach their 30s. Few of these people are suffering heart attacks – yet – but some already are experiencing kidney complications, neuropathies and other problems that normally strike diabetics later in life.

"It took a long time for these children to get to where they are today," Shah says. "Reversing the process may take even longer."

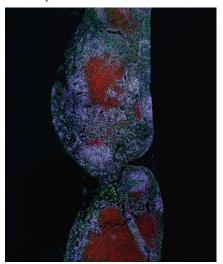
Corralling Natural Born Killers to Save Lives

by Nick Miller

tephen Waggoner, PhD, wants to harness the innate abilities of natural born killers to improve medicine and save lives. The immunologist and researcher – a member of the Center for Autoimmune Genomics and Etiology at Cincinnati Children's – leads a team of scientists who study the immune system's natural killer cells (NK cells). They are using a \$2.5-million Avant-Garde grant from the National Institutes of Health to help develop vaccines against viruses that have long lacked effective inoculations, including HIV, tuberculosis and hepatitis C.

Their work so far reveals that the aggressive nature of NK cells can prevent other elements of the immune system from producing the response that vaccines are designed to invoke. Now, the team is searching for safe ways to tame that aggression.

"The primary role of NK cells is to eliminate unwanted infectious or cancerous cells," Waggoner says. "While T and B cells in the immune system serve in a similar capacity, through recognition of specific attributes of these unwanted cells, they require a lengthy process of arming similar to the assembly and loading of a firearm. In contrast, NK cells are first responders and more like a loaded



gun with the safety off, capable of rapidly killing a broad array of infected or cancerous cells."

This gunslinger mentality can be beneficial when the target is a cancer cell or herpes virus. However, Waggoner and other researchers have found NK cells can keep vaccines from working properly by subduing other immune cells that must be stimulated to battle life-threatening infections. Thus, NK cells can become too much of a good thing.

DOUBLE IDENTITY

NK cells have dual roles in immunity, Waggoner says. As first-response soldiers, they attack whatever foreign invaders they encounter. As sentinels, NK cells also play a role in deciding when to summon reinforcements from other parts of the immune system, including our T cells and B cells, and how many.

Scientists are still working to understand exactly when, why and how NK cells affect the immune system's on-or-off process. Waggoner and colleagues shed new light on how NK cells work in a paper published earlier this year in *Nature Communications*.

The study analyzed mice infected with lymphocytic choriomeningitis virus (LCMV), a rodent virus that can cause diseases of the central nervous system, liver, and lungs. The researchers found that NK cells suppress the development of T and B cells that should be programmed with a sustained memory for staging a prolonged attack against LCMV.

By subduing T and B cells at a crucial point, NK cells allowed the infection to take root and spread. This is important in the context of vaccines because part of a vaccine's function includes imparting programmed memory for immune cells against a specific virus, Waggoner explains. If NK cells subdue

the development of these programmed memory cells, the vaccine is not effective.

TIMING MAY BE EVERYTHING

Finding a way to inhibit NK cells could increase vaccine effectiveness against viruses that cause malaria, AIDS, tuberculosis and some forms of cancer. But this approach is not risk-free.

In studies of mice, Waggoner's team has shown that inhibiting or deleting NK cells does stimulate a bigger and better immune response. However, long-term absence of NK cells also can ramp up other immune components to the point where mice develop markers of autoimmune disease in their kidneys.

"The practical question is how to take the brake off?" asks Waggoner. "It's unrealistic to think we can go into people like a mouse and deplete those cells, because they might be preventing a herpes infection or cancer. We want to maximize the B and T cell response in a targeted way that doesn't entirely remove the NK cell side of the coin."

The team's research now focuses on learning more specifics about how NK cells function in their respective beneficial and harmful roles, and then targeting the cells precisely to boost the effectiveness of vaccines. The researchers are teasing out different genes, proteins and biological mechanisms that might make this possible. Studies like the one in *Nature Communications* suggest this could lead to a drug or formulation that serves as an adjuvant therapy to a vaccine or that could part of the vaccine itself.

"What if you could include a small molecule in a vaccine that binds to NK cells for a few days to keep them from activating?" Waggoner says. "We want something specific to repress NK cells during a certain period of time, and then allow them to come back to full functionality."





Drs. Vivian Hwa and Andrew Dauber have identified gene variants in DNA damage repair, cell cycle dynamics, growth plate signaling and other aspects of development. Their findings suggest that severe growth disorders require a wider menu of treatments than most medical centers provide.

Much More Than a Hormone Problem

by Tim Bonfield

ndrew Dauber, MD, uses an old joke to illustrate the old ways of thinking about how to treat growth disorders.

A woman heading home from a restaurant encounters a man under the glow of a streetlight, searching for his lost keys. The woman asks the man, "Is this where you think you dropped the keys?" The man says, "No. I think I dropped them back there." So the woman asks, "Why are you searching for them here?" The man replies, "This is where the light is."

For a long time, the core approach to correcting severe growth disorders has been to give daily injections of growth hormone, a therapy that sometimes goes on for several years. The therapy can be quite effective when a hormone deficiency is the actual cause of short stature.

However, experience has shown that many children with growth disorders have no hormonal abnormalities. In fact, a 2013 paper in the *Journal of Pediatrics*, authored by Philippe Backeljauw, MD, and colleagues, reports that standard hormonal metabolic workups provided no answers for at least 80 percent of the patients referred to Cincinnati Children's to determine the cause of their short stature.

Now, thanks to an explosion of genetic and genomic analysis technology, scientists are learning just how complex the seemingly straightforward outcome of short stature can be.

"As endocrinologists, we have tended to focus heavily on hormonal factors. But if you take a step back, there are many, many biological processes involved in growth," Dauber says. "Disruptions can start as early in the developmental process as DNA replication or in the centrosomes that regulate cell division. There can be defects that affect DNA damage repair, the growth plates of bones, or the extracellular matrix. And yes, there can be defects in growth hormone and the growth hormone receptor."

Hundreds, if not thousands, of genes may be involved, and variants anywhere along the line can affect growth.

A NEW CLINIC TAKES SHAPE

The new Center for Growth Disorders at Cincinnati Children's was formed in August 2014 to bring together an expanded team of experts in endocrinology and genetics.

