


2016

RESEARCH
DISCOVERIES



An abstract oil painting on canvas. The background is a soft, textured wash of light blue and white. Scattered throughout are numerous small, circular, and oval shapes. These shapes have dark, almost black outlines and are filled with various colors including deep blue, purple, red, orange, and yellow. Some of these shapes appear to have a central dot or a small opening, giving them a cellular or organic quality. The overall composition suggests a microscopic view of nature or a collection of small, interconnected elements.

Cover and throughout:

RUTH WARTMAN

Oil on Canvas

Constant recurring patterns throughout nature connect and shape our global village. The collection and clustering of small things create the big picture.

This work was inspired in collaboration with Cincinnati Children's research staff, Kolar Design and the Art Academy of the Cincinnati Community Education Department. The original installation appears in the Schubert Research Clinic in our Clinical Sciences Pavilion.

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2016

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Dear Colleagues,

The Research Annual Report for 2016 again focuses on a truly remarkable set of innovations and discoveries fueled by our equally remarkable faculty.

As we advance our Strategic Plan, we continue to approach our goal to lead the world in improving child health through our collaborative culture of discovery, translation, and learning. We are proud of the six breakthrough discoveries showcased in 2016. A number of other attainments also make this a record-shattering year.

Our total for extramural grants and contracts was \$207 million, a 3.5 percent increase over our previous high. Cincinnati Children's also achieved its largest single research grant, the \$32.5 million Bench to Bassinet data coordinating center with co-PIs from Biostatistics and Epidemiology (Eileen King, PhD) and Biomedical Informatics (Peter White, PhD). This work resulted in a very competitive template that underpins future collaborative proposals in this arena as well. Yet it is worth emphasizing that these attainments represent just a portion of the high-impact research happening at Cincinnati Children's. Very few pediatric medical centers can match this level of excitement, collaboration, and productivity.

The content of this report also outlines many other ways in which Cincinnati Children's supports our mission to improve child health through scientific discovery. A wide variety of internally funded pilot programs to nurture emerging innovations are in place from residency through fellowship and junior faculty positions to the most senior ranks of our faculty. We invest in more than 20 research core facilities to make the very best technology available. Recruitments of young faculty with high potential and of senior leaders as division directors continue to build the strengths of our faculty.

Our ability to invest in outstanding people and our long track record of collaboration have positioned Cincinnati Children's to be a significant force in the emerging world of team science. We continue to forge new partnerships with other leading pediatric institutions and to deliver on our promise to make bold progress against the greatest challenges in child health.

A handwritten signature in black ink that reads "Margaret K. Hostetter". The signature is fluid and cursive, with a long horizontal line extending from the end.

Margaret K. Hostetter, MD

B.K. Rachford Professor

Chair, Department of Pediatrics

Director, Cincinnati Children's Research Foundation

Chief Medical Officer

Cincinnati Children's Hospital Medical Center

Science moves us. Discovery inspires us.

These two short phrases speak clearly to the culture of the Cincinnati Children's Research Foundation.

For many years, our Board of Trustees has helped build this culture by supporting substantial investments in our own researchers and their efforts, which goes beyond the external grants and industry support we already receive.

This ongoing commitment underscores the importance we place on innovation, the confidence we have in the talented scientists who work here, and our focus on research to transform child health.

As stated in our 2020 strategic plan, we are working to enhance discovery in the following areas:

- Biomedical Informatics
- Genomics, Metabolomics, Proteomics, Microbiome
- Systems Biology and Collaborative Networks
- Shared Research Cores

The progress highlighted in this report is impressive and inspiring, and is helping us move closer to our 2020 goals.

We look forward to changing the outcome together as we begin a new year of discovery. And, we thank all of our supporters, partners, funders, donors and the community for their help to advance science, as we strive to be the leader in improving child health.



Thomas S. Cody

Thomas Cody
Chair, Board of Trustees



Nancy Krieger Eddy

Nancy Krieger Eddy, PhD
Research Chair



Michael Fisher

Michael Fisher
President and CEO



A background image showing a microscopic view of cells, likely from a tissue sample, with various colored structures and a blueish tint.

Top Six Breakthrough Discoveries of 2016

In the past fiscal year, the outstanding faculty of the Cincinnati Children's Research Foundation published more than 2,200 papers in peer-reviewed scientific and medical journals. Their insights illuminate how the human body develops and how diseases begin. Their innovations are leading to improved therapies and new research tools. Their breakthroughs bring hope to a generation of children in need. From this impressive body of work, a committee of senior research leaders selected six discoveries as the most significant of the year. The stories behind these impressive accomplishments begin here.



"This is a powerful demonstration
of precision medicine guided
by fundamental research."

— Harinder Singh, PhD



Michael Jordan, MD, and colleagues found that the arthritis drug abatacept also can serve as a life-changing treatment for children with rare LRBA deficiencies. The drug mimics a braking function on the immune system that these children lack.

Breakthrough Therapy Improves Life for Children with LRBA Deficiency

PUBLISHED JULY 24, 2015

Science

Abatacept, a drug primarily used to treat arthritis, mimics the function of the CTLA4 protein. In children with this rare condition, the drug improved lung function and reduced other autoimmune symptoms.

For many years, this disease was so rare it barely had a name. As far as scientists could tell, it affected only a few hundred children and adults worldwide.

These children were living with a complex set of symptoms that included repeated respiratory tract infections, frequent gastrointestinal problems, and a variety of autoimmune complications.

