

Research Horizons

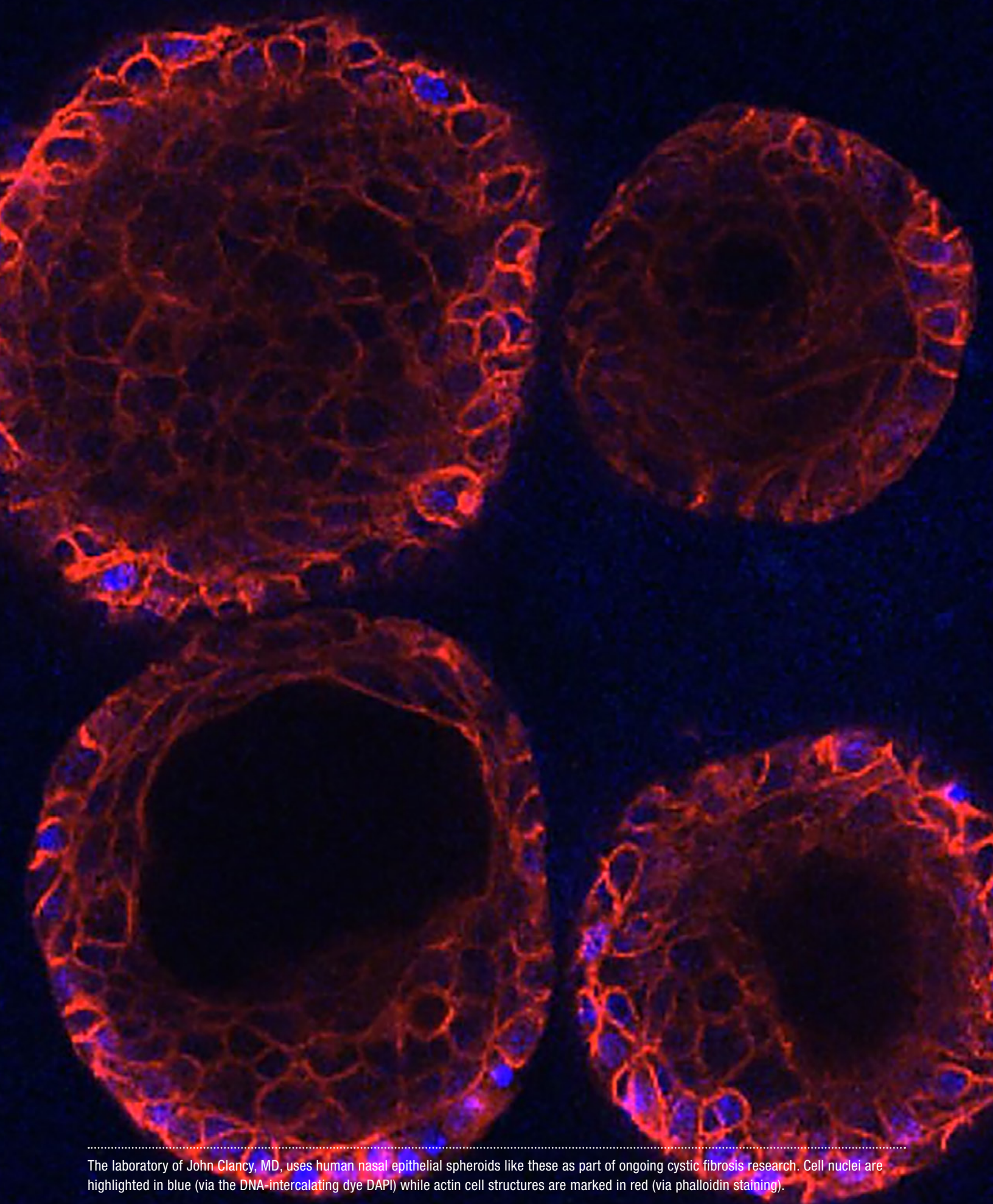
A PUBLICATION OF THE CINCINNATI CHILDREN'S RESEARCH FOUNDATION
FALL 2015



To Air is Human

Research Breathes New Life into Pulmonary Care





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The laboratory of John Clancy, MD, uses human nasal epithelial spheroids like these as part of ongoing cystic fibrosis research. Cell nuclei are highlighted in blue (via the DNA-intercalating dye DAPI) while actin cell structures are marked in red (via phalloidin staining).

Research Horizons

FALL 2015



Cincinnati Children's Ranked No. 1
in the country for pediatric pulmonology by
U.S. News & World Report, 2015-16

Cover: Meet one of the 4,700 students with asthma in the Cincinnati Public Schools. Cincinnati Children's is working with school nurses and others to identify and support students with poorly controlled asthma as part of a pilot project to create an "asthma-free" school.

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HONORS

David Cooper, MD, MPH,
Chief Safety Officer, Heart Institute,
has been elected to a three-year term on the Board of Directors of the Pediatric Cardiac Intensive Care Society (PCICS). Cooper also serves as the society's associate treasurer.

Gurjit (Neeru) Khurana Hershey, MD, PhD,
Director, Division of Asthma Research, has been awarded the 2015 World Allergy Organization (WAO) Scientific Achievement Award. The WAO is an umbrella organization that includes 95 allergy and immunology societies from around the world. The honor was presented in October at the XXIV World Allergy Congress in Seoul, Korea. Hershey also presented a keynote lecture at the congress about the Ohio Pediatric Asthma Repository Collaborative.

David Moore, PhD,
Director, Communication Sciences Research Center, received the 2015 Career Award in Hearing from the American Academy of Audiology (AAA). The distinguished auditory neuroscientist has conducted pioneering work on auditory processing disorder (APD) in children. Moore also founded MindWeavers PLC, which creates auditory learning experiences, and won the George Davey Howells Prize of the Royal Society of Medicine in 2010 for editing the Oxford Handbook of Auditory Science.

Rita Pickler, PhD, RN,
Research in Patient Services,
was appointed in April 2015 to the science committee of the Council for the Advancement of Nursing Science.

Wendy Pomerantz, MD, FAAP,
Co-Director, Comprehensive Children's Injury Center,
was voted president-elect of the national Injury Free Coalition for Kids. Pomerantz also is a member of the Ohio Emergency Medical Services Board, an executive board member of the National AAP Section on Injury, Violence and Poison Prevention Committee, a member of the Ohio AAP Committee on Injury and Poison Prevention, the American Red Cross Medical Assistance Team and the Greater Cincinnati Safe Kids Coalition.

Amy Shah, MD, MS,
Endocrinology, received the Young Investigator Award from the National Lipid Association at its annual meeting held in June in Chicago.

Sandra Staveski, PhD, RN,
Research in Patient Services,
has been elected to a three-year term on the Board of Directors for the Pediatric Cardiac Intensive Care Society (PCICS). This is the first time PCICS has included nurses as full-fledged board members. Staveski has also been elected as the first Executive Vice President of Nursing for PCICS and will serve as the first nurse President of PCICS next year.

Ian Windmill, PhD,
Clinical Director, Division of Audiology, has been named 2015-16 president-elect of the American Academy of Audiology (AAA).

Cincinnati Children's,
Received the annual Dr. Frank Dono Best Practice Award from the Ohio Patient Safety Institute in recognition of a hospital-wide quality improvement project that reduced central line associated blood stream infections (CLABSI) by 70 percent in the last six months of 2014.





Daniel von Allmen, MD, was appointed in July 2015 as Surgeon-in-Chief at Cincinnati Children's. He succeeds Richard Azizkhan, MD, who has become president and CEO of Children's Hospital & Medical Center in Omaha, Neb.

Von Allmen earned his medical degree from the University of Vermont. He performed two years of clinical work and two years of research during his surgical internship and residency at the University of Cincinnati, and completed a pediatric surgery fellowship at Cincinnati Children's.

Von Allmen served in faculty positions at the University of North Carolina Memorial Hospital in Chapel Hill and then at Children's Hospital of Philadelphia. He returned to North Carolina as division director and surgeon-in-chief at North Carolina's Children's Hospital, then moved back to Cincinnati in 2010 to direct the Division of Pediatric and Thoracic Surgery at Cincinnati Children's.

In his new role, von Allmen will oversee the technical and clinical operations of surgical services, including perioperative services, while providing institutional leadership in strategic, operational and programmatic planning.

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Daniel von Allmen, MD.

Von Allmen Becomes Surgeon-in-Chief

Jorge Bezerra, MD, was selected earlier this year as the new Director of the Division of Gastroenterology, Hepatology and Nutrition at Cincinnati Children's. In this role, he will oversee well-funded research programs, state-of-the-art clinical centers, 32 physicians and eight PhDs.

Bezerra earned his medical degree from the Federal University Rio Grande Norte in Brazil, and completed his residency in pediatrics at the University of Arizona. He joined Cincinnati Children's in 1990, initially as a fellow.

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Jorge Bezerra, MD.



"My goal is to build on our tradition of providing the best possible care for children with digestive disease," Bezerra says. "This will mean continually improving our existing models of care, pursuing research that increases our knowledge so that we can design new prevention and treatment strategies, and training future GI specialists through our fellowship program."

In addition to his role as Division Director, Bezerra is Medical Director of the Cincinnati Children's Pediatric Liver Care Center and maintains an active research career. He serves as an associate editor for the medical journal, *Hepatology*, and he has authored more than 114 peer-reviewed publications and 41 book chapters on topics including molecular control of biliary atresia, the genetic basis of liver disease and tissue engineering.

Bezerra succeeds Mitchell Cohen, MD, who has become Chair of the Department of Pediatrics at the University of Alabama at Birmingham School of Medicine and Physician-In-Chief of Children's of Alabama.

Bezerra Named Director of Gastroenterology

GRANTS

David Bernstein, MD, MA, Infectious Diseases, was awarded a four-year, \$13 million grant from the National Institutes of Health to continue his role in a nationwide group of institutions that conducts clinical trials of promising candidate vaccines and therapies for infectious diseases.

Jorge Bezerra, MD, Gastroenterology, Hepatology and Nutrition, will use a two-year, \$4.3 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases for his role with the Digestive Health Center: Bench to Bedside Research in Pediatrics.

Frank Biro, MD, Adolescent and Transition Medicine, received a two-year, \$4 million grant from the National Institute of Environmental Health Sciences to study environmental epigenetics.

Patrick Brady, MD, MSc, Hospital Medicine, was awarded a five-year, \$1 million grant from the Agency for Healthcare Research and Quality to study family-physician partnerships to improve child safety.

Jose Cancelas-Perez, MD, PhD, Experimental Hematology and Cancer Biology, will use a four-year, \$1.1 million grant from the National Institute of General Medicine Sciences to study the granulocyte colony-stimulating factor receptor in severe congenital neutropenia.

Robert Coghill, PhD, Anesthesia, received a five-year, \$2.9 million grant from National Institute of Neurological Disorders and Stroke to study brain mechanisms supporting individual differences in pain.

James Cnota, MD, Heart Institute, will use a two-year, \$2.3 million grant from the National Heart, Lung and Blood Institute for his work with the Pediatric Heart Network Prairieland Consortium, a collaborative effort between Cincinnati Children's and the Riley Hospital for Children in Indianapolis.

Stella Davies, MBBS, PhD, Bone Marrow Transplantation, will use a one-year, \$1.8 million award from Novartis Pharmaceuticals to study the efficacy and safety of its CTL019 personalized cell therapy in patients with relapsed and refractory B-cell acute lymphoblastic leukemia.

Lee Denson, MD, Gastroenterology, Hepatology and Nutrition, received a five-year, \$2.9 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases for training in pediatric Gastroenterology and Nutrition.

Senad Divanovic, PhD, Immunobiology, will study the immunopathogenesis of non-alcoholic fatty liver disease with a three-year, \$1.8 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases.