Dauber, a clinician with expertise in genomic analysis, had been based at Boston Children's Hospital. He had published research in the field in collaboration with Vivian Hwa, PhD, a microbiologist-turned-endocrinologist who worked on growth hormone-IGF-I axis defects at the Oregon Health & Science University. Both relocated to Cincinnati to work with a growing team that also includes Backeljauw and geneticist Nancy Doan Leslie, MD.

Patients with severe short stature from more than a dozen nations have been referred to the center for deeper evaluation. Data from exome sequencing, hormonal evaluations and other tests are fueling several research advances.

"We have already identified gene variants in DNA damage repair, in proteoglycans and extracellular matrix, in growth plate signaling genes, in the IGF-1 axis, in cell cycle dynamics, and more," Hwa says.

This explosion of data is redefining our understanding of growth disorders, including the very names of the syndromes.

"I'm a strong believer in the idea that we need to stop calling things by old syndromic names based on physical characteristics," Dauber says. "We need to think about these conditions in terms of classes and subclasses based on molecular-genetic definitions."

BETTER DEFINITIONS, BETTER TREATMENTS

It likely will take years to accomplish on a national or global scale, but efforts have already begun to provide therapies that more precisely address the actual causes of short stature.

For example, if a child has a certain gene defect that affects the function of their growth plates, they might benefit from receiving aromatase inhibitors; drugs that are known to prevent growth plates from closing. Growth hormone may not be necessary, or may serve only as a secondary treatment.

One immediate research goal will be to re-evaluate existing hormone-based therapies to document their effectiveness against emerging genetic subclasses of severe short stature. Improved outcomes could flow simply from adjusting dose levels among different groups.

Another level of research will be to find existing, approved drugs that may affect the molecular profiles of particular patient groups; drugs that may never have been thought to be useful in treating short stature.

Longer-term, scientists also will strive to develop new medications that specifically target molecular pathways revealed by rapidly expanding genomic research technology.

Eventually, Hwa and Dauber say treating short stature could become a matter of using gene testing to detect biomarkers that could be used to guide young children as soon as possible to the best available therapy for their conditions, thus giving them more time to grow.

In some cases, there may not be a way to help a child reach normal stature. Even so, knowing more about their condition could allow early interventions to manage co-morbidities that can have their own impacts upon quality of life.

Muscular Discovery

by Tim Bonfield

xamine a fully formed muscle cell under a microscope and even untrained eyes can see a striking feature. Unlike most other cells in our skin, bones, organs and blood, muscle cells are elongated structures that have not one, but multiple nuclei.

Biologists have understood for many years that muscle cells possess the unusual ability to fuse together as they develop into the fibrous strands that put our skeletons into motion. But only recently have scientists begun to unlock the genetic secrets of the fusion process, an advance that could have extensive implications for health.

While working as a post-doctoral fellow at the University of Texas Southwestern in Dallas, Doug Millay, PhD, and his mentor found the first muscle-specific gene shown to play an essential role in embryonic muscle cell fusion. In a paper published in 2013 in *Nature*, they dubbed the gene "myomaker." Then in a 2014 follow-up paper in *Genes and Development*, the team showed that the myomaker gene also is necessary for normal adult muscle cell regeneration.

Now Millay works at Cincinnati Children's, returning to his hometown and to the institution where he previously trained, to continue exploring the implications of the myomaker gene. His work received a major boost this summer when he became one of about 20 outstanding young researchers nationwide to be named a Pew Scholar. (See more about the award on page 2.)

GENOME SEARCH PRODUCES RESULTS

Millay says they found the myomaker gene by extending concepts he learned working as a graduate student at Cincinnati Children's in the laboratory of Jeffery Molkentin, PhD, a Howard Hughes Medical Institute (HHMI) investigator in the Division of Molecular and Cardiovascular Biology.

"Jeff had been working on how calcium regulates aspects of heart development and disease," Millay says. "We took some of the observations from his work on the heart and asked similar questions in skeletal muscle, so this experience was the foundation for my future work on skeletal muscle."

Millay and colleagues searched available databases for genes explicitly expressed in skeletal muscle. They found about 30 gene candidates, some of which had been well annotated with descriptions of their functions, while others had incomplete annotations. Myomaker was among the incompletely annotated genes on the list.

Further testing revealed that, unlike other genes on the candidate list, myomaker was crucial for normal muscle cell formation. That finding implies that it may be possible to restore normal muscle function by introducing a "normal" myomaker gene to muscle stem cells that lack the gene or have a malfunctioning version

Once the team determined that myomaker plays an essential role in normal development, they made another vital observation.

GENE CAN HITCH RIDES ON NON-MUSCLE CELLS

The myomaker gene is not found in cardiac muscle nor in the smooth muscles that drive other organ functions. However, in mice, the gene can be expressed on nonmuscle cells, which then allows these cells to fuse to skeletal muscle, Millay has learned.

This implies that myomaker might be useful as a delivery vehicle for future therapeutic approaches to specifically target muscle cells. Millay cautions, however, that myomaker appears to be only one part of the machinery of muscle cell development. Other yet-to-be-defined elements may have even more value as potential therapy targets. Also, the gene manipulations that researchers can do with mice may not be possible in humans.

"We still have much work to do to understand the feasibility of this approach. We are a ways off from clinical applications," Millay says.

MUSCULAR DYSTROPHY IMPLICATIONS AND MORE

Even so, the implications are intriguing.

"If we can understand the machinery of how muscle cells fuse, then we eventually might be able to manipulate that process in a disease setting," Millay says.

One possibility that immediately jumps to mind among pediatric medical researchers is Duchenne muscular dystrophy, along with similar genetic diseases that gradually erode muscle function.

"Boys with Duchenne have a mutation in a gene called dystrophin, which results in muscle weakness but these muscle still harbor multiple-but-defective nuclei," Millay says. "So one question is, would it be possible to use myomaker to deliver functional nuclei and a normal copy of dystrophin to those cells to help the muscles retain their function?"

If muscle function can be restored or preserved in muscular dystrophies, the next question would be could muscle loss be reversed in other, more common conditions such as cancer, AIDS, COPD, or even the natural aging process? And what would restoring muscle function mean?