By process of eliminating other diagnoses, doctors had placed these children under an obscure umbrella disease category known as common variable immune deficiency (CVID). However, unlike the larger numbers of CVID cases that tend to emerge in adulthood, this tiny group became sick as young children. They also tended not to respond well to established CVID treatments, such as immunoglobulin replacement therapy and antibiotics.

Some did not survive to reach adulthood.

Then in 2012, researchers discovered a shared genetic mutation among these children that finally led to giving the disease a more precise name: LRBA deficiency. Now, scientists from Cincinnati Children's, the National Institute of Allergy and Infectious Diseases (NIAID), and other collaborating institutions may have figured out how to control it.

The drug abatacept, already FDA-approved for treating rheumatoid arthritis, has been shown to reverse deadly symptoms of LRBA deficiency. Not just in fruit flies or mice, but in children. The team's findings appeared July 24, 2015, in *Science*.

OBTAINING RESULTS TOOK YEARS

Michael Jordan, MD, and colleagues found that LRBA deficiency interferes with cytotoxic T

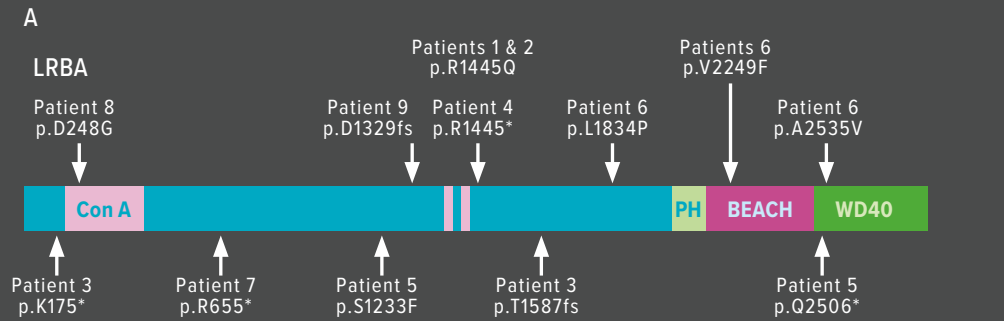


Fig A. Novel biallelic LRBA mutations of nine patients appear along a schematic map of LRBA protein domains.

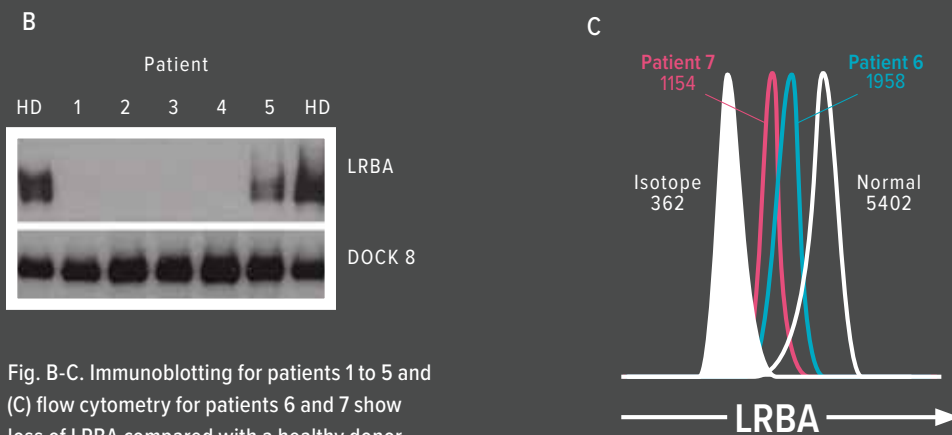


Fig. B-C. Immunoblotting for patients 1 to 5 and (C) flow cytometry for patients 6 and 7 show loss of LRBA compared with a healthy donor (HD). DOCK8 is included as a loading control.

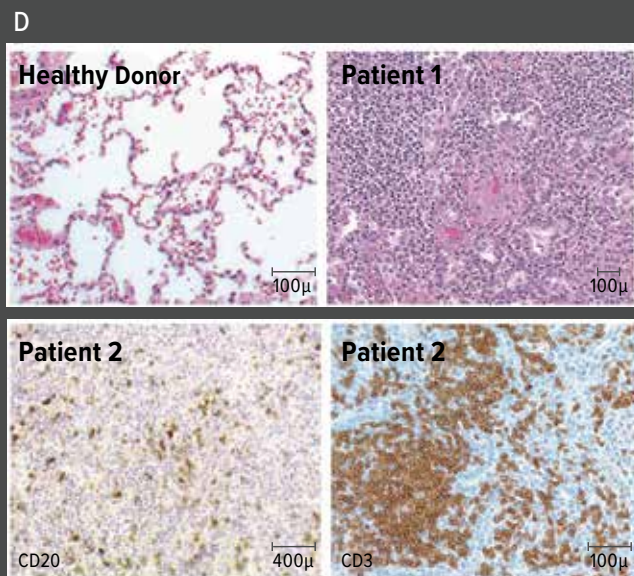


Fig D. Hematoxylin and eosin staining illustrates the contrast between a healthy donor lung and the lung of patient 1. Also shown are immunostains for CD20 (B cells) and CD3 (T cells) in the lung of patient 2.

lymphocyte-associated protein 4 (CTLA4). This important protein acts as a brake that prevents immune cells from becoming over-active. Children with LRBA deficiency have dramatically reduced levels of CTLA4 protein.