Marie-Dominique Filippi, PhD, Experimental Hematology and Cancer Biology, received a four-year, \$1.2 million grant from the National Institute of General Medicine Sciences to study the molecular regulation of neutrophil transcellular migration. She also received a five-year, \$1.7 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases to study the regulation of hematopoietic stem cell self-renewal.

Brian Gebelein, PhD, Developmental Biology, received a two-year, \$1.6 million grant from the National Institute of General Medicine Sciences to study the control mechanisms of cell-specific EGF signaling during development.

James Greenberg, MD, Perinatal Institute, will use a four-year, \$3.8 million grant from the Health Resources and Services Administration for his role with Healthy Start Cincinnati, an initiative to reduce infant mortality.

Lee Grimes, PhD, Immunobiology, received a four-year, \$1.6 million grant from the National Heart, Lung and Blood Institute to study the mechanisms of granulocyte homeostasis.

Alan Jobe, MD, PhD, Perinatal Biology, received a two-year, \$1.4 million grant from the National Research Institute for Child Health and Development to study the initiation and progression of pre-term lung injury.

Simon Hogan, PhD, Division of Allergy and Immunology, will use a five-year \$2.5 million grant from the National Institute of Allergy and Infectious Diseases to study food allergy and the passages of goblet cell antigen.

Kevin Hommel, PhD, Behavioral Medicine and Clinical Psychology, received a two-year, \$1 million grant from the National Institute of Child Health and Human Development to study improvements in treatment adherence.

Bin Huang, PhD,
Biostatistics and Epidemiology, has been awarded a three-year, \$1.4 million grant from the Patient-Centered Outcomes Research Institute (PCORI) to study patient centered adaptive treatment strategies using Bayesian causal inference.

Kakajan Komurov, PhD,
Experimental Hematology and Cancer Biology, earned a five-year, \$1.8 million grant from the National Cancer Institute to study proteotoxic stress in therapy-refractory HER2+ cancers.

Vladimir Kalinichenko, MD, PhD,
Pulmonary Biology, will study the Foxf1 transcription factor in the development of pulmonary capillaries with a four-year, \$1.6 million grant from the National Heart, Lung and Blood Institute.

Jane Khoury, PhD,
Biostatistics and Epidemiology, was awarded a two-year, \$1.2 million grant from the National Institute of Neurological Disorders and Stroke to study recanalization therapies.

Xinhua Lin, PhD,
Developmental Biology, will study molecular mechanisms regulating intestinal stem cells with a four-year, \$1.2 million grant from the National Institute of General Medicine Sciences.

Peter Margolis, MD, PhD,
James M. Anderson Center for Health Systems Excellence, received a one-year, \$1.4 million grant from ImproveCareNow, Inc., to advance the treatment of inflammatory bowel disease.

Punam Malik, MD,
Experimental Hematology & Cancer Biology, was awarded a three-year, \$8.9 million grant from the National Heart, Lung and Blood Institute for her work on sickle cell disease with the Cincinnati Center of Excellence in Hemoglobinopathies Research.

Doug Millay, PhD,
Molecular Cardiovascular Biology, will study the mechanisms of myoblast fusion with a five-year, \$1.9 million grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Stephen Muething, MD,
Hospital Medicine, will use a five-year, \$2.9 million grant from Ohio Children's Hospitals for his work with Solutions for Patient Safety, a network of more than 80 pediatric hospitals in the U.S.

Lou Muglia, MD, PhD,
Perinatal Institute, received a two-year, \$1 million grant from the Bill and Melinda Gates Foundation for approaches in systems biology to birth-timing and preterm birth.

Anjaparavanda Naren, PhD,
Pulmonary Medicine, received a five-year, \$1.9 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases to study LPA2 receptor-containing complexes.

Dao Pan, PhD,
Experimental Hematology and Cancer Biology, will study treatment of Gaucher disease, a neurodegenerative disease in which fatty substances accumulate in cells and organs, using a three-year, \$2 million grant from the National Institute of Neurological Disorders and Stroke.

Jeffrey Robbins, PhD,
Molecular Cardiovascular Biology, will study the signaling processes underlying cardiovascular function with a three-year, \$8.8 million grant from the National Heart, Lung and Blood Institute.

Mary Allen Staat, MD, MPH,
Infectious Diseases, will study enhanced surveillance of new vaccines for preventable diseases with a one-year, \$1.8 million grant from the National Centers for Disease Control and Prevention.

Elaine Urbina, MD, MS,
Preventive Cardiology, received a four-year, \$3.7 million grant from the American Heart Association to help create a Strategically Focused Research Network Center, which will focus on how blood pressure levels lead to damage of the heart, kidney, arteries and brain in adolescents.

Stephen Waggoner, PhD,
Center for Autoimmune Genomics and Etiology, received a four-year, \$3.8 million grant from the National Institute on Drug Abuse to study a revolutionary approach to an efficacious HIV vaccine.

Shari Wade, PhD,
Physical Medicine and Rehabilitation, will study methods of effective caregiver communication after adolescent traumatic brain injury, using a three-year, \$4 million grant from the U.S. Department of Education.

Stephanie Ware, MD, PhD, Human Genetics, will study genotype-phenotype associations in pediatric cardiomyopathy, using a two-year, \$1.6 million grant from the National Heart, Lung and Blood Institute.

Yutaka Yoshida, PhD, Developmental Biology, will study synapse elimination in the central nervous system with a five-year, \$1.9 million grant from the National Institute of Neurological Disorders and Stroke.

Margaret Zeller, PhD, Behavioral Medicine and Clinical Psychology, received a four-year, \$2.3 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases to study the psychosocial risks of adolescent bariatric surgery.

Yi Zheng, PhD, Experimental Hematology and Cancer Biology, received a five-year, \$1.8 million grant from the National Cancer Institute to study the targeting of Cdc42, a novel target in stem cells, for bone marrow transplantation. He also received a one-year, \$4 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases for his work with the Cincinnati Center For Excellence In Molecular Hematology, and a one-year, \$1.7 million award from the National Institute on Aging to study lineage determination and tissue homeostasis.

Nine Projects Win Innovation Funding

Cincinnati Children's has selected nine early-stage research projects with commercialization potential to receive bridge funding from two special programs.

Seven recipients have been selected for the fourth annual round of support from the Cincinnati Children's Innovation Fund. Two other projects are receiving funding through the new Alexion Rare Disease Innovation Fund, a collaboration between Cincinnati Children's and Alexion Pharmaceuticals, Inc.

Submissions were reviewed by the Innovation Fund Advisory Committee, which includes leaders from Cincinnati Children's, Alexion, and local entrepreneurs.

2015 CINCINNATI CHILDREN'S INNOVATION FUND RECIPIENTS

Human Assisted Needle Delivery System

Daniel von Allmen, MD; Surgeon-in-Chief, Cincinnati Children's

Model of Human Intestine

Michael Helmrich, MD, MS; Surgical Director, Intestinal Rehabilitation Program; Director of Surgical Research

Novel Systems Pharmacology Platform for Individualized Morphine Treatment in Neonates

Alexander Vinks, PharmD, PhD, FCP; Director, Division of Clinical Pharmacology; Scientific Director, Pharmacy Research, Research in Patient Services

Genetic Prediction Tool for Thrombotic Microangiopathy

Sonata Jodele, MD; Division of Bone Marrow Transplantation & Immune Deficiency

School Based Neuropsychiatric Point-of-Care Using Speech-to-Signal Processing to Identify Suicidal Behavior

John Pestian, PhD, MBA; Director, Computational Medicine Center

2015 ALEXION RARE DISEASE INNOVATION FUND RECIPIENTS

Enzyme Replacement Therapy in Patients with a Growth Failure Disorder

Andrew Dauber, MD, MMSc; Program Director and Director of Translational Research, Cincinnati Center for Growth Disorders

Controlling Inflammation in Gaucher Disease

Manoj Pandey, PhD; Division of Human Genetics



Andrew Beck, MD.

Inner-city children are at greater risk of needing hospitalization for common respiratory illnesses, say Cincinnati Children's researchers.

They published their findings online July 20, 2015, in *JAMA Pediatrics*, after studying census tract data and hospitalization records.

Researchers believe that identifying hotspot geographic areas can help doctors predict which children are at greater risk of hospitalization and intervene, at a reduced cost, through patient- and population-level management of acute conditions.

The study, led by pediatrician Andrew Beck, MD, looked at children hospitalized for bronchiolitis or pneumonia at Cincinnati Children's between 2010 and 2013. Those hospitalized with bronchiolitis were younger than 2, those with pneumonia younger than 18. Patients were identified using discharge diagnosis codes, then geocoded to their home census tract.

The findings showed great disparities based largely on where children lived.

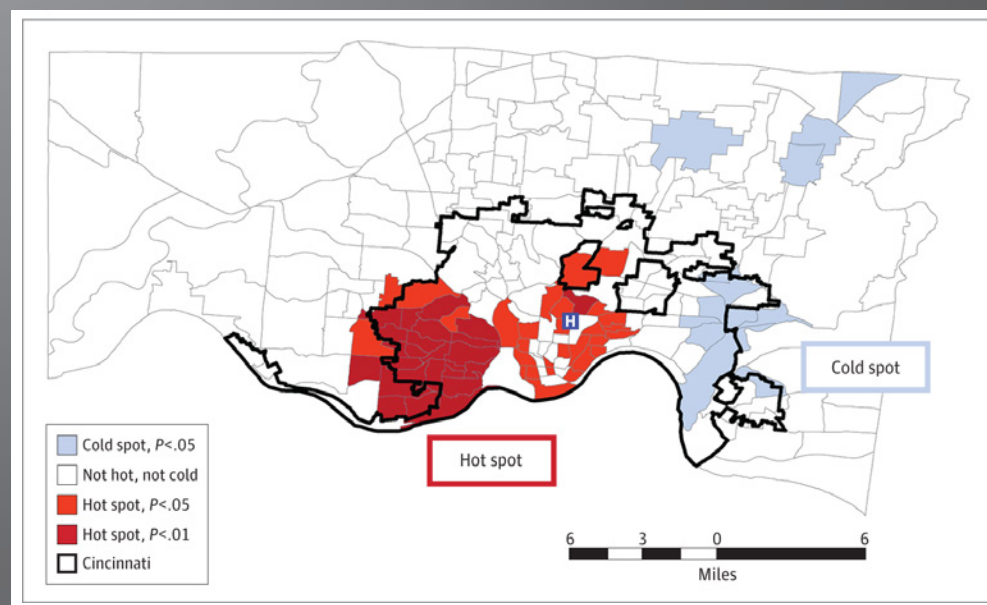
"The most-hospitalized group with bronchiolitis had a hospitalization rate six times that of the least hospitalized," says Beck. "Those most hospitalized with pneumonia had a hospitalization rate 11 times that of the least hospitalized."

Todd Florin, MD, who co-authored the study with Beck, adds, "The inequalities were associated with underlying differences in socioeconomic measures and were clustered geographically, with hospitalization hot spots in the inner city and cold spots in outlying suburbs."

Findings were similar to a 2013 Cincinnati Children's study of asthma hospitalization demonstrating that rates varied 18-fold across local neighborhoods. The neighborhoods in the new *JAMA Pediatrics* study often overlapped those in the asthma study.

"This has substantial clinical and public health implications, suggesting small areas that could be targets for prevention and cost containment," says Florin.

Inner City Hot Spot for Respiratory Problems



Anesthesia Can Damage IQ

Researchers at Cincinnati Children's have found that using general anesthesia during surgery in children younger than age 4 could have damaging effects on language comprehension and IQ.

Their findings, published July 8, 2015, in *Pediatrics*, are spurring work to lessen anesthesia's effects and to understand how the drugs affect brain function and composition.