"In all of these conditions, muscle loss reduces the quality of life," Millay says. "But restoring muscle cell growth may likely do even more than impact quality of life. It could also slow the progression of the disease itself."





Gut Reaction

by Nick Miller

urns out the old adage, "You are what you eat," is true - although there is much more to the story.

Researchers have long understood that what we breathe, drink and swallow can play important roles in triggering disease. Now, new research at Cincinnati Children's is helping explain why our well-being depends so much upon the relationships between what we ingest, the cells lining our intestine, and the trillions of commensal bacteria (normal flora) living there.

Theresa Alenghat, VMD, PhD, is a researcher in the Division of Immunobiology who was recently named a 2015 Pew Scholar. (See Page 2.) She is working to decipher the crosstalk that occurs between mammalian cells and bacteria that normally reside in the intestine, whose diversity and location can be affected by factors ranging from diet to medications to emotional stress.

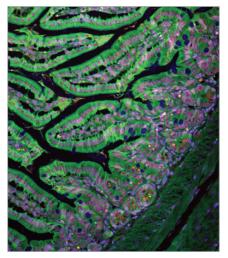
"When I was working on my PhD, whether the intestine could be involved in what we were studying did not cross my mind," Alenghat says. "Now, as numerous diseases are being linked to intestinal health, it is interesting to see how this mentality has changed. Over the last decade or so we have come to recognize that commensal bacteria and the intestinal microenvironment are essential factors in disease development."

EPITHELIAL INTERFACE

The epithelial cells lining our intestines do much more than help our bodies absorb nutrients and provide a physical barrier. They also constantly interact with our commensal bacteria, secreting small proteins called antimicrobial peptides and cytokines, which in turn affect bacterial populations and regulate immune cells.

"These epithelial cells are sometimes overlooked, so we are interested in studying how they mediate crosstalk between intestinal bacteria and immune cells to affect health," she explains.

Research increasingly shows several significant public health challenges – diabetes, allergies, asthma, cancers, autism and inflammatory bowel disease – develop from complex geneenvironmental interactions. The mystery is where, why, and how these interactions are triggered. More and more, evidence points to processes that get started in the intestine.



Changes in intestinal bacteria can lead to changes in our epigenome; or the way our genes are turned on and off over time by environmental factors. When all goes well, beneficial bacteria survive in the intestine and send signals that maintain a healthy epigenome. However, environmental exposures that impact commensal bacteria may trigger epigenomic dysregulation, and prolonged exposures can set up a negative cycle that leads to disease.

Alenghat and her colleagues have identified a key factor in how this process works. Histone deacetylase 3 (HDAC3), an enzyme in intestinal epithelial cells, acts as an epigenomic modifier that regulates healthy intestinal function. In mice, deleting HDAC3 from intestinal epithelial cells impaired intestinal function, caused intestinal damage and

led to inflammation, according to a 2013 *Nature* study Alenghat co-authored while at the University of Pennsylvania. The paper showed that HDAC3 integrates signals from commensal bacteria to regulate gene networks, calibrate epithelial cell function, and maintain normal intestinal health.

NEXT STEPS

With HDAC3 as one focal point, the researchers are teasing out which of the trillions of commensal bacteria are critical to regulating the epigenome. They want to see how intestinal bacteria interact with HDAC3 and its downstream pathways to impact immunity and trigger disease.

The efforts include a collaboration with Lee Denson, MD, Medical Director of the Inflammatory Bowel Center, to study intestinal biopsies from patients with inflammatory bowel disease. If they can detect disease-causing changes in the epigenome and commensal bacteria, it may be possible to develop new ways to improve treatment and predict prognosis.

Alenghat also plans to test how bacterial factors affect intestinal biology by analyzing organoids of human intestinal tissue, a new research tool developed by the laboratory of Jim Wells, PhD, Developmental Biology and Endocrinology. Combining the organoid findings with methods involving unique mouse models that lack commensal bacteria will create a robust system for deciphering the links between the microbiota and intestinal health.

"Multiple studies have come out recently that indicate that the microbiota may be interacting with epigenomic pathways in different mammalian cells," Alenghat says. "Now that we know this is happening, I think we are just beginning to explore what it all means, how it relates to disease and how this will enable new approaches for managing chronic diseases."

A Fuzzy Debate About A Foggy Condition

by Mary Silva

debate has been going on among psychologists since before Stephen Becker, PhD, was born. Becker, now a clinical psychologist in the Division of Behavioral Medicine and Clinical Psychology, would like to settle it once and for all.

The debate is about sluggish cognitive tempo (SCT), a set of behavioral symptoms characterized by excessive day-dreaming, mental fogginess and lethargy. Becker observed it first-hand while working with children during his graduate training and clinical residency.

The kids he worked with all had been diagnosed with ADHD. Yet some of them behaved in unexpected ways.

"When you think about the classic child with ADHD, you think about hyperactivity, running around, impulsiveness," Becker says. "But these kids were withdrawn, often confused, and even slower in the ways they seemed to process information."

A DEBATED CONDITION

SCT has been a subject of discussion and controversy for decades. Some psychologists and psychiatrists dismiss it altogether. Some believe it is a subset of symptoms within ADHD. Some think it should be its own disorder. Interest in settling the debate is growing because estimates indicate that SCT affects as many as 2 million children in this country.

Becker is interested because he has seen what SCT can do to a child.

"These symptoms can cause academic and social problems and difficulties with regulating emotion," he says. "Yet kids who show these SCT behaviors are likely not being identified. They are not the kids blurting out answers or causing disruptions in the classroom."

But they are kids who face social challenges. Becker's study of the peer functioning of children with SCT symptoms, published in June 2014 in Psychiatry Research, found that 75 percent of children with high levels of SCT were rated as functionally impaired, compared to just 8 percent of children with low SCT. Becker says despite the prevalence of ADHD – now estimated to affect some 6 million children in the U.S. – there is still much we need to learn, and scientists know far less about SCT.

"We need to understand how these kids differ – and do they differ in meaningful ways?" he says. "We have hunches that they do, but we haven't compared children with SCT to other children in a rigorous way."