Abatacept mimics the function of this protein. When given to six children with LRBA deficiency, in an off-label, compassionate use basis, all of the children demonstrated improved lung function and/or reduced autoimmune symptoms. A seventh patient was treated with hydrochloroquine and reported similar—but less extensive—improvements.

Treatment periods have ranged from six months to eight years.

“We have seen some remarkable responses,” Jordan says. “Some of the children we treated had failed all other approaches. Yet on this medication, they have managed to live longer, mostly healthy lives.”

One of Jordan’s early patients, who was near death as a young child, has grown to adulthood, completed high school and has a job. He still has symptoms that require regular treatment, but they are under control.

IMPROVED TECHNOLOGY HELPED BLAZE THE TRAIL

Doctors tried abatacept on an educated hunch. Experience with using the drug in other autoimmune conditions suggested it might have a beneficial role.

It was only after whole-exome sequencing methods became available that investigators were able to find enough of these children to study, analyze them, and ultimately confirm why the drug seems to help.

“These findings provide a clear rationale for a larger prospective clinical trial that could further refine the most effective long-term treatments,” Jordan says.

WHERE MIGHT THIS NEW PATHWAY LEAD?

For children known to have LRBA deficiency, doctors in the U.S. already are prescribing abatacept as an off-label use. That may be enough to

save lives. Ideally, however, the drug should be tested across varying ages and stages of disease, Jordan says.

Meanwhile, Jordan and colleagues plan more studies to determine whether other immune disorders are connected to low levels of CTLA4 protein. Work also continues to evaluate hydrochloroquine as an alternative treatment option. This drug, used to treat lupus, is much less expensive than abatacept.

Immunobiology

RESEARCH & TRAINING DETAILS

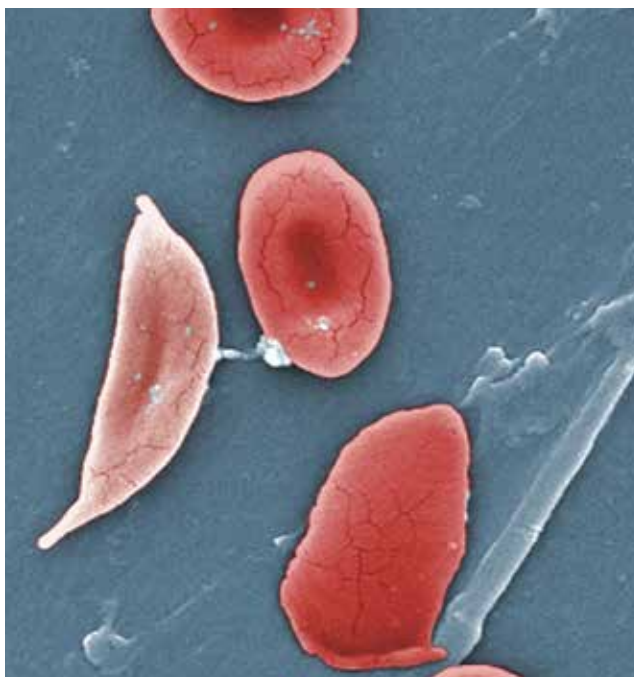
Faculty	13
Research Fellows & Post Docs	18
Research Graduate Students	16
Total Annual Grant Awards	\$4.9M
Total Annual Industry Awards	\$121,391
Total Publications	124

Lo B, Zhang K, Lu W, Zheng L, Zhang Q, Kanellopoulou C, Zhang Y, Liu Z, Fritz JM, Marsh R, Husami A, Kissell D, Nortman S, Chaturvedi V, Haines H, Young LR, Mo J, Filipovich AH, Bleesing JJ, Mustillo P, Stephens M, Rueda CM, Chougnet CA, Hoebe K, McElwee J, Hughes JD, Karakoc-Aydiner E, Matthews HF, Price S, Su HC, Rao VK, Lenardo MJ, Jordan MB. AUTOIMMUNE DISEASE. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. *Science*. 2015;349(6246):436-440.



“This finding is of major benefit in limiting the need for transfusions to prevent stroke in sickle cell patients. Importantly, hydroxyurea treatment serves as a more implementable strategy in low-resource settings around the world.”

— Louis Muglia, MD, PhD



Russell Ware, MD, PhD, has been a leading force in advancing the use of hydroxyurea as a low-cost, high-value treatment for controlling sickle cell stroke risk, pain and other symptoms.

Sickle Cell Breakthrough: A Pill to Replace Blood Transfusions

PUBLISHED ONLINE DEC. 6, 2015

Lancet

The 25-center TWiTCH clinical trial to evaluate hydroxyurea as a stroke prevention therapy was so successful that officials ended the study early.

Imagine replacing the expensive and tedious process of monthly blood transfusions with a simple pill that costs less than \$1 a day.

That is the dramatic improvement in care happening now for many children and teens with sickle cell disease, thanks to breakthrough research led by Russell Ware, MD, PhD, and colleagues at Cincinnati Children's.

Stroke is one of the deadliest complications of sickle cell disease. As many as one in 10 children born with this common genetic condition will suffer at least one stroke before reaching adulthood. Many will become disabled and some do not survive.