"We have to better understand to what extent anesthetics and other factors contribute to learning abnormalities in children before making drastic changes to our current practice, which by all measures has become very safe," says Andreas Loepke, MD, PhD, FAAP, anesthesiologist at Cincinnati Children's and the study's lead author.

Loepke and his colleagues pursued the study after finding evidence of neurocognitive impairment in mice exposed to general anesthesia. Those previously published studies raised the researchers' concerns about similar effects in young children.

The *Pediatrics* study compared language study scores of 106 children, ages 5 to 18. Half had not had surgery, and half had surgery before age 4. Children exposed to anesthesia scored significantly lower in listening comprehension and performance IQ. Age, gender, socioeconomic status, and the types of surgeries and



Andreas Loepke, MD, PhD.

length of anesthetic exposure were factored into the calculations.

Although Loepke and his team are conducting laboratory studies into alternative anesthetic methods, they emphasize that current practices are quite safe — particularly when viewed in the context of life-saving procedures.

"The ultimate goal of our research is to improve safety and outcomes in young children who have no choice but to undergo surgery with anesthesia," he says.

Arthritis Drug Shows Promise for Rare Immune Disorder

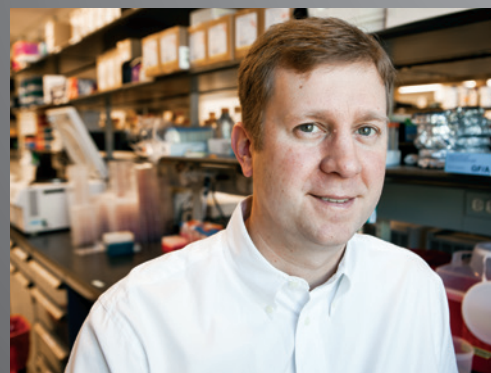
Abatacept, a drug already approved for treating rheumatoid arthritis (RA), has shown promise in treating children with LRBA deficiency, a debilitating genetic immune disorder.

Michael Jordan, MD, Division of Immunobiology at Cincinnati Children's, was senior author of the study, which involved researchers from around the country. The findings were reported in the July 2015 issue of *Science*.

Lipopolysaccharide-responsive beige-like anchor (LRBA), is a gene essential for the normal function of the immune system. Mutations in the gene cause immunodeficiencies and autoimmune disorders, including one known as common variable immunodeficiency (CVID).

For the study, six patients with CVID took abatacept for periods up to eight years. The study found, "... patients with LRBA deficiency manifested a dramatic and sustained improvement in response to abatacept."

Abatacept appeared to regulate the inhibitory immune receptor CTLA4. Normally, CTLA4 is expressed on the cell surface, where it



Michael Jordan, MD.

prevents autoimmune activation. Patients with CVID cannot replace CTLA4 on the cell surface.

Because CTLA4 dysfunction is also present in RA, researchers suspected that abatacept might also work to treat LRBA deficiency. Besides improving patients' lung disease, the drug also appeared to decrease infection risk.

Researchers plan to continue exploring the safety and effectiveness of the drug.

A commonly used household pesticide could initiate or aggravate attention deficit hyperactivity disorder (ADHD) in some children.

The finding, reported by Cincinnati Children's researchers and published online in *Environmental Health* in May, 2015, found that pyrethroid pesticide exposure increased hyperactivity and impulsivity, particularly in boys with ADHD.

Pyrethroids have been used increasingly since the U.S. Environmental Protection Agency banned organophosphate pesticides from residential use in 2000. Pyrethroids are now the most commonly used for residential and public health pest control.

"Given the growing use of pyrethroid pesticides and the perception that they may represent a safe alternative, our findings may be of considerable public health importance," says Tanya Froehlich, MD, a developmental pediatrician at Cincinnati Children's and the study's corresponding author.

Although considered safer than the banned organophosphates, pyrethroid exposure in animal studies has shown increased hyperactivity, impulsivity and abnormalities in the dopamine

system of male mice. Dopamine is a brain neurochemical involved in many activities, including ADHD.

The researchers studied data on 687 children ages 8 to 15, taken from a 2000-2001 national health survey. The survey included information on children's ADHD symptoms and urine samples testing for the pesticide exposure biomarker 3-PBA. Boys with detectable 3-PBA were three times as likely to have ADHD than those without the biomarker. Hyperactivity and impulsivity increased by 50 percent for every tenfold increase in 3-PBA levels in boys. Biomarkers in girls did not correlate with increased ADHD.

Although the findings are significant, Froehlich cautions that further study is needed to determine their implications for public health.

"Given that pyrethroids are non-persistent and rapidly metabolized, measurements over time would provide a more accurate assessment of typical exposure," she says.

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Tanya Froehlich, MD.

Pesticide Linked to ADHD



HDL Subparticles Offer New Targets for Drug Development

High density lipoproteins (HDL) have long been recognized as the “good” cholesterol that helps protect against cardiovascular disease. But genomic studies have revealed that HDL has a much more complex composition and function than previously understood.

Researchers from Cincinnati Children’s and the University of Cincinnati report discovering 38 new HDL subparticles in an effort they hope will allow more precisely targeted treatments for cardiovascular disease. Led by Long (Jason) Lu, PhD, Division of Bioinformatics at Cincinnati Children’s, the scientists published their findings in the August 2015 *Journal of Proteome Research*.

In what they termed the “first report that employs a network-based approach to systematically infer HDL subspecies,” the scientists used genomic and computational analyses to identify the subparticles, backed by human plasma studies and gene knockout experiments in mice.

The study contributes significantly to a growing understanding that HDL serves as much more than a mechanism for whisking lipids from the body. Their findings, the authors state, “leave little doubt that HDL is not only



Long (Jason) Lu, PhD.

involved in lipid transport, but also proteinase inhibition, anti-inflammation, complement regulation, and innate immunity.”

Future work will aim to further isolate and characterize the subparticles biochemically as a step toward developing targeted tests and treatments that combat cardiovascular disease.

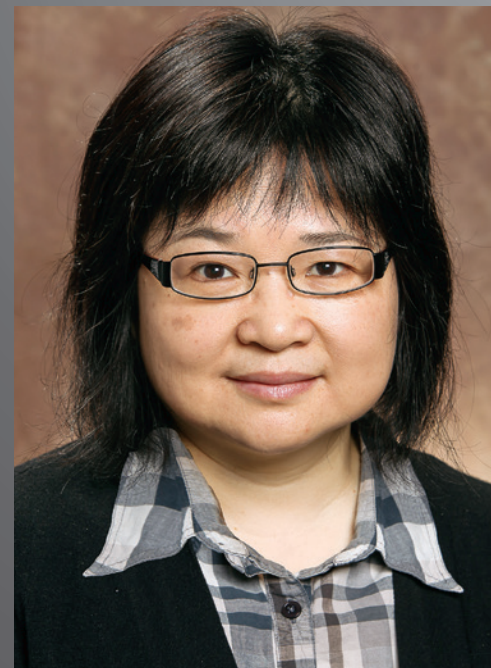
New, Free Tool Maps Genetic Landscape of the Lung

Researchers who want to better understand lung development have a new, free resource at their fingertips: LungGENS (Lung Gene Expression iN Single-cell).

LungGENS is a web-based tool that maps single-cell gene expression. Yan Xu, PhD, Division of Biomedical Informatics at Cincinnati Children’s, and her team developed the tool to help researchers access and visualize complex single-cell transcriptomic data. A report of their achievement was recently published in the journal *Thorax*.

Scientists can search the tool by gene or cell type. If a researcher enters a gene symbol or a list of genes, the tool provides quantitative RNA expression of the gene of interest in each lung cell type. A cell type query returns associated gene signatures and genes encoding cell surface markers as well as transcription factors in interactive heatmap and tables.

Xu and her colleagues hope that greater understanding of individual lung cell types and the ways they interact to form the lung may lead to better treatments in such areas as respiratory distress syndrome in premature infants.



Yan Xu, PhD. LungGENS is freely available for non-commercial use at <https://research.cchmc.org/pbge/lunggens/default.html>.

Maxing out the inherently stressed nature of treatment-resistant breast cancer cells may thwart their ability to find genetic workarounds to treatment, a new study shows.

"We present an alternative strategy for cancer treatment, which is removing cancer cells' defenses against their own intrinsic stress," says Kakajan Komurov, PhD, lead author and researcher in the Cancer and Blood Diseases Institute. "Our findings highlight the feasibility of maximizing cell stress by inhibiting adaptive pathways to cause cell death."

Findings were published May 26, 2015, in *Science Signaling*. The team focused on an especially hard-to-treat form of breast cancer driven by the HER2-mTOR molecular pathway. Standard treatment for the cancer is combination chemotherapy, including an agent that specifically targets the HER2 gene. But more than half the cases resist the treatment, and the disease progresses.

For this study, researchers used *in vitro* experimentation with human breast cancer cell lines and extensive computer analysis of genomic data from The Cancer Genome Atlas and International Cancer Genome Consortium.

They searched for non-oncogenic vulnerabilities in breast cancers that overexpress the ERBB2 gene. The authors found that cancers overexpressing ERBB2 have an important survival mechanism for HER2 cancer cells — the



Kakajan Komurov, PhD.

endoplasmic reticulum associated degradation pathway, or ERAD.

Researchers then tested a combination treatment that genetically deletes or pharmacologically inhibits ERAD. The treatment killed the HER2-positive breast cancer cells.

They are now testing the experimental regimen in mouse models and plan to begin testing an experimental cancer drug that blocks a component of the ERAD pathway.

Stressing Out Breast Cancer



Yui-Hsi Wang, PhD.

IL-9-producing mucosal mast cells (MMC9 cells) play a key role in amplifying allergic response to ingested food, according to new research.

The study, led by Yui-Hsi Wang, PhD, a researcher in the Division of Allergy and Immunology, was published Sept. 22, 2015 in the journal *Immunity*. The findings, based on data from mouse models, eventually could lead to a blood test to identify children at highest risk of severe food allergies.

The authors say MMC9 cells produce large amounts of interleukin 9 (IL-9), which amplifies anaphylactic shock response. Prior to this study, the key cellular source of IL-9 was unknown.

"Our study suggests that although you need to have some level of IgE to trigger a food allergy response, you also have to produce MMC9 cells to get a severe response and anaphylaxis," Wang says. "Without these cells you will not get severe food allergies."

Mucosal Mast Cells Play Role in Severe Allergic Reactions

Beginning the End of Cystic Fibrosis

Just a few decades ago, adult cystic fibrosis (CF) was a mostly abstract concept. After all, most children born with one of the 1,900 known mutations of the CFTR gene were fortunate to reach their teen years. Now, thanks to dramatic and continuing improvements in treatment, living deeply into adulthood with CF is a reality. Reaching retirement age appears achievable.

Experts at Cincinnati Children's are playing many leading roles in this emerging revolution. Scientists here contributed significantly to two important, recently approved CF drugs. They are making breakthroughs in imaging technology, developing new approaches to wellness education, and creating powerful learning networks that bring highly motivated parents together with far-flung researchers and physicians to accelerate discovery.



The Revolution is Here for Cystic Fibrosis

With two FDA-approved drugs on the market and several more in the pipeline, expectations of long-term survival run high as an era of personalized medicine begins

by Tim Bonfield

As recently as 1980, most children born with cystic fibrosis (CF) could not expect to live long enough to legally buy a glass of wine.

Now, growing numbers of CF survivors can look forward to toasting their own retirements thanks to a wave of scientific breakthroughs that has begun to conquer a feared childhood killer.

"We are rapidly moving toward the day when people will live long, full lives and ultimately die with cystic fibrosis instead of dying prematurely of cystic fibrosis," says John Clancy, MD, research director for the Division of Pulmonary Medicine at Cincinnati Children's.