APPLYING SCIENCE

Becker has undertaken a first-ever study recruiting kids based on the presence or absence of SCT symptoms.

He hopes the study, which is funded by a Trustee Award of the Cincinnati Children's Research Foundation, will provide pilot data for a larger-scale grant. His team began recruiting in September 2014, and as of March, had enrolled 50 children. Their goal is 100. The study will look at four groups: children who have developed normally, those with SCT only, those with ADHD only, and those with both. As of this writing, most participants were in the combined or ADHD-only groups, but 10 were in the SCT-only group. Children in this study range in age from 8 to 12 because, says Becker, "It's a time when kids encounter a lot of challenges, and many are first diagnosed with ADHD."

Wherever the study of SCT leads, Becker believes a better understanding will help identify how to help children showing SCT behaviors. "We know that when these symptoms are present, they come with impairment – poor emotion regulation, more social withdrawal, more loneliness, and more academic problems," he says.

The most convincing argument for further study of SCT is the response Becker has received from families. "Parents have emailed me out of the blue," he says. "I have no idea how they found me, or my research. But I've been touched by their response."

Needed: Children Who Daydream, Are Slow Moving and/or Seem to be "In a Fog"

hildren's Attention Problems Study



What

This is a research study to learn more about how children with specific attentional difficulties differ from other children, in their cognitive and sleep functioning.

Who

Children 8 to 12 years old who daydream, are slow moving, and/or seem to be "in a fog" may be eligible.

Pav

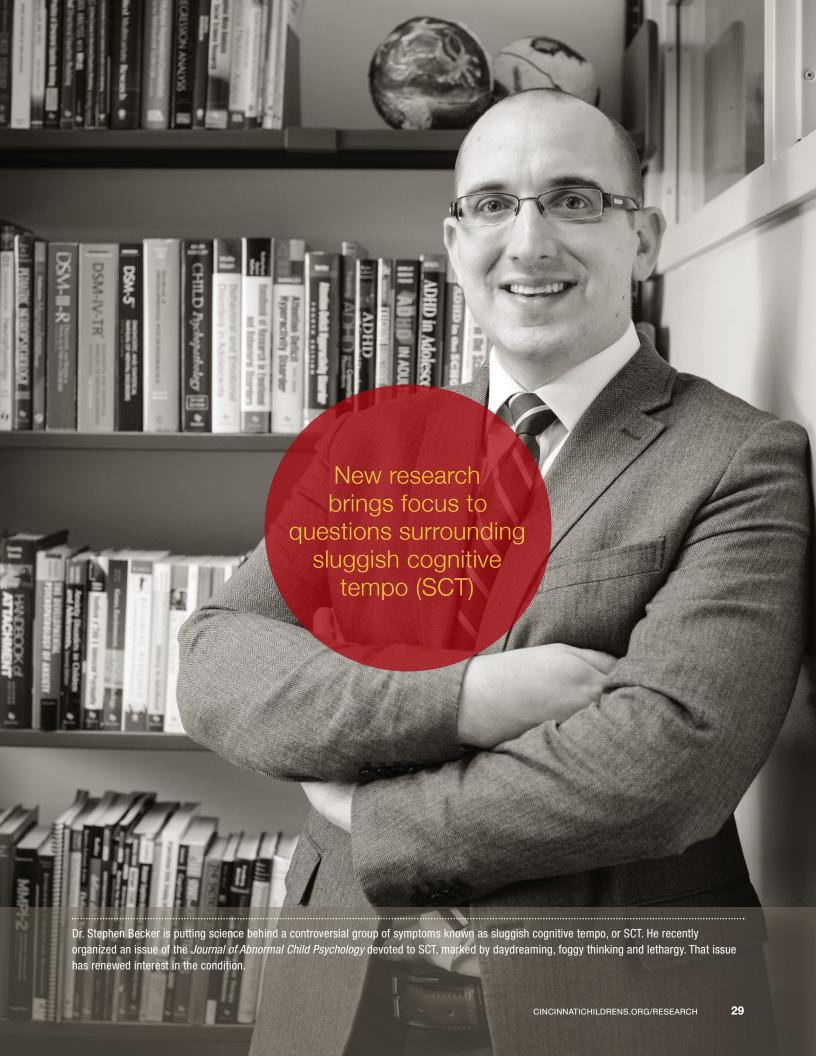
Families may receive up to \$100 for time and effort.

Contact

The study coordinator at CTADHD@cchmc.org or 513-803-0771

Cincinnati Children's Research Foundation

cincinnatichildrens.org/clinical-studies facebook.com/cincinnatichildrensstudies pinterest.com/cincykidstrials





Medicinal Motivation

by Mary Silva

orget beakers and Petri dishes, microscopes and mice. Scientific studies today are as likely to be conducted in clinics, around conference room tables or on laptops as they are in the laboratory.

That is certainly the case for Meghan McGrady, PhD, a researcher in the Division of Behavioral Medicine and Clinical Psychology, whose insights into behavior could be as important to creating better outcomes as discovering the latest gene pathway.

McGrady wants to know what motivates young people to take their prescribed medications – or not. She works with young people who have high-stakes illnesses, such as kidney transplants, diabetes, or cancer. In the face of such serious conditions, you would think sticking to a medication regimen would not be a problem. You would be wrong.

MEDICATION MUST FIT LIFESTYLE

"More so than for many other age groups, adolescents who feel taking a medication doesn't fit into their daily lives may not be motivated to be adherent," says McGrady, who became interested in working with adolescents during her clinical internship at Cincinnati Children's.

"They are trying to figure out who they are and what they want," she says. "They may not always see how a strict medication regimen fits into their plans for the future."

She wants to figure out how to remedy that, starting with young people who have cancer. Her first step was a pilot study that asked adolescents and young adults ages 15 to 31 what influenced their decision to take their medications.

"We asked, 'What makes you decide 'Yes, I am going to take it or no, I'm not'?

What factors are changing your decision in the moment?"

Responses ranged from not wanting to be inconvenienced when out with friends to the hope that skipping three or four doses would not be harmful since "I've already had so much chemotherapy."

NO SINGLE SOLUTION

What McGrady learned was that solving the problem of treatment adherence in this age group will require a multi-faceted approach.