For years, the medical community has used blood transfusions to battle this risk. The treatment helps, but it requires bringing children to facilities properly staffed and equipped to store and transfuse blood month after month, indefinitely. Meanwhile, for many, the transfusions carry risks

of transmitting infections and inevitably lead to iron overload, which requires an expensive medication to correct.

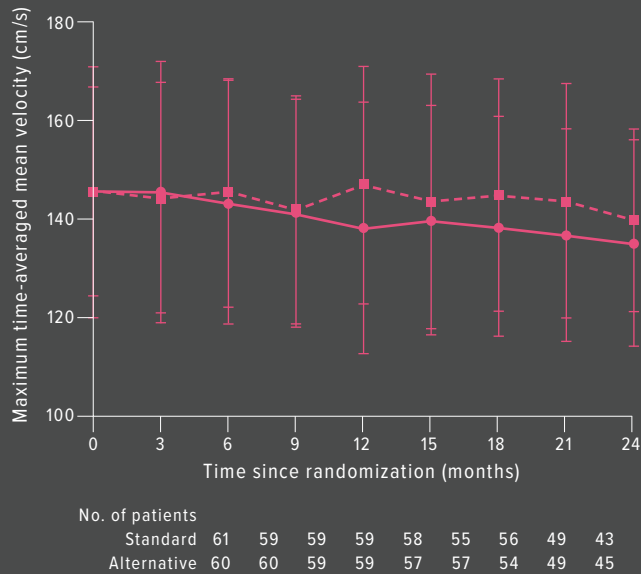
"Unfortunately, this First World solution is not adequate for a disease that actually strikes far more children in the Third World," Ware says.

Enter hydroxyurea.

CLEAR SUCCESS LEADS TO EARLY END FOR TWiTCH STUDY

Ware served as the national principal investigator for a study launched in 2011 called, "TCD With Transfusions Changing to Hydroxyurea (TWiTCH)." The project sought to compare how well this inexpensive medication prevents stroke compared to traditional blood transfusions.

The drug worked so well that the National Heart, Lung, and Blood Institute (NHLBI) stopped the study in late 2014, over a year earlier than projected, after treating just 83 patients.



This chart shows the similarities in outcomes between standard blood transfusions and hydroxyurea treatment in reducing transcranial Doppler velocities among patients with sickle cell disease.



Tracking the velocity of blood flow in the brain is a key measure of stroke risk for patients with sickle cell disease. Cincinnati Children's has donated equipment and trained local medical teams to perform transcranial Doppler tests in three nations so far.

Ware presented these results in December 2015 as a plenary talk at the American Society of Hematology Annual Meeting in Orlando:

- 42 in the transfusion arm and 41 in the hydroxyurea arm completed two years of treatment.
- Average transcranial Doppler (TCD) velocities of intracranial blood flow were similar between both patient groups (143±1.6 cm/sec transfusion vs. 138±1.6 cm/sec hydroxyurea).
- A posthoc analysis suggests that hydroxyurea may be superior at lowering TCD velocities and reducing stroke risk.

"No child should ever suffer a stroke, which is why it was so important for the NHLBI to support the TWiTCH trial," NHLBI Director Gary Gibbons, MD, said when the study stopped. "This critical research finding opens the door to more treatment options for clinicians trying to prevent strokes in children living with sickle cell disease."

ACTING LOCALLY AND GLOBALLY

At Cincinnati Children's and other centers in the U.S. and Canada, more children identified by TCD testing as high risk for stroke are now switching from blood transfusions to hydroxyurea as the preferred first-line treatment for stroke prevention.

Meanwhile, experts from Cincinnati Children's have donated TCD equipment and trained medical teams in the Dominican Republic, Jamaica, and Uganda on how to track stroke risk among children with sickle cell disease. These efforts could serve as models for even wider-scale adoption of this new treatment.

"We want to take the lessons learned here and export them to low-resource countries," Ware says.

In the U.S., doctors are prescribing hydroxyurea earlier in life for growing numbers of sickle cell patients. Previous research led by Ware and others has demonstrated the drug's value in managing pain and other symptoms that can occur long before elevated stroke risks emerge.

"With the wider use of hydroxyurea continuing in even younger patients, the need to use it specifically to prevent stroke may become a non-issue in 10 years," Ware says.

WHAT'S NEXT?

Research to evaluate hydroxyurea use in lower-income countries continues. More information could be published in 2017 about how the drug works in populations with high rates of malaria, Ware says.

Eventually Cincinnati Children's plans to teach medical teams in the Caribbean and sub-Saharan Africa about the use of hydroxyurea, which will lessen sickle cell's morbidity and mortality on a global scale.

Cancer and Blood Disease Institute: Hematology

INSTITUTE RESEARCH & TRAINING DETAILS

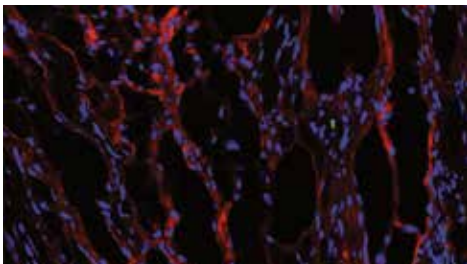
Faculty	81
Joint Appointment Faculty	23
Research Fellows & Post Docs	38
Research Graduate Students	31
Total Annual Grant Awards	\$20M
Total Annual Industry Awards	\$4.6M
Total Publications	212

Ware RE, Davis BR, Schultz WH, Brown RC, Aygun B, Sarnaik S, Odame I, Fuh B, George A, Owen W, Luchtman-Jones L, Rogers ZR, Hilliard L, Gauger C, Piccone C, Lee MT, Kwiatkowski JL, Jackson S, Miller ST, Roberts C, Heeney MM, Kalfa TA, Nelson S, Imran H, Nottage K, Alvarez O, Rhodes M, Thompson AA, Rothman JA, Helton KJ, Roberts D, Coleman J, Bonner MJ, Kutlar A, Patel N, Wood J, Piller L, Wei P, Luden J, Mortier NA, Stuber SE, Luban NL, Cohen AR, Pressel S, Adams RJ. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial. *Lancet*. 2016;387(10019):661-670.