The advanced research and state-of-the-art treatment provided through the Cystic Fibrosis Center at Cincinnati Children's are two of several reasons why *U.S. News & World Report* recently ranked the medical center as the nation's best for pediatric pulmonology. Cincinnati Children's is one of only 10 Cystic Fibrosis Foundation Research Centers in the United States and one of the first centers to join the foundation's Therapeutics Development Network. Researchers here have supported CF drug discovery and development from the early days.

Clancy has served in various research leadership roles with the CF Foundation and currently serves as chair of the NIH Rare Disease Research Network. He was a co-author of the seminal paper, published in 2010 in the *New England Journal of Medicine*, which unveiled the world's first medication proven to act upon the root causes of cystic fibrosis. Clancy's role included reviewing the blinded data for one of the key biomarkers in the study.

That once experimental drug, VX-770, became ivacaftor (now marketed as Kalydeco), which won U.S. Food and Drug Administration approval in 2012. This drug has a powerful effect on cystic fibrosis patients with a mutated version of the gene G551D-CFTR, and similar mutations. For these 5 percent to 7 percent of patients, the drug can restore lung function from near zero capacity to better than 50 percent of normal, Clancy says.

Clancy also was lead author of the first published study of lumacaftor in CF patients, which became part of the newest CF drug, which won FDA approval in July 2015. Dubbed Orkambi, this combination treatment (lumacaftor 200 mg/ivacaftor 125 mg) is not quite as dramatic as Kalydeco as it increases lung function to about 15 percent of normal. However,

the treatment works against the most common genetic cause of CF, those who have two copies of the F508del mutation. About 45 percent of the 30,000 people with CF in the United States have two copies of this gene mutation.

"Fifteen percent lung function is still a long way from normal, but that level of function can make it possible for many more people to survive much longer," Clancy says. "More importantly for survival, the clinical trial showed a 40 percent decrease in pulmonary exacerbations. For many CF patients, these episodes of inflammation and infection have become leading predictors of lung function decline and death."

As important as the two new drugs may be, even more treatments are coming.

ANOTHER 1900 MUTATIONS TO GO

Now the race is on to develop more medications to address all of the emerging classes of CF patients. Some of those advances will likely be based upon the work of a research team led by Anjaparavanda Naren, PhD, co-director of the Cystic Fibrosis Research Center.



John Clancy, MD, Research Director for the Division of Pulmonary Medicine at Cincinnati Children's.

CF has become a prime example of the potential power of personalized medicine, Naren says. Since the discovery of the cystic fibrosis transmembrane conduct regulator gene (CFTR) in 1989, researchers have gone on to find more than 1,900 mutations of the gene. The sheer variety of mutations means that no single drug is likely to have a cure-all effect. Instead, clinicians will need to build genetic profiles of each patient, and then tailor treatments accordingly.

Clancy and Raouf Amin, MD, Director of the Division of Pulmonary Medicine, recruited Naren to Cincinnati Children's in 2013. Now Naren works to expand the connections between CF-related mutations and drugs known to act upon them.

Earlier this year, Naren and his research team, including Chang Suk Moon, PhD, and Kavisha Arora, PhD, reported finding an interplay between CFTR and the multidrug resistance protein 4 (MRP4). In cystic fibrosis, chloride channels on epithelial cells underperform, keeping fluids in the lungs. In diarrhea, the channel over-performs, releasing fluids into the intestines and bowel.

The study was featured on the May 1, 2015, cover of *The Journal of Biological*

Chemistry for two reasons. The chloride channel findings have potentially broad implications for controlling medication-induced diarrhea, an all-too-common therapy side effect for diseases far beyond cystic fibrosis. In addition, the model the scientists developed to conduct the study has its own implications.

ENTER THE 'ENTEROID'

Naren's team, in collaboration with Michael Helmrath, MD, successfully developed intestinal organoids he calls "enteroids," which were grown from stem cells obtained from tiny amounts of biopsy material. The enteroids functioned as living test platforms that allowed the team to evaluate the effects of drug exposures in real time.

"Until now, we did not have a good model system to study intestinal biopsies, because the tissue samples that could be safely collected have been so small," Naren says. "Now we have multiple approaches."

Enteroids like these will help accelerate cystic fibrosis drug development and the larger concept of genome-based personal treatment. "Enteroids allow us to

use stem-cell techniques to develop a better index of chloride channel function, which gives us the kinds of tools we need to move into personalized medicine," Naren says.

Cincinnati Children's has played a leading role in organoid research. James Wells, PhD, was among the first to succeed at developing functional intestine and stomach tissues from induced pluripotent stem cells (iPSCs). Wells and Helmrath have collaborated to demonstrate a method to grow human organoids to much larger sizes in mice, which suggests that organoids created from a patient's own cells may be able to grow on their own once implanted. Naren has been working with both of these scientists to advance treatment for cystic fibrosis.

"One of the reasons I came to Cincinnati was the unique opportunity for collaboration here," Naren says.

At Cincinnati Children's, Naren has gained greatly expanded access to human tissue samples and new opportunities to connect his once-isolated animal-based research directly to the human clinical trial pipeline. He has collaborated with experts in fields ranging from endocrinology to bioinformatics. He also found the funding to build the customized

equipment needed to obtain confocal microscope imagery of living enteroids in action.

MEDICINE GETS PERSONAL

Here, personalized medicine is no longer an abstract goal; it is an expanding reality, Naren says. For example, he recently worked with Clancy and Gary Lewis McPhail, MD, the director of the Division of Pulmonary Medicine's Cystic Fibrosis Center, to successfully treat three CF children from the United Arab Emirates.

The team determined through DNA sequence information that the children shared a specific S549N mutation of the CFTR gene. Naren was familiar with this mutation through previous research he published in 2012. The team agreed that this unusual CFTR mutation was similar enough to the G551D mutation affected by Kalydeco to believe the drug would help.

Prescribed off-label, the daily drug regimen has worked. Within a month,

sweat chloride levels for the children had dropped to near normal, FEV1 tests of lung capacity had improved, and their CF-driven insulin resistance had resolved, Naren says.

This is the personalized medicine revolution coming for children with cystic fibrosis, and eventually for children with all sorts of rare diseases, Naren says. Treatment flow will move from the patient to the research lab then back to the patient. To carry out this kind of work, many medical centers will need to organize new types of care teams.

"We can do the exome sequencing for an individual patient. We can develop an organoid based upon that patient's genomic profile. We can determine how that organoid responds to intervention and then choose the best treatment for that patient," Naren says. "It is not common to see all the specialized expertise needed to achieve this all in one place. It takes a whole series of researchers, specialist physicians, nurses, network analysts and other support personnel all working together to help an individual get better." ■

Anjaparavanda Naren, PhD, Co-Director of the Cystic Fibrosis Research Center and his research team, Chang Suk Moon, PhD, and Kavisha Arora, PhD.



Twin Breakthroughs in CF Imaging

Ultrashort echo-time, hyperpolarized gas MRI methods make it safer to assess new treatments

by Tim Bonfield

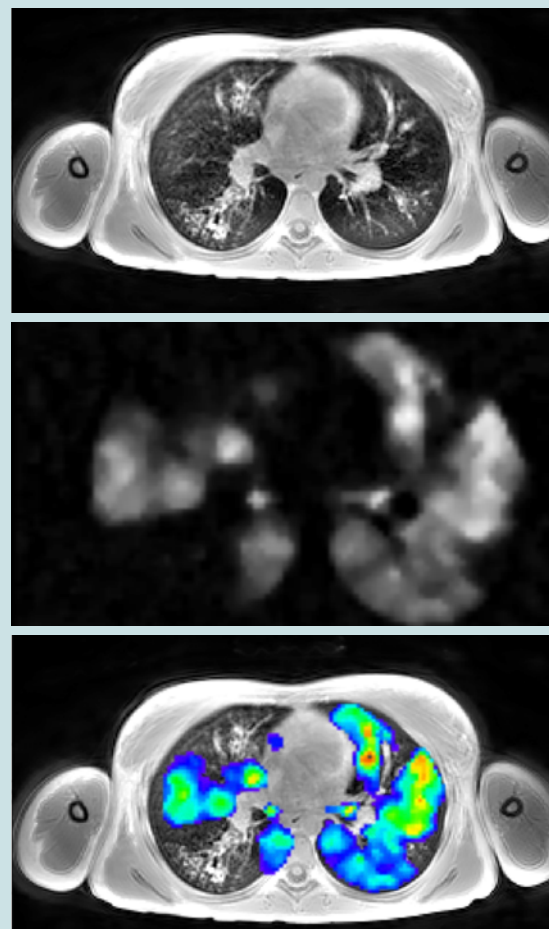
Two teens with cystic fibrosis (CF) blow into spirometers. Both tests come back with 100 percent scores on a key measure of lung capacity, the FEV1 (forced expiratory volume in one second). Both patients appear to be doing well.

Not necessarily.

A closer look at the patients' lungs, using a new approach called ultrashort echo-time magnetic resonance imaging (UTE MRI), reveals striking structural differences in the lungs. Meanwhile, an MRI scan using hyperpolarized gas as a contrast agent reveals clear differences in lung function. Despite having similar FEV1 results, these MRI tests reveal that one patient is doing much worse than the other, and likely needs prompt intervention.

As recently as a few years ago, detecting such differences in lung function for children and young adults with cystic fibrosis had minimal practical value because the menu of treatment interventions was so limited. Now, however, two new cystic fibrosis drugs have reached the market and several more are in development. Now, clinicians need to decide exactly when these exciting-but-expensive new treatments should be employed.

"We are right on the cusp of individualized medicine for cystic fibrosis. As new pharmaceutical agents continue to be developed, it becomes critical to obtain detailed data to assess which therapies are working best for particular patients," says Jason Woods, PhD, Director of the Center for Pulmonary Imaging Research at Cincinnati Children's. "The FEV1 is a standard clinical test, but results can be widely variable."



Jason Woods, PhD, is a leader in developing safer lung imaging methods for children. These images demonstrate the results of UTE MRI (top), hyperpolarized gas MRI (middle), and a colorized image that combines both results (bottom).

Another well-established imaging method — CT scanning — also can provide useful, detailed data on lung function. However, a single CT scan delivers as much as 200 times more radiation than a standard chest X-ray. While the risks of triggering cancer later in life are small, those risks are real enough to make clinicians reluctant to use CT scanning as a frequent surveillance tool, especially for the youngest CF patients.

Enter the MRI. With improved techniques, MRI scanning can produce lung imagery that rivals the quality of a CT scan. In fact, UTE MRI in particular can be a safe and effective tool for evaluating lung health in patients as young as six months. David Roach, PhD, (a fellow in Woods' lab) recently presented pilot study data about UTE MRI in Denver at the annual meeting of the American Thoracic Society. The findings also were published May 1, 2015, in the abstract issue of

the *American Journal of Respiratory and Critical Care Medicine*.

Woods reports that UTE MRI can assess bronchiectasis, bronchial wall thickening, parenchymal opacity and air trapping. "We show that MRI can detect the same abnormalities that can be detected with CT," he says.

The next steps for wider adoption of UTE MRI include larger, multicenter clinical trials to confirm the pilot study findings.

Meanwhile, Woods continues his work as a leading expert in the use of hyperpolarized-gas MRI. Cincinnati Children's is participating in stage II clinical trials to evaluate the use of Xenon-129 MRI scanning for cystic fibrosis patients. The noble gas can be tracked during breathing, which provides much more information about lung function than can be obtained from the FEV1 test.

Initial results from a study of hyperpolarized-gas MRI in CF patients will be

presented by his group at the International Workshop on Pulmonary Functional Imaging in Edinburgh, Scotland, and at the North American Cystic Fibrosis Conference in Phoenix.