"What's motivating to one adolescent or young adult may be irrelevant to another," she says. "Because we are hypothesizing that motivation is a key driver of adherence, it's crucial that

we understand what motivates a given individual."

She has used her study findings to apply for a National Institutes of Health Career Development Award that will use behavioral economic methods – techniques developed to understand what drives consumer preferences such as what car to buy – to ask young patients what motivates them to take their medications.

Based on their responses, she will develop a tool that could be used by the patient's medical team to match the right medication regimen to the patient.

"If we could administer the tool in clinic, it would help the medical team know what they could do to motivate these patients," McGrady says.

The Economics of Adherence

Cincinnati Children's colleagues Meghan McGrady, PhD, and Kevin Hommel, PhD, published a review in October 2013 in *Pediatrics* confirming that chronically ill children with poor adherence spend more time in the hospital and emergency room.

McGrady now hopes to show that interventions targeting psychosocial difficulties like non-adherence also reduce costs. Her ongoing study compares overall healthcare costs for cancer patients who did receive psychosocial services to those who did not.

"It's important for psychologists to understand how we can contribute to the goal of cost reduction," McGrady says. "We've done a good job of showing how our interventions can improve outcomes, but our economic analyses have lagged behind."

The Science Behind the Art of Communication

EMERGING RESEARCH INTO SHARED DECISION-MAKING IS DRIVING THE WAY DOCTORS TALK TO — AND LISTEN TO — PARENTS

by Tom O'Neill

he lanes of communication between pediatrician and parent were not always a two-way street. Or, for that matter, perfectly paved. Cincinnati Children's is changing that.

Under the old, generations-tested formula, doctors explained medical options with gentle authority and families tried to comprehend and follow directions.

Today, improved treatment of chronic diseases that require committed family input – particularly the behavioral challenges of ADHD and autism – have helped push innovation. But as recently as a decade ago, national research on shared decision-making was limited, and what did exist focused not on outcomes, but the process.

That historical backdrop led researchers at Cincinnati Children's to take a new look at an old dilemma, initiating studies on decision-making and family dynamics. In one 2011 study, published in *Archives of Pediatrics & Adolescent Medicine*, researchers used a validated measure to quantify the amount of shared decision-making observed in video-recorded office visits with parents whose children were newly diagnosed with ADHD.

The project revealed insufficient shared decision-making and potential disparities and barriers. It also reinforced earlier lessons from direct interviews with parents about biologic medications, from which a jarring truth emerged.

"We were struck by just how emotional these decisions are for families," says Ellen Lipstein, MD, MPH, of the Division of Adolescent and Transition Medicine. "In our first set of interviews, we were a bit unprepared. For instance, I didn't know parents were going to cry. And these were parents of kids who are doing well now. But they still worried, particularly about side effects."

Findings from this research prompted new approaches to communication in pediatric care. Cincinnati Children's began developing new educational videos, including parent testimonials, booklets and sets of information cards that clinicians use to better engage families. They saw that potentially complicated decision-making processes could be simplified, and parents could become coowners of decision-making and more adept navigators of online resources. Equally importantly, providers could become better listeners. Now, researchers are digging deeper into how these new

strategies can improve care for other chronic childhood conditions.

AN UNDEREXPLORED FIELD EMERGES

"This is decision-science," says Bill Brinkman, MD, MEd, MSc, Director of Research in the Division of General and Community Pediatrics. His research projects involve a wide range of divisions, including Developmental and Behavioral Pediatrics, and Behavioral Medicine and Clinical Psychology.

"It's one of the most fascinating parts of pediatrics, where we have the most to learn," Brinkman says. "I think we're just starting to scratch the surface. Every family dynamic is a little different."

Family buy-in is crucial to the long-term treatment of such chronic conditions as ADHD, sickle cell disease, autism, arthritis and inflammatory bowel disease. Each can be managed. But behavioral modification and adherence can be tricky, and the science of it all is, as several researchers put it, "underexplored."

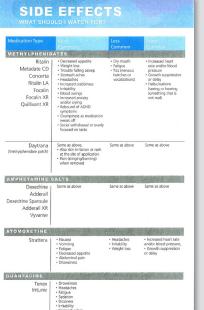
"If you asked about the importance of families participating in decisionmaking 50 years ago," Lipstein says, "I suspect the physician would have said, 'No' and the family would have said,

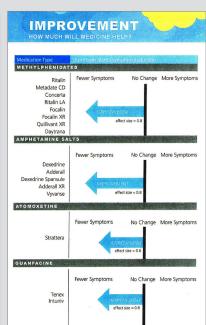
CINCINNATI CHILDREN'S FUELING NEW INSIGHTS

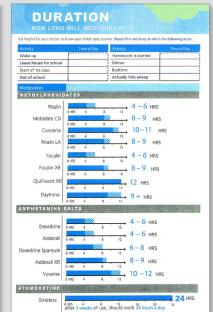
The card system study and other decision-making projects received support from the Cincinnati Children's Place Outcomes Research Award and the medical center's Center for Education & Research on Therapeutics (CERTs). Both programs support innovations to improve healthcare delivery outcomes.

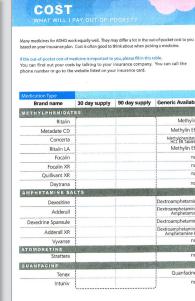
These and other internal grant programs often provide the initial support needed to develop a good idea into a project capable of earning highly competitive NIH grant funding. Indeed, preliminary data generated from these initial projects led to grant funding from the National Institute of Mental Health, the National Institute of Child Health and Human Development, and the Agency for Healthcare Research and Quality.