"This paper reports the exciting finding that induced expression of a single transcription factor, Tbx20, can enhance adult cardiac muscle cell proliferation, cardiac repair and survival, suggesting future therapeutic potential."

— Burns Blaxall, PhD



Katherine Yutzey, PhD, led a research team that uncovered a new approach to inducing damaged hearts to grow new muscle cells after an infarction. In mice, the new cells led to significant, but not complete, restoration of cardiac function.

A New Path to Helping Hearts Heal Themselves

PUBLISHED MARCH 15, 2016

Circulation

Overexpression of Tbx20 promotes cardiomyocyte proliferation in mice and improves cardiac function.

Developing a way to help cardiac muscles repair themselves after a heart attack has been one of the Holy Grails of modern medicine.

After all, unhealed heart attack damage is a leading cause of heart failure, which in turn contributes to approximately 287,000 deaths a year in the U.S.

In recent years, scientists had hoped that emerging stem cell technology would become the solution to prodding adult hearts into making new cardiomyocytes. So far, however, stem cell approaches have largely failed.

Now a potential new path to that elusive Grail is emerging. Research led by Fu-li Xiang, PhD, (now working at Novartis) and Katherine Yutzey, PhD, Molecular Cardiovascular Biology, has established that overexpression of the transcription factor Tbx20 prompts damaged hearts to heal themselves in mice.

Their findings appeared March 15, 2016, in *Circulation*.

FROM CURIOSITY TO DISCOVERY

The work started with an unexpected observation. Santanu Chakraborty, PhD, a post-doctoral fellow in Yutzey's lab, was working with a mouse model on an unrelated project when he noted that Tbx20 overexpression promotes fetal-stage heart development. He went on to begin exploring whether the transcription factor could promote adult cell growth.

"We did not expect it to work," Yutzey says. "But we tested the concept in several different ways and the proliferation persisted."

Intriguing, but a crucial question remained: Could a process that appears to work in a lab also work at repairing actual damaged hearts?

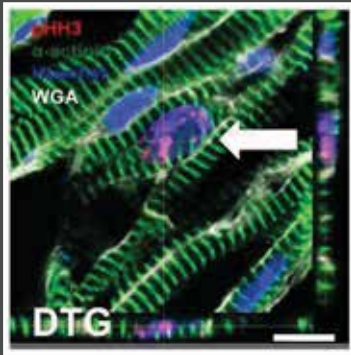


Fig 2A: The green striations in this confocal microscope image helped confirm that inducing overexpression of the Tbx20 protein in mouse heart tissue can promote heart muscle cell growth.

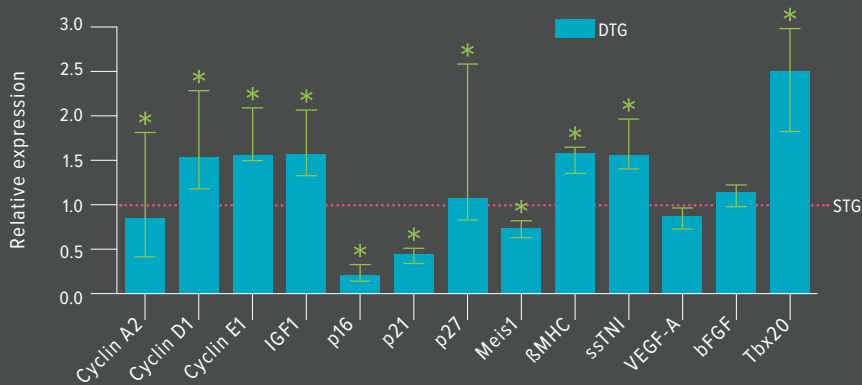


Fig 2E: This chart, based on mRNA isolated from mouse heart tissue, shows the important role of Tbx20 relative to the expression of other fetal contractile proteins, cell-cycle activators and inhibitors.

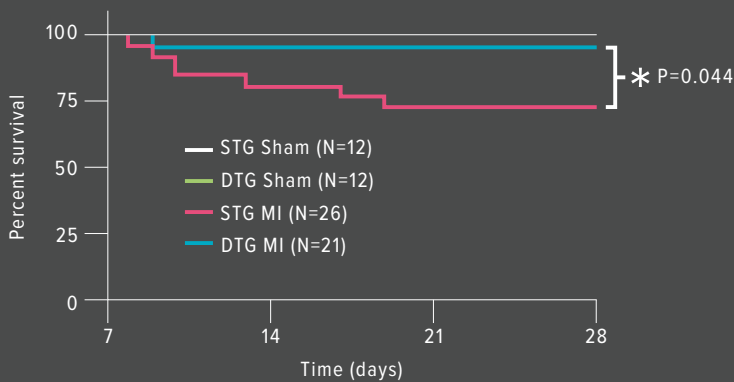


Fig. 4f: This chart, based on analysis four weeks post-injury, shows better survival rates for double transgenic (DTG) mice injected with tamoxifen to induce Tbx20 overexpression compared to single transgenic mice (STG) that did not receive the injection.