Woods sees the UTE and hyperpolarized-gas methods as complementary tools that do not pose the radiation risk of CT scanning. Within the next several years, he predicts that new MRI techniques will be used well beyond the cystic fibrosis population to evaluate lung function and development in premature infants and other children with rare lung diseases.

Also, hospitals will not need to make major investments to adopt these technologies, Woods says. Many clinical MRI scanners already have the software needed to support UTE MRI. The hyperpolarized-gas method does require equipment upgrades, but not entirely new scanners. ■

Empowering Networks

One of the most powerful weapons against cystic fibrosis may be the smartphone

by *Tim Bonfield*

Few people personify the power and potential of health care learning networks more than Erin Moore.

Five years ago, Moore and her husband Martin were the proud, excited parents of a growing family. They were raising a healthy 2-year-old girl named Ella, and the family had just expanded with the birth of their twins, Drew and Lily.

Shortly after the twins were born came the sobering news: testing confirmed that Drew had cystic fibrosis. From that moment, the course of Moore's life began to transform from business-

woman and mother into full-time patient advocate. Now she is part of an effort at Cincinnati Children's to build a collaborative chronic care network (C3N) to accelerate research and share best practices in cystic fibrosis treatment.

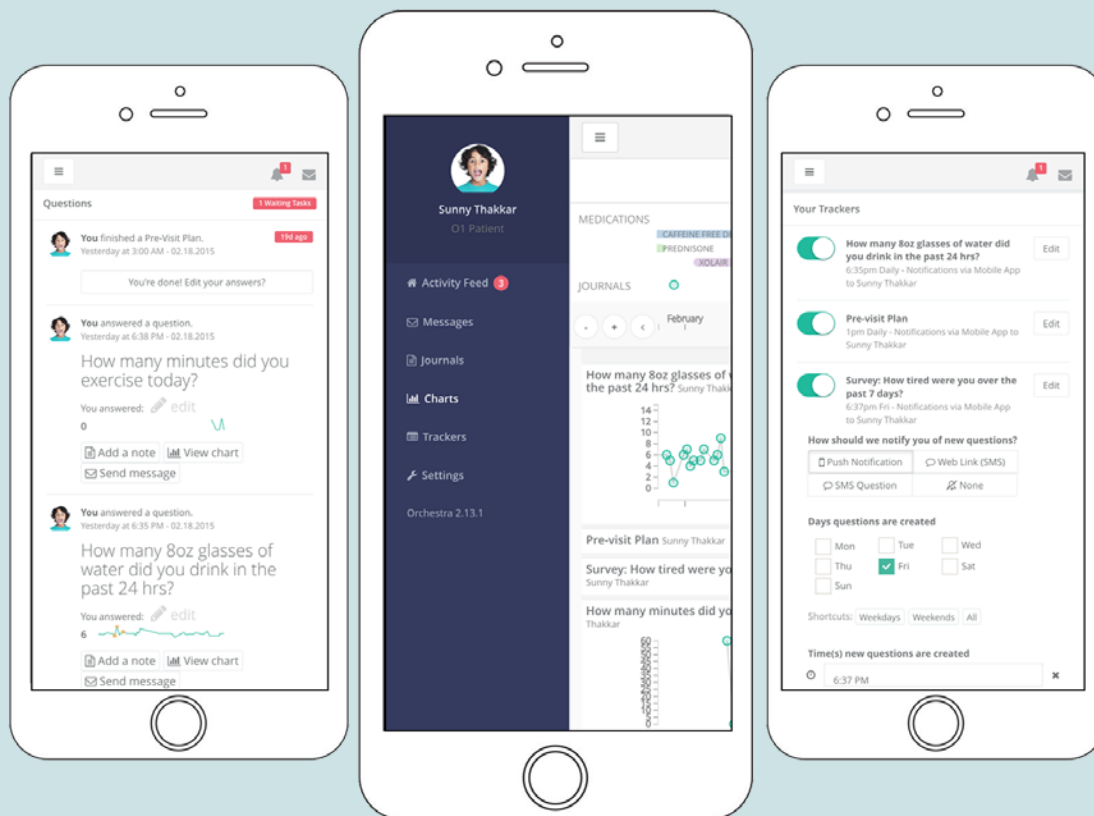
Moore's influence upon cystic fibrosis care reaches to the national level. She chronicles her son's CF journey in a blog called 66 Roses. She has been interviewed by *U.S. News & World Report* and was recently invited to the White House to attend a "Champions of Change" event. She has served as an advisor to Genentech and the Robert Wood Johnson Founda-

tion. She currently serves on a patient engagement committee of the Cystic Fibrosis Foundation and as a patient representative with the U.S. Food and Drug Administration. Since 2013, Moore has been employed by Cincinnati Children's as a family partner, where she works with the pulmonary care team to design social media engagement strategies for patients and caregivers.

"Right after Drew was diagnosed with CF, I immediately felt 100,000 different feelings," Moore wrote in a 2010 blog post. "You're scared because you don't know what it is. You're sad because your baby is sick. You're guilty, knowing that this genetic disease was passed onto your baby through you, and you wish more than anything that you could take that away. But then you look at your beautiful little being and can't help but be overwhelmed by love."

Moore is a voracious learner and a dynamic builder; highly motivated, highly organized and ready to act. And like all strong mothers, she is utterly committed to the well-being of her son. Moore is exactly the type of parent who breathes life into the esoteric-sounding C3N concept.

"The model is connecting a vast network of microexperts who are coming together to create something bigger than any one of us can create alone."



Cincinnati Children's has been a pioneer in developing learning networks that use social networking technology to bring scientists, physicians, parents and patients together in new ways. Members of these networks pool experimental data and real-world experiences to accelerate research, improve communication and spread best practices faster and farther than ever before.

Peter Margolis, MD, PhD, Director of research at the James M. Anderson Center for Health Systems Excellence at Cincinnati Children's, was an instrumental force in launching the first major C3N — the ImproveCareNow network that focuses on Crohn's disease and ulcerative colitis. Now Margolis is working with Moore, Michael Seid, PhD, Director of Health Outcomes and Quality of Care Research in the Division of Pulmonary Medicine, and several other colleagues at Cincinnati Children's to apply the C3N concept to transforming cystic fibrosis care.

A NETWORK IS BORN

Moore was among the early advocates who pushed to begin a C3N-style network for CF, while she was serving as the state advocacy chair of the Cystic Fibrosis Foundation in Ohio. Her

awareness of the approach began in 2012 after attending the North American Cystic Fibrosis Conference in Orlando.

"One of the key things I understood through that conference was that what's missing in CF is a better understanding of what happens to patients between visits," Moore says. "Well, I have that knowledge and so do the other 30,000 families who have kids with CF. So I started searching online for more information. That's where I read about Dr. Seid and learned more about this chronic care model, and I thought, 'This is what we need. This

Erin Moore (below) has served as an advisor to Genentech and the Robert Wood Johnson Foundation. She currently serves on a patient engagement committee of the Cystic Fibrosis Foundation and as a patient representative with the U.S. Food and Drug Administration.



is what they were talking about at that conference. Why don't we have this?"

Moore convinced CF Foundation leaders to visit Cincinnati to learn first-hand about work led by Margolis and Seid. They were impressed. Now, Cincinnati Children's, the CF Foundation and the Dartmouth Institute (a long-time adviser to the foundation) are collaborating to build the "CF Care Model of the Future." Initial design meetings were held in January and May.

"Through this process we're building a new system. We're building a new way to work together," Moore says. "The model is connecting a vast network of microexperts who are coming together to create something bigger than any one of us can create alone."

Ideas for the care model include new emphasis on self-tracking metrics, home health care and telemedicine, shared decision making, even creating a centralized IRB for multicenter CF research. As the

work progresses, Cincinnati Children's and other accredited CF care centers plan to launch pilot projects to evaluate new approaches.

"A lot of this is coming from families pushing ideas," Moore says. "Families are saying, 'We demand better. We need this. We need you to work with us.'"

CONDUCTING CARE WITH A SMARTPHONE

One part of the new care model could include a new mobile application (app) under development by a team of researchers at Cincinnati Children's and the California-based Vital Labs Inc. They are designing and testing a symptom tracking and communication tool called Orchestra to improve interactions between families and clinicians. Moore is one of the early adopters.

The tool can be used on tablets, desktops and smartphones. It allows Moore to

constantly feed data about Drew's health status to his care team. Every day, the app automatically sends out questions seeking information about symptoms, medication usage, nutrition and other topics. Families respond with just a few keystrokes. "It takes about 40 seconds a day to respond to the prompts," Moore says.

New data points get plotted instantly into tracking charts, and if desired, the app can alert clinicians to abnormal trends. The app's design team — Lisa Opiari-Arrigan, PhD, and Heather Kaplan, MD, at Cincinnati Children's and Ian Eslick, PhD, at Vital Labs — explained the app during a webinar recorded in April 2015.

In a typical chronic care scenario, families meet with clinicians for about 20 minutes per visit, three or four times a year. Everything else about the patient's health experience occurs in the weeks and months between. However, information about what happened during those time

Caring for their son Drew (left) is a non-stop duty for the Moore family, but improving treatments and staying in constant contact with their care team has allowed Drew to enjoy a normal, active life with his siblings (center).



spans usually gets relayed to clinicians in unobjective, incomplete fashion, all colored by the limitations of memory.

Orchestra can help fill in the gaps, the designers say. When families use the tracking app, patients and parents come to the clinic visit armed with much more comprehensive data, which makes the limited time they share with doctors more meaningful and effective.

"The platform enables patients and providers to be equal partners, co-producing health and health care together," Opiari-Arrigan says.

Moore says the system empowers families. She recalls a situation when Drew was 4 and he started coughing more frequently during a family vacation. Doctors in the local hospital's emergency room wanted to admit Drew for a 10-day course of antibiotics. However, Moore could see from the data she had been gathering that Drew was not acting like he had during previous infection-related

exacerbations. She doubted that antibiotics would help. Her information was solid enough that she convinced the doctors to administer a steroid instead, and Drew was back to normal within a day.

"Doctors are coming to realize that I have more knowledge about Drew than anybody else. I'm with him every day," Moore says. "Now our clinicians engage with me where I'm at, not where they're at."

A BRIGHTER FUTURE

These days, Drew is doing well. He started kindergarten this year and loves to romp around with his older sister Ella, twin sister Lily, and younger brother, Jake.