DAILY ROUTINE DOES MY CHILD NEED TO SWALLOW A PILL? METHYLPHENIDATES Swallow whole or 2 - 3 / day 4 hrs 4 hrs Ritalin CRUSH to put in food Swallow, or sprinkle 45 minutes before in applesauce, pudding, or yogurt Metadate CD 1 / day 90 minutes before Concerta 1 / day Swallow ONLY Swallow, or sprinkle 45 minutes before Ritalin LA 1 / day in applesauce, pudding, or yogurt 4 hrs 4 hrs Swallow whole or Focalin CRUSH to put in food Swallow, or sprinkle 45 minutes before Focalin XR 1 / day class or activity in applesauce, pudding, or yogurt Swallow liquid 45 minutes before Quillivant XR 1 / day 2 hours before class Patch 1 / day Davtrana or activity, lasts 3 hours after removal AMPHETAMINE S Swallow whole or CRUSH to put in food Dexedrine Swallow whole or CRUSH to put in food Adderall 2-3 / day AM 60 minutes before class or activity Swallow ONLY Dexedrine Spansule 1 / day 45 minutes before class Swallow, or sprinkle Adderall XR 1 / day in applesauce, pudding, or yogurt 60 minutes before class Vyvanse 1 / day ATOMOXETINE Strattera 1 / day OR OR Swallow GUANFACINE Swallow whole or 2 / day Tenex Swallow ONLY OR OR Intuniv 1 / day * Take pill in the morning, or at night if causing drowsiness It takes 2 to 3 weeks for medicine to reach beneficial level. Updated: 09/18/2013









'No.' That speaks to the changing culture of medicine."

Lipstein, Brinkman and colleagues recently published several papers that help establish why family decision-making deserves closer attention. One provided a stark review of the last half-century.

In 2012, in *Medical Decision Making*, the team examined a general lack of longitudinal data about family decision-making in pediatrics. Their review analyzed 52 previous studies in the U.S. dating back to 1989. Their search actually went back to 1966, but in those first 23 years, they found no studies on decision-making beyond topics like vaccinations and screening tests.

In subsequent studies, including in the *Journal of Pediatrics*, possible solutions came into better focus. Meanwhile, surveys of both parents and physicians helped Cincinnati Children's better quantify their sides of the decisionmaking experience.

HOW LISTENING CAN LEAD TO HEALING

Decision-making research at Cincinnati Children's is revealing how much treatment outcomes can be influenced by being attentive to the highly fluid priorities of parents and children.

One day the key concern might be behavioral challenges or schoolwork. The next day, anxiety or adherence. Or an illness' impact on siblings and friends.

Even the words used during a clinic visit can be a source of miscommunication. For parents, "long-term" often

means their child's lifetime. To an adolescent, "lifetime" might mean next week.

In 2013, Brinkman led a study published in *Patient Education and Counseling* that showed the effectiveness of decision-making cards for helping parents decide about treatments for ADHD, the most common childhood neurobehavioral disorder in the U.S.

The bright, 5-inch-by-11-inch cards were designed by the Cincinnati Children's research team and graduate students from the University of Cincinnati's College of Design, Architecture, Art, and Planning. They are light on text, heavy on images, and they provide information about everything from duration of a medication to negotiating the side effects to whether it is available in generic form.

Clinicians shared one set of cards with parents before clinic follow-up visits, which helped families drill down to subsets of concerns, allowing them to ask, "If we do this, how does it impact that?" Another set of cards were used to facilitate discussion during the visit. As a result, parents were more knowledgeable about options and more involved in decision making, but visits were not more time-consuming.

PARENTS BECOME EFFECTIVE RESEARCHERS

Becky Siler has two adopted sons, ages 10 and 7, who are being treated for ADHD at a Northern Kentucky pediatrician's office associated with Cincinnati Children's. At first, she resisted medication as a solution.

"We tried everything," she says. "We tried behavioral things like reward systems, but it just wasn't enough."

Siler and her husband were swamped amid unfamiliar therapy choices. But her pediatrician, Mark Deis, MD, used the card system to help organize the family's needs. Siler used it as a launch-point for her own online research. The boys are now on medication and doing well.

"It's very easy to get overwhelmed by these things," she says. "So it was a matter of picking and choosing what was important and what we could let go. And Dr. Deis, he always listens."

Drs. Ellen Lipstein, left, and William Brinkman have collaborated on a 2014 study in *Medical Decision Making* titled, "An Emerging Field of Research: Challenges in Pediatric Decision Making."



NEW WAYS TO TACKLE OLD CHALLENGES

Lipstein and colleague Julia Anixt, MD, of the Division of Developmental and Behavioral Pediatrics, are part of a new generation of physician-scientists who see shared decision-making as a crucial element of health improvement, right alongside more traditional biological, psychological and social factors.

Anixt splits her time roughly evenly between autism research and clinical work.

"It's hard because we can't cure the autism," Anixt says. "So we look at ways to address challenging behaviors. But no two kids have the same set of behaviors. Often, there is no single best answer."

The best course might not involve medication but might require special training for parents and caregivers, working closely with teachers, and other intervention strategies. "These cards aren't replacing the provider's knowledge," Anixt says. "They're just helping families visualize the options so they can be informed participants in the decision making process."

A CRITICAL GOAL: ESTABLISHING TRUST

Asking families to consider new or unfamiliar approaches to chronic conditions is rarely easy, but can be even more difficult in underserved, lower-income, minority communities where historic relationships with the medical world often have been strained.

Anixt focuses on improving those bridges. So does Lori Crosby, PsyD, a clinical psychologist in the Division of Behavioral Medicine and Clinical Psychology who works with families impacted by sickle cell disease.

She works to calm those undercurrents of distrust. Numerous studies have revealed disparities in how effectively providers connect with families of varying races and socio-economic status. That is changing.

"They say, 'It's so nice just to be listened to," Crosby says. Still, new treatments require a leap of faith.

Cincinnati Children's has become a leader in encouraging more children with sickle cell to begin taking hydroxyurea, a beneficial treatment, at younger ages, even as young as 9 months. Once reserved as a treatment for older, sicker patients, a major shift occurred last year, when the National Heart Lung and Blood Institute terminated a clinical trial of the drug because it so clearly demonstrated its ability to reduce stroke risks and pain.

It was a huge scientific validation of the effectiveness of hydroxyurea, which was originally developed as a cancer drug. Although hydroxyurea has been studied in treating sickle cell for over 20 years and has an FDA indication, only recently has information about the treatment spread among the sickle cell community. "This can be a scary treatment because it's a chemotherapy and we can't tell parents what that's going to mean 40 years down the line," Crosby says. "We don't know. So we're asking them to make a decision without knowing what the future holds."