TURNING OFF AN OFF SWITCH

The research team generated mice with induction of Tbx20 overexpression in adults. Xiang led much of the work, including inducing non-fatal infarctions in adult mice, and then injecting the drug tamoxifen for three days to activate the Tbx20 overexpression.

They soon found that the mice began to generate new, beating cardiomyocytes with immature, proliferative characteristics. Compared to controls, the treated mice had more cardiomyocytes after four weeks without leading to cardiac hypertrophy, fibrosis, or arrhythmia.

After eight weeks, the treated mice demonstrated a significantly higher survival rate than the untreated mice.

Further analysis revealed that the overexpression of Tbx20 promotes cell cycle activity through multiple molecular signaling pathways and represses cell cycle inhibitors p21, Meis1, and Btg2.

“In essence, this approach turns off genes that normally turn off cell proliferation,” Yutzey says.

The involvement of Btg2 as an inhibitor of cardiomyocyte proliferation was not expected. Other scientists have reported that this gene plays a role in slowing tumor growth, but none had reported that Btg2 also influences heart cell proliferation.

MORE WORK AHEAD

While the treated mice showed improved function, they did not fully heal.

“The mice attained 60 to 75 percent of their pre-infarction levels,” Yutzey says. “The new, fetal-like cells likely are smaller and weaker than normal adult cardiomyocytes.”

Still, that much improvement in cardiac function would make a powerful difference in terms of living with heart failure—if experts can translate these mouse model findings to humans. Several challenges lie ahead.

The gene manipulations used in the mouse study are not feasible in people, so investigators will need to explore other delivery methods. These could include using viral vectors or modified RNA technologies, Yutzey says. Some research teams

also have reported success in animal studies with applying treatment delivery patches directly to heart tissue.

It remains unclear how long the search for a viable treatment may take, but these latest findings suggest that the search may be worth the effort.

“The accumulating evidence that resident cardiomyocytes can be stimulated to proliferate holds promise for the development of new and more effective treatments for the most devastating types of cardiovascular disease,” Yutzey says.

Heart Institute: Molecular Cardiovascular Biology

INSTITUTE RESEARCH & TRAINING DETAILS

Faculty	60
Joint Appointment Faculty	2
Research Fellows & Post Docs	22
Research Graduate Students	11
Total Annual Grant Awards	\$12.7M
Total Annual Industry Awards	\$719,459
Total Publications	233

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Xiang FL, Guo M, Yutzey KE. Overexpression of Tbx20 in Adult Cardiomyocytes Promotes Proliferation and Improves Cardiac Function After Myocardial Infarction. *Circulation*. 2016;133(11):1081-1092.



“This publication is the most comprehensive examination to date of underlying causes of racial disparities in asthma morbidity. The paper uses novel statistical approaches, and the collaboration involved crossed several traditional silos.”

— William Brinkman, MD, MEd



Andrew Beck, MD, MPH, (left), Robert Kahn, MD, MS, and Bin Huang, PhD, (not shown) led a study exploring why black children with asthma are more likely than white children to be readmitted to the hospital.

Six Variables Explain Wide Racial Disparity in Asthma Readmission Rates

PUBLISHED ONLINE MAY 16, 2016

JAMA Pediatrics

Biological, environmental, disease management, access to care, socioeconomic and hardship factors collectively explain 80 percent of the disparity across racial groups.

Racial disparities in asthma readmission rates aren't always black and white, but in many cases they are.

Researchers have long known that African American children suffer from asthma at higher rates than white children. Now, a team from Cincinnati Children's offers six reasons why black children are 2.26 times more likely than white children to be readmitted within 30 days of hospital treatment for asthma.

They examined a range of potential explanatory variables rarely looked at together: biological, environmental, disease management, access to care, socioeconomic issues and hardships.

The team found that, collectively, these explained 80 percent of the disparity across racial groups. The study, published online May 16, 2016, in *JAMA Pediatrics*, shows that African

Americans fared worse than their white counterparts on almost every measure.

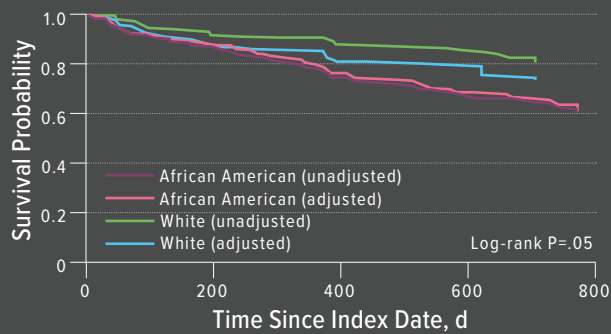
Research was led by senior author Robert Kahn, MD, MS, and first authors Andrew Beck, MD, MPH, and Bin Huang, PhD. Kahn and Beck are from the Division of General and Community Pediatrics; Huang, the Division of Biostatistics and Epidemiology. The team also included researchers from the Division of Hospital Medicine.

"Such a comprehensive, well-framed approach to exposures that are associated with morbidity is critical as we attempt to better understand and lessen persistent child asthma disparities," the authors wrote.