Drew is the only one of the children with CF; the others are carriers. Three times a day, 30 minutes per session, Drew wears a vibrating vest to help clear mucus from his lungs while breathing medicated

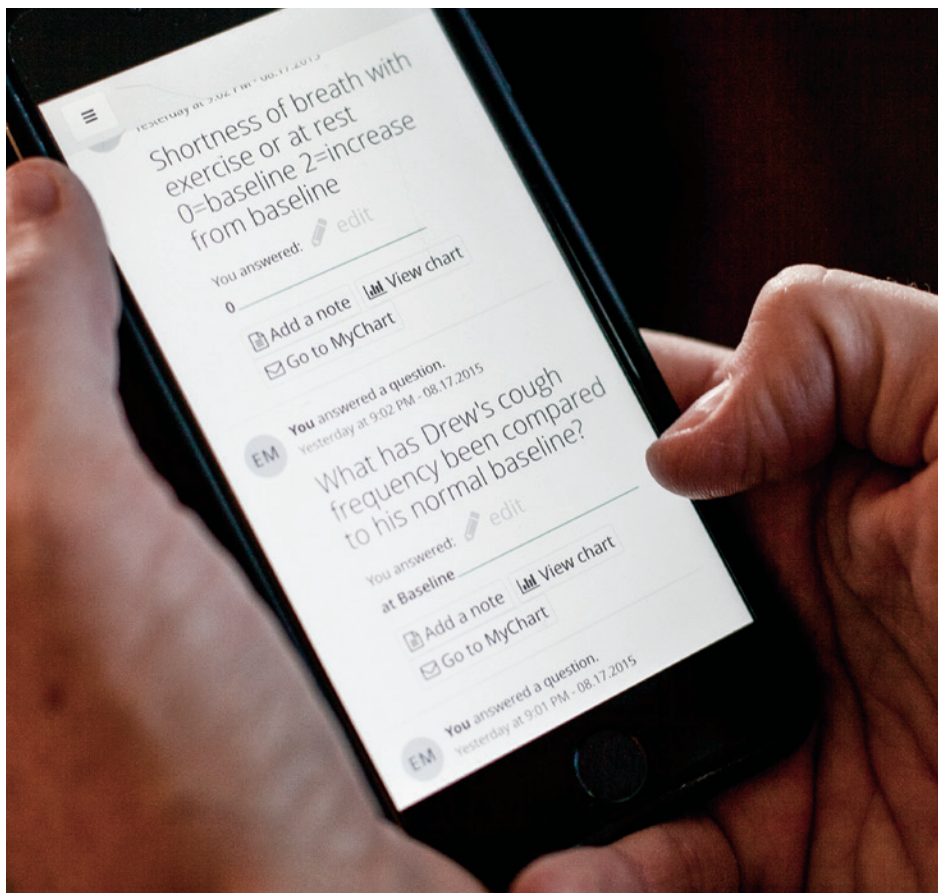
mist through a nebulizer. The rest of his medications fill a kitchen cabinet.

"I credit a lot of Drew's health to the pulmonary team at Cincinnati Children's. They have been terrific," Moore says. "But I also credit a lot of it to the advocacy, engagement and empowerment that I have. It really has been a partnership."

Moore plans to continue putting the Orchestra app through its paces and to continue advocating for family empowerment and engagement. She sees a huge role for social networking as the CF Care Model of the Future embraces personalized medicine.

Moore points to her smartphone and says, "This will transform health care." ■

Erin Moore uses an app called Orchestra, under development at Cincinnati Children's, to submit and track data about Drew's condition. Daily data entry requires just seconds to complete and unusual blips can be automatically flagged.



CF Learning and Education Center to Emphasize Novel Approaches to Health and Wellness

by *Tim Bonfield*

Better sleep. Reduced stress. Improved fitness. Support for school performance.

These prescriptions for improving day-to-day life may have as deep an impact upon health outcomes for children and adults with cystic fibrosis (CF) as the introduction of new medications. So says the leader of the new Cystic Fibrosis Learning and Education Center at Cincinnati Children's.

Thomas Boat, MD, recently returned to the medical center after serving as Dean of the University of Cincinnati College of Medicine. Boat's long career includes extensive experience in CF care and in supporting CF research. Now he is coordinating an effort involving faculty and staff from Cincinnati Children's and UC Health's CF Center to create and adopt innovative concepts in cystic fibrosis care.

"This is a frontal assault on the social, behavioral and economic dimensions of cystic fibrosis," Boat says. "It is certainly very exciting to see new medications and new technologies coming along for individuals with CF. But if families

struggle to manage the basic aspects of their lives, these new developments won't make as much difference as they could. The ability of parents and patients to manage their own care is 95 percent of the game, and we don't know how best to meet this challenge."

One of the new learning center's missions is to prepare health professionals for a new era in CF care, an era in which many more children with CF will survive long into adulthood. Initial funding comes from the Boomer Esiason Foundation, the charity launched by the former NFL quarterback whose 24-year-old son Gunnar has cystic fibrosis. Since 1993, the foundation has raised more than \$100 million for CF research, scholarships and other support.

Through the new learning center, Boat says the CF program at Cincinnati Children's will serve as an incubator for launching and evaluating more comprehensive promotion of health and wellness. The most successful ideas will be shared across a national network of CF care centers accredited by the Cystic Fibrosis Foundation.

"The ability of parents and patients to manage their own care is 95 percent of the game, and we don't know how best to meet this challenge."



Thomas Boat, MD, (left) leads development of the new Cystic Fibrosis Learning and Education Center at Cincinnati Children's. During an empathy exercise, a physician breathes through a straw with his nose pinched to gain more understanding of life with cystic fibrosis.

"One of our first focus areas will be sleep," Boat says. "It is well known that kids with CF, much like others with complex chronic disease, do not sleep as well or as much as healthier kids. Interestingly, their parents don't either."

Studies conducted at Cincinnati Children's and other research centers have confirmed that lack of sleep is linked to faster disease progression and declining pulmonary function for children with CF. The harder step is finding effective ways to help children get the sleep they need, Boat says.

"A lot of the adherence issues in CF have to do with the fact that routine care takes two or more hours every day," Boat says. "That's in addition to the frequent medical visits, plus taking care of the siblings, getting them to school, getting to work, and doing all the other things families have to do. It is no surprise that so many parents and patients think or even say, 'I'm whipped. I'm burned out.'"

Unrelenting stress takes a big toll. Another major effort of the center will study the ability of stress reduction

techniques to improve the quality of life for CF families. CF health professionals will likely also benefit.

The first sleep and stress management initiatives will roll out this fall, Boat says. Longer term, the center also is studying how it can be more effective at supporting the educational needs of children with CF.

"We know that school success is a huge resilience factor," Boat says. "The kids who do better in school also tend to do better emotionally, and they are likely to do better managing their therapy. School success also promotes economic and social stability in adulthood, an important outcome for CF patients, many of whom we predict will become older adults."

Unlike 30 years ago, many more children with CF are growing up healthy enough to lead productive adult lives. Many will want to go to college. Many will need to work. All this makes it increasingly important that small children with CF are prepared for success when they reach school age, Boat says.

The new CF learning center plans to tap into wide-ranging expertise at Cincinnati Children's in complex chronic care, adherence research, sleep disorders, behavioral health and more. The project includes specialists from the UC College of Medicine in sleep medicine, integrative medicine and other fields. Boat also envisions involving a variety of community organizations along the way.

A platform for planning and program development within the CF Learning and Education Center will use information technology to create communication "exchanges" that connect and encourage the contribution of ideas from CF families, health professionals, and others, both here in Cincinnati and ultimately from a national or even global network of the CF Center.

"Our first steps, however, need to raise awareness among CF health professionals," Boat says. "Because if they don't buy in, they won't be as effective at helping families." ■

Putting Sleep Disorders to Bed Once and for All

The Division of Pulmonary Medicine at Cincinnati Children's collaborates on a wide range of research projects, including computer-generated "virtual surgery" techniques that could one day transform surgical treatment of sleep apnea.

Their unusual secret weapon: The principles of aerospace engineering.

Scientists here also are exploring the mechanisms — and possible cause — of the sleep disorder narcolepsy; and analyzing a diabetes drug that has shown promise in alleviating sleep apnea. Meanwhile, the Sleep Center continues to grow its overnight-study program, with the recent expansion at the Liberty Campus in suburban Cincinnati.

Tireless collaboration works. They are, in a sense, the researchers who will not rest until every child can.



Virtual Surgery Could Help Children With Sleep Apnea Breathe Easier

by Tom O'Neill

Pediatric surgery and aerospace engineering might seem to occupy parallel universes — but not anymore for children with sleep apnea.

Researchers at Cincinnati Children's and the University of Cincinnati's Department of Aerospace Engineering and Engineering Mechanics are using the mechanical concepts of computational 3D modeling, air flow, turbulence, resistance and fluid dynamics to bring a new level of precision to a decidedly non-mechanical task: the surgical correction of obstructive sleep apnea (OSA).

Fueled by more than \$3.8 million in funding from the National Institutes of Health, a research team with a wide variety of talents has designed and begun testing a 3D computer software modeling system that can replicate the unique geometry of an individual child's upper-airway. Within three to five years, these rotating, interactive, full-color models may become available to help surgeons test surgical scenarios, select ideal approaches, and practice procedures long before patients reach the operating room.

Ten years ago, the idea of applying aerospace principles to surgical planning would have sounded unlikely at best, says Raouf Amin, MD, Director of the Division of Pulmonary Medicine.

"To think that bioengineers would be instrumental to advancing this research in sleep apnea, or to say we were going to import the science of aerospace and apply it to the airway, no, most probably, that would have been considered science-fiction," Amin says.

MEDICINE MEETS ROCKET SCIENCE

In Cincinnati, bridging the worlds of surgery and aerospace engineering has been as simple — and remarkable — as crossing a street called Albert Sabin Way that passes between the research

towers of Cincinnati Children's and the medical campus of the University of Cincinnati.

When he joined the project in 2010, engineering expert Goutham Mylavarapu, PhD, had no biomedical experience. Yet by 2014, he had co-authored a paper in the *Journal of Biomechanics* that used computational fluid dynamics to characterize how air ebbs and flows as it moves through the human airway.

"It took me a year just to understand the medical principles," he says with a slight laugh. "Now, I tell my wife, perhaps I should go back to school and become an MD."

Indeed, learning each other's terminology and scientific procedures required plenty of communication. But team members were motivated by the stakes involved.

In the past three years, Cincinnati Children's has experienced a 20 percent spike in children visiting its sleep study lab to be assessed for sleep disorders. The assessments have grown from 2,184 in fiscal year 2013 to 2,626 in fiscal year 2015.

The prevalence of sleep apnea, the most common form of sleep disorder, is rising for a number of reasons. Childhood obesity plays a role, as do improved diagnostic systems and increased public awareness of the health risks of sleep apnea.

Any child can be affected by a sleep disorder; children with Down syndrome or craniofacial abnormalities are particularly susceptible. Untreated, sleep disorders can lead to compromised cognitive function, excessive daytime sleepiness, academic struggles, behavioral challenges and weight fluctuation. Some studies suggest that sleep apnea symptoms can mimic ADHD, bringing the risk of misdiagnosis.

Many children with sleep apnea can be treated with non-surgical options like weight-loss programs or CPAP breathing devices. But some children, particularly those with Down syndrome, find the CPAP mask and its head straps intolerable. These and other children with significant structural issues affecting their airways require a more invasive, surgical approach.



Raouf Amin, MD, Director of the Division of Pulmonary Medicine, believes computational modeling, with an assist from aerospace engineering principles, could be transformative in planning upper-airway surgical strategies.

CREATING AN AIRWAY SURGERY RESEARCH AGENDA

Aerospace science has the potential to transform surgical techniques, says Stacey Ishman, MD, MPH, Surgical Director of the Upper Airway Center and Director of Otolaryngology Outcomes Research.

“This could fundamentally change our approach in two ways,” she says. “Some patients should never undergo surgery, so by seeing the outcome beforehand, you can avoid the side effects and the pain. The other is in considering several surgical options. Which is best, what are the priorities?”

Amin agrees that the upper airway presents a tricky surgical landscape. Below the larynx, the airway is stiffer, which supports long-lasting surgical outcomes. But above the larynx, the elasticity of softer tissues complicates everything. Treating residual obstruction at multiple levels of the upper-airway can require multiple procedures, and success rates hover at about 60 percent.

“Sometimes the improvement is not sustained,” Amin says. “The most challenging problem is how to estimate the soft tissue.”

The new modeling system can help surgeons better understand the dynamics of how soft tissue will react to resection. With more data to characterize the phenotype, the odds of providing a lasting treatment improve, Amin says.