When doctors say the medication can ease pain and reduce risk of organ damage and stroke, parents wonder if the medicine is too new to be trusted, or too good to be true. The two-lane approach to communication has made a difference.

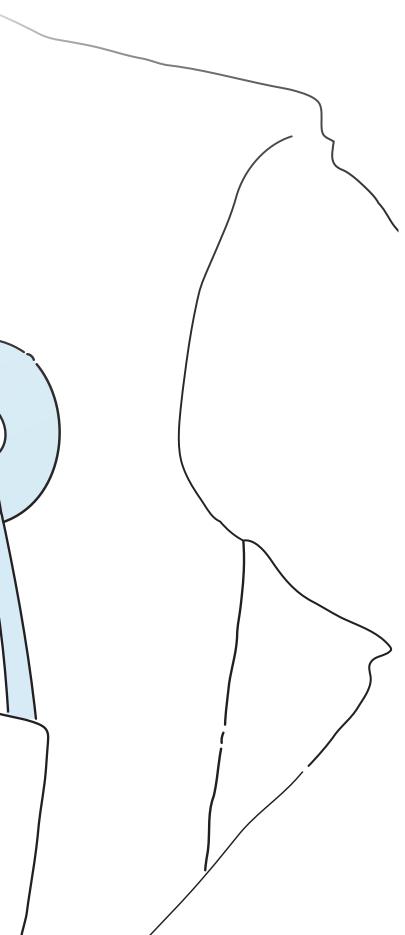
"There was a light-bulb moment for providers," Crosby says of this decisionscience. "We had no idea how unprepared parents were. We didn't understand how overwhelming this is."

We do now.

Drs. Julia Anixt, left, and Lori Crosby focus on health issues in underserved communities; Anixt on ADHD and autism, Crosby on sickle cell disease.







hen two Nobel prize-winning scientists advise you to pursue a joint MD/PhD program, you should probably pay attention. When Gurjit Khurana Hershey, MD, PhD, did, it turned out really well.

Hershey was a junior at the University of Iowa when her advisor sent her to a conference in California. The keynote speakers were Michael Brown and Joseph Goldstein – doctors who had just won the Nobel Prize for their cholesterol studies that led to the development of statin drugs. Awestruck by their presentation, Hershey remembers thinking, "This is what I want to do." So she walked up and asked them how she could do what they were doing.

"They suggested I go into an MSTP (Medical Scientist Training Program). I didn't even know what that was."

But she quickly learned, and went on to complete such a program at Washington University in St. Louis, earning both an MD and a PhD. It was a first big step in what has been a highly successful career. Today, Hershey works as both clinician and scientist, overseeing the highly regarded Division of Asthma Research at Cincinnati Children's. She also oversees our MSTP program.

SOUGHT-AFTER SCIENTISTS

NIH-funded MSTP programs have been around since the mid-1960s, created to encourage young doctors to pursue additional training in research. There are 40 such programs across the country, all of which are highly competitive. Their graduates are much sought-after, and for good reason, says Hershey.

"The outcomes for MSTP graduates are incredible. MD/PhDs make up just 2.5 percent of all medical school graduates, yet they hold nearly 50 percent of all NIH grants awarded to MDs," she says.

The MSTP program started here in 1985 when John Hutton, MD, then Dean of the University of Cincinnati College of Medicine, joined with William Schubert, MD, then President of Cincinnati Children's.

"Ours was the only MSTP with a pediatric base," says Hershey. "Our program offers a unique opportunity to pursue pediatric medicine and research. More than 70 percent of our MSTP students work in our laboratories."

The program produces a steady stream of talent in pediatric research.

"Twenty-five percent of our MSTP graduates go on to do pediatrics, and match at the top pediatric residency programs," Hershey says. "Even if they don't stay here, they spread the word. And they often come back for fellowships."

ANOTHER PATH FOR PURSUING RESEARCH

For pediatricians who have completed subspecialty training and want to pursue pediatric research, Cincinnati Children's offers the Child Health Research Career Development Award (CHRCDA).

Cincinnati Children's was among the first institutions funded by the National Institutes of Health (NIH) to provide these awards; we have been funded continuously since 1991. Now, 19 institutions participate.

Here, awards go to up to four senior fellows or recently appointed faculty members each year. The scholars are expected to spend at least 75 percent of their time on research, with the ultimate goal of obtaining independent research grants.

Margaret Hostetter, MD, Director of the Cincinnati Children's Research Foundation, is principal investigator of the grant. Louis Muglia, MD, PhD, Co-Director of the Perinatal Institute, directs the program. Muglia says receiving CHRCDA support while a young faculty member at Boston Children's Hospital had a powerful effect on his career.

"It gave me institutional support to focus on my science and it provided protected time to do my research, which is the most important thing," he says.

Today, Muglia continues the research that began with his CHRCDA award – exploring the pathways that mediate stress response and those that control the timing of birth. "The grant allowed me the freedom to explore the connectedness between these areas."

"The (CHRCDA) grant allowed me the freedom to explore the connectedness between these areas."

Louis Muglia, MD, PhD

Former scholars have not forgotten the impact of the CHRCDA's foundational funding on their careers many now serve as mentors to current scholars.

"There's a real spirit of collaboration. Everyone here is willing to give of their time and thoughts to help someone who's at a critical stage in their career succeed," Muglia says.

Drs. Gurjit Khurana Hershey, Margaret Hostetter and Louis Muglia







More Programs Promoting Careers in Science

TRUSTEE AWARD & PROCTER SCHOLAR (TAPS) PROGRAM:

Supports clinical fellows or faculty in the first year of their appointment to the Departments of Pediatrics, Surgery, Radiology, and Anesthesia. Scholars must have a strong commitment to pursuing a career in academic research.

ARNOLD W. STRAUSS FELLOW AWARD:

Provides one-year, \$10,000 funding to five clinical fellows (MDs) and five postdoctoral fellows. It was instituted in 2014 in honor of the former Director of the Cincinnati Children's Research Foundation.

OFFICE OF FACULTY DEVELOPMENT MENTORING PROGRAM:

Supports career advancement activities for fellows and faculty; seeks to improve promotion rates and increase leadership opportunities for women and minority fellows and faculty; and works to improve career satisfaction and work-life integration.