ANALYZING MULTIPLE VARIABLES CRUCIAL TO SEEING UNDERLYING CAUSES

The research is part of the Greater Cincinnati

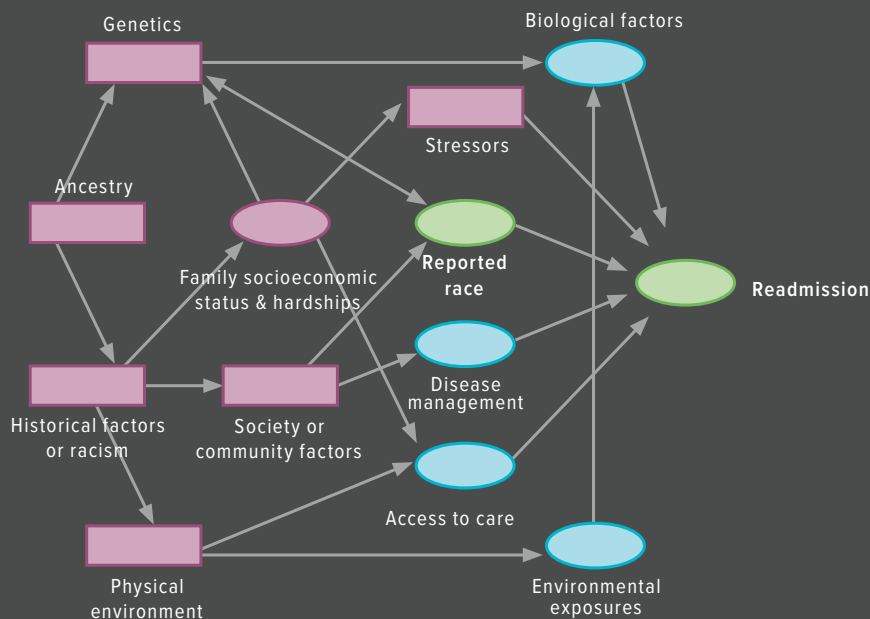
A. Unadjusted Model Vs Model Adjusted For Socioeconomic Variables



Number at risk				
African American (unadjusted)	441	363	242	89
African American (adjusted)	424	357	234	81
White (unadjusted)	254	221	160	59
White (adjusted)	220	184	130	46

This chart depicts survival probabilities according to adjusted and unadjusted models of racial diversity.

B. Illustration of the Directed Acyclic Graph Developed to Guide Analyses



The light blue ovals indicate variables thought to be directly associated with readmission; pink oval, patient, parent, and family factors thought to be directly associated with race and certain variables; pink rectangles, unavailable or unmeasured variables thought to be associated with race or readmission; and green ovals, reported race is the primary predictor or exposure variable and time to first asthma-related readmission is the outcome of interest.

Asthma Risks Study, a population-based, prospective study of 695 children aged 1 to 16 years who were admitted to Cincinnati Children’s for asthma or bronchodilator-responsive wheezing. The median age of the children was 5.4 years.

The key to understanding why readmissions occur, they concluded, was to account for a broad range of variables, as opposed to looking at them one by one.

“This moves us toward sounder explanations for why children of different races continue to face different clinical outcomes across a range of conditions,” they wrote. “Better explanations could, in turn, inform interventions aimed at reducing morbidity and narrowing unnecessary gaps.”

Chief among those gaps: socioeconomic hardship variables explained 53 percent of the disparity.

“If you’re concerned about your next meal,” Beck says, “you might not be thinking of taking your daily inhaled steroids.”

HOME CONDITIONS MIRROR THE SEVERITY OF SYMPTOMS PHYSICIANS SEE

It matters not only how you live, but where. The researchers assessed home living conditions for children readmitted for asthma exacerbations across several variables. These included tests for mold, smoking, traffic-related pollution and insect, mouse and pet dander.

The study found that African American children with asthma are more likely than whites to live in inner-city rental homes. These homes not only carry higher risks of asthma-triggering factors, but families may also fear retribution from landlords if they lodge complaints.

Beyond prescribing medications, clinicians also may need to intervene or advocate on behalf of more African American families to help improve their housing conditions, Kahn says.

“The lives of racial minorities,” researchers wrote, “differ markedly from the lives of those in the majority for both health outcomes and for the lived experience, highlighting their potential relevance to one another.”

General and Community Pediatrics

RESEARCH & TRAINING DETAILS

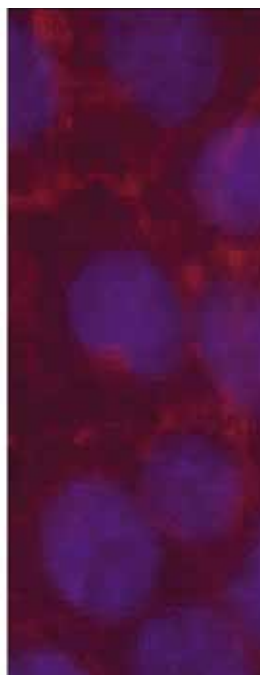
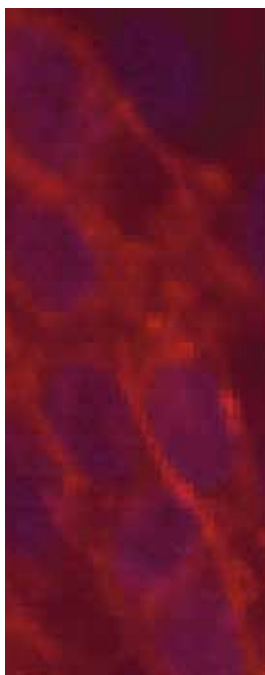
Faculty	28
Joint Appointment Faculty	6
Research Fellows & Post Docs	6
Total Annual Grant Awards	\$2.3M
Total Annual Industry Awards	\$136,202
Total Publications	68

Beck AF, Huang B, Auger KA, Ryan PH, Chen C, Kahn RS.
Explaining Racial Disparities in Child Asthma Readmission Using a Causal Inference Approach. *JAMA Pediatr.* 2016;170(7):695-703.