DYMOSA STUDY PROVIDES DATA

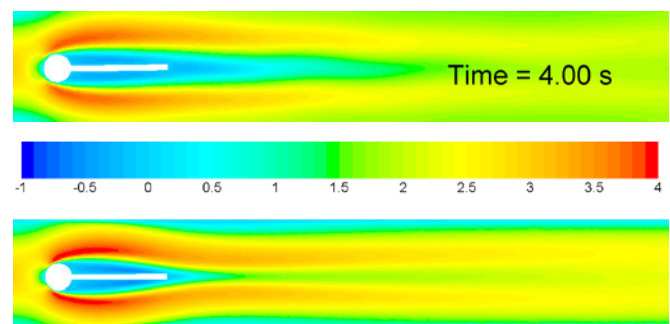
Since 2010, Amin, Sally Shott, MD, Division of Otolaryngology, and other colleagues have been conducting a study called Dynamic Computational Modeling of Obstructive Sleep Apnea (DYMOSA). The NIH has supported the work with an initial three-year RO1 grant and subsequent extensions.

The project involves experts from Otolaryngology, Pulmonary Medicine, Sleep Medicine, Radiology, Anesthesia and, of course, the space guys at UC. The team is one of very few in the world conducting cine MRI imaging of the airways of children with Down syndrome who also have persistent OSA. Cine is a form of MRI that captures the flow of cerebrospinal fluid.

“There’s not a lot of great data out there,” Ishman says. “And kids with Down syndrome were underrepresented in what studies did exist.”

Researchers knew this much: By age 4, almost 60 percent of children with Down syndrome suffer abnormal sleep, and eight out of 10 exhibit sleep apnea by age 9. Studies show that virtually every child with Down syndrome will develop sleep apnea at some point in childhood.

Anatomy betrays them. They have higher prevalence of midface hypoplasia with smaller airway size in the oral cavity, nose, nasopharynx and at the base of tongue. They have a larger-than-average volume of tongue tissue. Poor muscle tone also contributes to airway collapse.



Measuring air flow over a cantilever attached to a cylinder, researchers can see how upper-airway walls (above) respond differently from rigid structures (below).

In addition, a 50 percent incidence of underlying heart abnormalities in children with Down places them at higher risk for developing the more severe consequences associated with sleep apnea.

To date, 55 children with Down syndrome have participated in the DYMOSA study. If virtual surgery modeling proves

effective for this group, the approach can be adjusted for other pediatric populations with OSA, the researchers contend.

CASE REPORTS APPEAR PROMISING

Amin, Ishman, Short and colleagues examine DYMOSA's encouraging progress in a prospective case report called "New Frontiers in the Treatment of OSA in Children: Computational Modeling of the Airway for Surgical Planning."

The report focuses on three types of virtual surgeries performed on airway models created for each subject: A 2-millimeter base-of-tongue resection, a 4-millimeter resection, and a virtual palate reconstruction (palatoplasty). At 10 liters/minute of air flow, upper-airway resistance decreased by 46 percent for the 2-mm resection and 48 percent for the 4-mm approach. When the palate also was excised, air resistance decreased an additional 16 percent.

"Computational modeling of the airway and associated virtual surgery allow for pre-operative planning that provides the surgeon with information both on 'where' to operate, and on 'how much' tissue to remove for potentially improved post-operative success," the authors wrote. ■

Stacy Ishman, MD, MPH.



How the Modeling System Works

by Tom O'Neill

The airway computational modeling system in development in the Pulmonology and Otolaryngology divisions is similar to recent work at Cincinnati Children's Heart Institute, where surgeons are using computer-generated 3D-printed models of individual hearts to plan operations.

"We haven't utilized a printer yet, but the modeling employs the same principle as 3D hearts," says Raouf Amin, MD. "It's based on formulas to understand the effect of flow and pressure within a structure, whether it's a muscle or a blood vessel or a heart or an airway. That's why we bring in the physicists who are the experts in this computational model."

This is where Goutham Mylavaram comes in. The first author of the "New Frontiers" report had studied mechanical engineering in his native India, at the Indian Institute of Technology. He had no particular interest in medicine when he came to Cincinnati to pursue his PhD at UC's Department of Aerospace Engineering and Engineering Mechanics.

"It all happened by chance," Mylavaram says. Instead of working on aircraft, he wound up studying under Ephraim Gutmark, PhD, an Ohio Eminent Scholar at UC who happened to have experience collaborating with Cincinnati Children's to study air flow and sound waves in children with damaged larynxes.

For airplane wings and car exhaust systems, the fluid dynamics involved can be fairly straightforward. Human anatomy has more complex and individualized structures.

Mylavaram, Gutmark and colleagues outlined how it works in a 2014 paper published in the *Journal of Biomechanics*. The work starts with data from three medical technologies:

- **cine MRI images** that capture a child's cerebrospinal fluid flow. As the heart beats, this fluid flow is forced out of the ventricle of the brain and down the spinal canal.
- **polysomnography sleep studies**, which record brain wave activity, oxygen level in the blood, breathing and heart rate, and eye and leg movement
- **sleep endoscopy**, in which a patient is given incremental amounts of anesthesia to induce sleep for a short time to the point where apnea occurs, but before there is a drop in blood-oxygen level. An endoscopy camera shows the key areas of obstruction, effectively taking out some of the guesswork.

These pre-op test results produce a baseline measure quantifying flow velocity, turbulence, pressure and wall shear stress. "There is so much physics and mechanics involved," Mylavaram says. "The challenge is that the upper-airway is a very flexible structure."

Diabetes Drug Shows Early Promise in Alleviating Sleep Apnea

A drug approved to combat diabetes, and later obesity, is showing early promise in treating sleep apnea in adults.

Raouf Amin, MD, Director of the Division of Pulmonary Medicine, is cautiously optimistic that liraglutide could one day help in alleviating pediatric apnea.

In a pilot study sponsored by Cincinnati Children's, researchers found that in 18 adult non-diabetics with apnea, 12 showed an average decrease in severity of 44 percent. The clinical trial also involved nine control non-diabetics who also have OSA but did not receive liraglutide for the four-week period.

Amin presented the findings in May earlier this year to the American Thoracic Society. "We made some very interesting observations," Amin says.

"Liraglutide affects the central and peripheral networks. Some are metabolism-related, which is why it is good for diabetes. But it also affects the central control of breathing."

Still, he points out, the result means a third of participants using liraglutide showed no response. And, of course, the sample size was small. "There is a difference in how they responded," Amin says. "The next step is understanding the mechanism."

As a peptide-1 receptor agonist, liraglutide works by binding to the same receptors as the metabolic hormone GLP-1, which increases the secretion of insulin. The drug gained FDA approval as a type 2 diabetes treatment in 2010 and was approved in 2014 for some patients with obesity.

Researchers hypothesize that liraglutide could cause significant increases in orexin, a neuropeptide that regulates arousal and wakefulness, as well as carbon dioxide chemosensitivity. The drug also appears to prompt a decrease in leptin, which regulates energy balance.

In an update filed Aug. 3, 2015, with the National Institutes of Health, researchers wrote: "The development of a new pharmacological treatment for sleep-disordered breathing could bring a breakthrough discovery that will impact a rapidly growing population of children and adults with this disorder."

Primary completion of the clinical trial is expected in December.

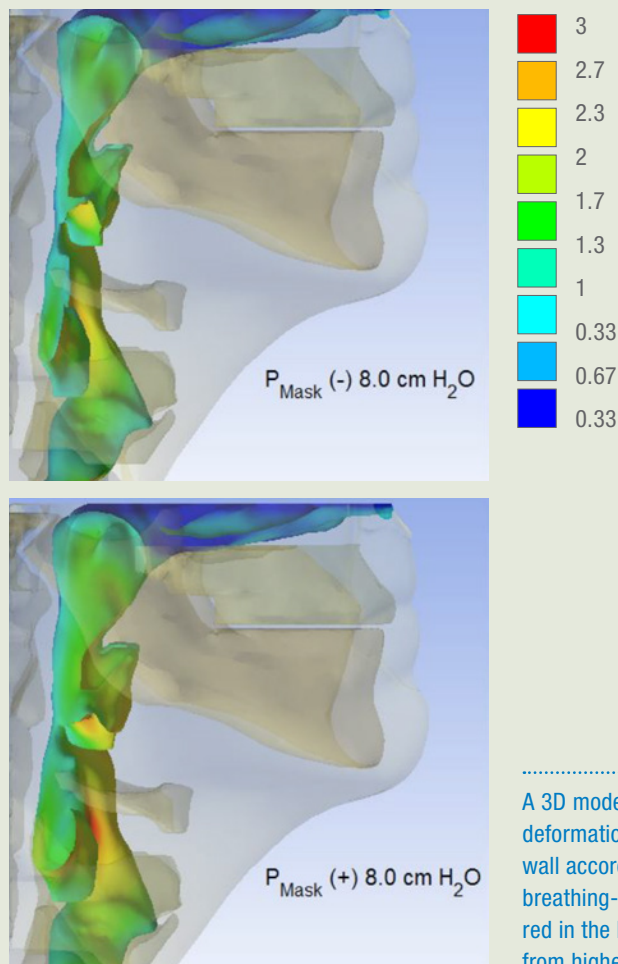
With the baseline established, "virtual surgery" begins. When tissue is virtually resected, the algorithms change, revealing new airflow results. Surgeons can explore variations in approach until they find the optimal flow.

The system is not perfect. For example, the airways of some children balloon out as they breathe, a type of movement that cannot be captured in cine MRI images. But in most cases, the computer models vastly reduce the educated guesswork involved in traditional surgery.

Amin plans to establish a center within a year specifically dedicated to "virtual surgery." He predicts such a center could play a key role in improving diagnostic techniques and establishing best practices for sleep apnea treatment.

Plenty more research is needed. In a systematic review published July 7, 2015, in *Laryngoscope*, Amin, Ishman, Sally Shott, MD, and colleagues found a general lack of data regarding patient selection, outcomes for OSA surgery, and the effectiveness of some commonly used tools to identify OSA sites.

The study raises tough questions, but Amin predicts the ongoing work of the new virtual surgery center will soon begin providing stronger answers.



A 3D model illustrates deformation of the airway wall according to variations in breathing-mask pressure. The red in the bottom image results from higher air pressure.

The Mystery of Narcolepsy's Secret Triggers

Autoimmune response and the brain neurotransmitter hypocretin might hold crucial clues to solving this elusive sleep disorder

by Tom O'Neill

In children with narcolepsy, the body's light switch regulating sleep has faulty wiring somewhere behind the wall.

Daytime wakefulness blinks into dream sleep lasting for several seconds or minutes, and sometimes much longer. It works in reverse as well, with frequent night-sleep interruptions.

Narcolepsy is unrelenting. But so is Narong Simakajornboon, MD, a sleep specialist and Director of the Sleep Center at Cincinnati Children's. He is a leading researcher in the field of narcolepsy who also heads the pediatric working group of the Sleep Research Network.

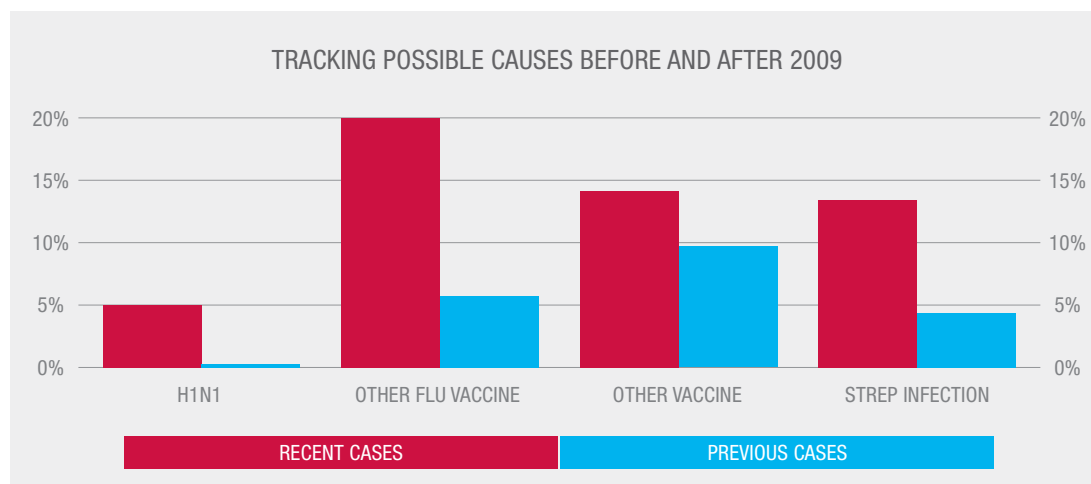
"There appears to be several factors, but there is an autoimmune component that affects the development of narcolepsy," he says. "The goal is to better understand those potential triggers."