RESEARCH IN RESIDENCY PROGRAM:

Many competitive fellowships require that residents do some research. Residents who remain at Cincinnati Children's for their fellowships can continue their research right into their fellowship; others win fellowships at other top institutions.

BUILDING INTERDISCIPLINARY RESEARCH CAREERS IN WOMEN'S HEALTH:

Begun in 2010 with a five-year \$2.48 million NIH grant, this program provides a mentored research and career development experience for junior faculty, leading to an independent career focused on women's health.

THE KL2 RESEARCH SCHOLARS CAREER DEVELOPMENT AWARD:

This NIH-funded award supports junior faculty pursuing careers in clinical and translational research. During the award period, scholars are expected to pursue their own K23 or similar individual career development awards, or R01 grants.

'FELLOWS CROSSTALK' BRIDGES GAPS FOR YOUNG RESEARCHERS

Kathryn Wikenheiser-Brokamp, MD, PhD, an experienced investigator in the Division of Pathology and Laboratory Medicine, devotes much of her time to helping young fellows and faculty adapt to the world of research.

One way she does this is through "Fellows CrossTalk," a twice-monthly forum where clinical fellows involved in research can present their findings and receive guidance from faculty and peers.

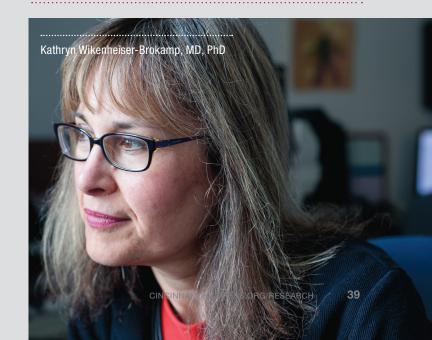
Fellows CrossTalk was started by the Office of Pediatric Clinical Fellowships in January 2014. The program, coordinated by Wikenheiser-Brokamp and Louis Muglia, MD. PhD, help less experienced researchers build confidence and skill in conducting and presenting science.

"We wanted to have more interaction at different stages of the physician scientist career pipeline - from medical school to residency to fellow to early faculty. This is one way to do that," says Wikenheiser-Brokamp, who completed her own medical scientist training here. "We want our physician scientists to continue on and be successful."

A survey of fellows, conducted last summer, indicates that the CrossTalk program is achieving its goals. Each session draws between 30 and 50 fellows, from a variety of disciplines. Fellows say they appreciate the feedback they receive, and they are especially interested in learning even more about securing grant funding and earning faculty positions.

"We want our physician scientists to continue on and be successful."

Kathryn Wikenheiser-Brokamp, MD, PhD



MEET A CHRCDA SCHOLAR

Elizabeth Schlaudecker, MD, MPH, Division of Infectious Diseases, is in the second year of the CHRCDA program. She studies immunity in pregnancy — specifically, the effectiveness of flu vaccine in pregnant women.

Her interest in the topic began with study she pursued as a Procter Scholar - another career-developing funding program - while a fellow here.

"I discovered that pregnant women responded poorly to flu vaccines," she says. "Their antibody response is about half that of non-pregnant women."

It was a new finding. "We presume that a pregnant woman's immunity changes during pregnancy, but it was shocking to see that it was only half," she says.

Schlaudecker worked with Fred Finkelman, MD, in the Division of Allergy and Immunology, to understand this antibody response. "I started learning about working in the laboratory and about the immunology of pregnancy. That's when I applied for this grant."

Under Finkelman's mentorship, Schlaudecker has learned there are specific antibody isotypes unique to pregnancy, and these antibodies may interfere with protection against the flu virus.

She recently conducted a clinical study that took periodic blood samples from 75 women who had been given flu vaccine. About half were pregnant. She wants to see if the pregnant women produce an immune response unique to pregnancy that interferes with the vaccine's effectiveness.

She has applied for a K23 award to expand her research, and says the CHRC grant has definitely helped her forge her career path.

A Powerful Pipeline

The CHRCDA program at Cincinnati Children's has funded **49 scholars**, including many top researchers and division leaders here.

BY THE NUMBERS

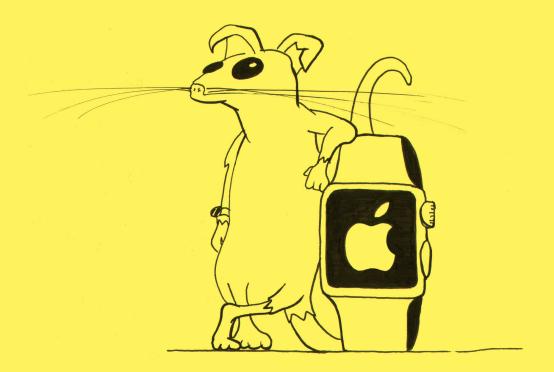
More than **2,300** articles published More than **\$334 million** in grant funding **53** R01-level NIH grants awarded "The next step is to find out, if we can get high antibody response in pregnant women, can we get high antibody response in the baby as well?" Schlaudecker says. "We know the flu vaccine protects the baby, but it's not as good as it could be. That's what I hope to figure out."

She particularly appreciates the opportunity to use what she learns as a clinician to inform her research and vice versa. Her experiences have shown her how important vaccines can be.

"The main reason we vaccinate pregnant women is to protect their babies," she says. "We have seen devastating flu cases this year, kids with lots of complications."

Elizabeth Schlaudecker, MD, MPH

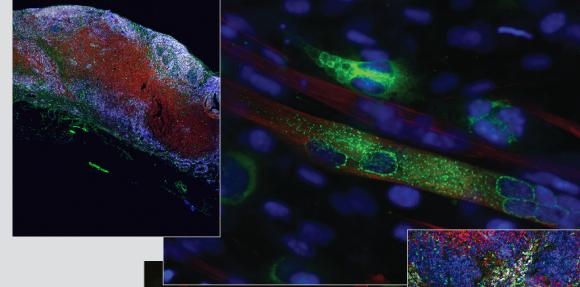




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In This Issue

The surprising influence bacteria can have upon our immune systems

How listening can lead to healing

How we invest in the future of pediatric research