Worldwide, narcolepsy affects about 30 per 100,000 people. Five years ago, rapid increases in childhood narcolepsy

in Europe were linked to a single manufacturer of a vaccine for the H1N1 influenza virus. The vaccine connection was surprising, but it could not explain a corresponding rise in Northern China, where the virus itself was a suspected environmental trigger. Nor could the vaccine link explain narcolepsy cases rising in the U.S., where H1N1 vaccination rates were low and the European vaccine was never made available.

Something more complicated is going on, Simakajornboon contends.

In a case report published March 15, 2013, in the *Journal of Clinical Sleep Medicine*, a team of researchers led by Simakajornboon reported a case following streptococcus infection. Researchers at Stanford theorized that the body's response to streptococcal infection could trigger narcolepsy in children who have a genetic predisposition to the disorder. The Stanford team noted that the risk of narcolepsy was 5.4 times higher in patients with a physician-diagnosed strep infection. Also, prior to onset



In comparing clinical characteristics in the rise of narcolepsy and possible correlations to infections and vaccinations, researchers found a seasonal pattern to recent cases but no clear link to vaccinations.

Source: Multi-center Study of Early Onset Childhood Narcolepsy: Recent Cases and the Role of Infection, Sleep Research Network



Narong Simakajornboon, MD, suspects that narcolepsy onset could be rooted in a mistaken autoimmune response.

of narcolepsy, there was a higher rate of strep infection in children who had yet to go through puberty than those who had. “There is an increase in cases that are pre-puberty,” Simakajornboon says. “From five to 10 percent to about 30 percent, and these cases have a pretty rapid onset.”

The body’s autoimmune response to infection might play a key role in what ultimately could be a simple case of mistaken identity.

Studies have shown a strong genetic association between narcolepsy-cataplexy (an abrupt loss of muscle control) and processes in the brain involving leukocyte antigen (HLA) and a T-cell receptor that responds to antigens.

Simakajornboon says there could be “cross-reactivity” between those antibodies and the neurotransmitter hypocretin, which controls alertness. Hypocretin is secreted by the approximately 70,000 neurons in the hypothalamus. Children with narcolepsy have significantly decreased levels of hypocretin.

Simakajornboon and other investigators speculate that the Group A Strep and viral antigen may have or share some epitopes that are similar to the antigen in hypocretin neurons. Epitopes are the parts of an antigen that allow an antibody to attach.

“Therefore,” he says, “after strep or viral infection, the antibody to strep may mistakenly recognize the antigen of hypocretin neurons and attack the neurons.”

Those same neurons also regulate appetite and feeding behavior, which could explain why narcolepsy patients have higher-than-average rates of obesity and weight fluctuation.

Simakajornboon and many other researchers believe that both genetic and environmental factors are at work. Some cases are clearly inherited, but others are not.

In the U.S., however, longitudinal data on narcolepsy are limited. Because it is both rare and non-communicable, narcolepsy does not require reporting to the national Centers

for Disease Control and Prevention or the National Center for Health Statistics.

Simakajornboon is helping to change that through the Sleep Research Network, which has grown to 22 institutions from 14 since he took a leadership role in its pediatric working group in 2010. Before his involvement, the network had no database on pediatric narcolepsy. Now the group has data on 357 cases, with a goal of reaching 700.

“I think that this database will be an important first step in multicenter collaborations for clinical trials in pediatric narcolepsy,” Simakajornboon says. “Also, identifying early cases may lead to more effective early intervention such as immunotherapy.”

Simakajornboon spoke on behalf of the network in June in Seattle at SLEEP 2015, the annual meeting of the Associated Professional Sleep Societies. He noted that symptoms in cases since 2009 differ from previous cases. More recent cases share higher rates of cataplexy and higher likelihood of anxiety, excessive weight gain, abnormal movement and behavior change.

Unlocking the causes of those changing trends could be critical to solving the mystery of the sharp rise in childhood narcolepsy diagnosis. In addition to excessive daytime sleepiness, other symptoms could include sleep paralysis and hypnagogic hallucinations that are unusually vivid and at times very frightening to children.

For now, narcolepsy is treated with medications that minimize excessive daytime sleepiness and other symptoms. Behavioral changes such as avoiding caffeine and adhering to a set schedule for sleep and napping also help.

Finding better treatments is important because sleep is as important to the human body as food and air, Simakajornboon says. “We always see sleep as a normal physiological thing that happens, but people tend to underestimate how sleep impacts your overall life.” ■

Kicking Asthma Out of School

The prevalence of asthma in Cincinnati's inner-city schools is breathtaking. As many as one in five kids in the city has it, and many barely realize their condition. As one out-of-breath student said after ballet practice: "Is this my asthma? I always breathe like this."

Scenes like this may soon be changing as leaders at Cincinnati Children's bring years of nationally-renowned asthma research experience to bear as they launch a pilot project to create an asthma-free school.

The plan: identify high-risk students, enlist school nurses and health assistants, and use the latest in tracking technology and electronic medical records to improve chronically poor adherence patterns. The goal: to reach that day when no child misses school due to an asthma exacerbation.



Quest Begins to Create an ‘Asthma-Free’ School

by Sarah Stankorb

Of the 36,000 children with asthma in Hamilton County, more than 4,700 are students in the Cincinnati Public Schools (CPS).

The number reflects the high rates of asthma common to urban populations. Most of the school district’s students are African American, who have a 60 percent higher asthma prevalence than the overall population. Many live in high-risk neighborhoods where poverty, lack of transportation to healthcare, chaotic housing, and low health literacy among parents all combine to make it hard to keep asthma under control.

These are the children who feel an alarming but all-too-familiar tightness when a smoker lights up in the apartment, who risk having an exacerbation during football practice, who go without medication when their inhaler runs out and no one at home has the time or resources to pick up a new one.

These are the children who miss too much school because of their poorly controlled asthma. So this is where Cincinnati Children’s, through its Asthma Population Health Initiative, wants to help create an “asthma-free school.” It might sound like a near-impossible dream, but this is exactly where the expertise of one of the nation’s top asthma centers is needed the most.

The mission is to test and change the system, says Carolyn Kerckmar, MD, Director of the Asthma Center at Cincinnati Children’s, to see if it is possible to create a school environment where students with asthma are “free from exacerbations.”

Success would mean “students would be free from the need to miss school due to asthma. They would have good asthma control,” she says. “Our goal was to put resources in schools to make that happen.”

PILOT PROJECT TAKES OFF

Beginning in spring 2015, the asthma population health team began piloting a \$300,000 asthma-free schools program at Oyler School in Price Hill and South Avondale School, both of which have well-established school-based health centers. The program includes support from Cincinnati Children’s James M. Anderson Center for Health Systems Excellence, the Luther Foundation and the Verizon Foundation.

High-risk students and those who frequently miss school due to asthma are invited into a program in which daily controller medication can be administered at school, supervised by the school nurse or health assistant. Students, school staff and parents will take part in asthma education and training, which will include public service videos produced by Cincinnati students.

An inhaler cap sensor and mobile software management program called Propeller Health will provide school nurses and primary care physicians with real-time feedback of medication adherence and symptom reporting. Cincinnati Children’s also will provide telehealth visits with asthma specialists for students who don’t have a medical home or need a specialist consult.



Carolyn Kercksmar, MD, directs the Asthma Center at Cincinnati Children's.

Making these schools “asthma-free” will mean zero asthma-related absences — except perhaps for the most severe cases who have no optimal treatment options. The program will be able to document that students’ asthma was well controlled during the school year and that they suffered no severe asthma exacerbations.

A HISTORY OF INVOLVEMENT

Cincinnati may be the perfect place to test the feasibility of creating just such an environment, says Gregg Sabla, project manager for the Asthma Center.

As many as one in five kids in the city has asthma, and the medical center knows from experience how hard it can be to keep them connected to care. No more than half of patients keep their appointments or fill their prescriptions. Families move frequently and parents’ cell numbers change constantly, making it hard for schools and physicians to follow up.

But Cincinnati Children’s also has years of experience working with CPS.

Starting in 2007, when Kercksmar joined the medical center, the Asthma Center partnered with Mona Mansour, MD, MS, and the Division of General and Community Pediatrics to forge a partnership with local schools. The Cincinnati Children’s team works directly with school nurses to identify children with asthma and coordinate care. Interventions have included training school nurses, providing home delivery of

As many as one in five kids in the city has asthma, and the medical center knows from experience how hard it can be to keep them connected to care.

prescription medications, developing a home health nurse educator program, even providing school nurses “read-only” access to Cincinnati Children’s medical records for their shared students to support coordination of care.

Improving asthma care in the community has been a strategic goal at Cincinnati Children’s for several years. In 2010, one goal set for the Asthma team was to reduce emergency department visits and hospitalization due to asthma by 20 percent by June 2015. They achieved that goal a year ahead of schedule.

MUCH MORE WORK AWAITS

Even though Cincinnati Children’s provides a good safety net that has improved outcomes for kids with asthma, every net has holes. Over the next few years, the Asthma Center aims to demonstrate that comprehensive, managed asthma care that leverages partnerships with schools can create a safety net so finely woven that no child slips through the gaps.

Barb Wiley-Kroner, Supervisor of the School and Adolescent Health Program for the Cincinnati Health Department, has worked closely with Cincinnati Children’s asthma program and is well aware of the challenges ahead. With every new school year, the need to educate new classes of families and patients about asthma returns.

“We’ve had families that did not really view asthma as a chronic illness to be managed,” she says. “They just lived exacerbation to exacerbation. So long as their kid didn’t flare up, they thought they were fine.”

What’s more, Wiley-Kroner notes, some students with asthma do not realize how far their symptoms are from ordinary. She recalls a student at CPS’ well-known School for Creative and Performing Arts who shrugged off the fact that she was wheezing audibly after finishing ballet class.

“She said, ‘Is this my asthma? I always breathe like this.’ Many of our students with asthma don’t realize their friends without asthma don’t struggle as much to breathe.” ■

Asthma experts at Cincinnati Children’s are teaming with school nurses at South Avondale School to improve health education and medication adherence for students there.



International Symposium on Acute Kidney Injury in Children

June 24-26, 2016 | Cincinnati, Ohio, USA

Keynote Speaker – Claudio Ronco, MD

*Director of the Department of Nephrology, Dialysis and Transplantation
International Renal Research Institute at St. Bortolo Hospital, Vicenza, Italy*

Join us for the 2nd International Symposium on Acute Kidney Injury (AKI) in Children, an event of special interest to nephrologists, nephrology nurses, cardiologists, neonatologists, critical care physicians and intensive care nurses. This event will feature presentations on cardiorenal syndromes, neonatal AKI, hepatorenal syndrome, sepsis associated AKI, biomarkers and other scientific advances in AKI.

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Symposium sponsored by the Center for Acute Care Nephrology and the Heart Institute at Cincinnati Children's.

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Putting sleep disorders to bed

Kicking asthma out of school

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