“This system is broadly applicable to many contexts of development and disease. It will provide a new approach to understanding how any two DNA-binding proteins functionally interact in the genome—previously an unapproachable question.”

— Aaron Zorn, PhD



Matthew Hass, PhD, (left) and Raphael Kopan, PhD, have developed a new tool for studying how pairs of transcription factors interact during development. The tool could accelerate studies in areas ranging from kidney disease to plant biology.

When Two Halves Make More Than a Whole

PUBLISHED AUG. 6, 2015

Molecular Cell

New SpDamID tool opens doors for studying how pairs of transcription factors affect development and disease. Think of this innovation as replacing a hammer and chisel with a power drill.

Thanks to a breakthrough reported earlier this year at Cincinnati Children's, scientists worldwide have a new tool at their disposal for studying the inner workings of how tissues form and diseases begin. This tool, known as SpDamID, makes it easier and faster to gather data on the complex roles that transcription factors can play in regulating cellular processes.

Eventually, new understandings generated by the data could lead to breakthroughs in areas ranging from kidney disease to plant biology.

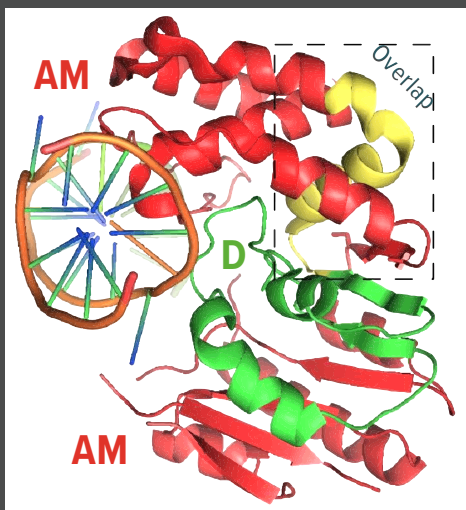
A team led by Matthew Hass, PhD, and Raphael Kopan, PhD, Director, Developmental Biology, developed the new tool. They described their discovery in a paper appearing Aug. 6, 2015, in *Molecular Cell*. Ever since, the team has been fielding requests from other scientists interested in putting SpDamID to work in their labs.

"With further development, this technology has the potential to give investigators glimpses into biological problems that cannot be answered with existing tools," Kopan says. "This method has been transformative for our research."

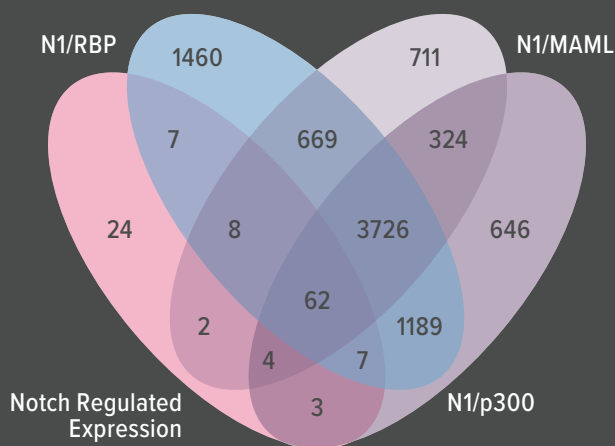
DISCOVERY BORN OF FRUSTRATION

Scientists have long understood that transcription factors play vital roles in regulating cellular processes. As these proteins bind to chromosomal sites, they deliver instructions that direct a cell's fate and function. When the instructions flow normally, cells perform their intended duties. When malfunctions occur, disease can begin.

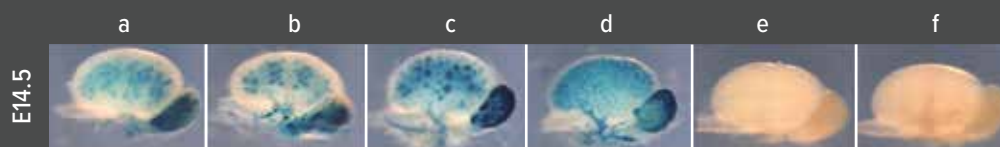
However, drilling down to the cellular level to measure how transcription factors interact—in what order, over time—has been a technical challenge.



This image shows the crystal structure of DAM. The N-terminal D half (green), C-terminal AM half (red), and overlapping region (yellow) are shown.



This Venn diagram details the overlap between Notch-regulated genes expressed in mK4 cells and the genes near a segment labeled by SpDamID-seq generated with the indicated Notch pairs.



Data obtained using the SpDamID tool sheds new light on kidney formation by confirming that Cdh6 is a direct Notch target during early organ development.

In recent years, developmental biologists have gathered rough snapshots of protein activity by using a combination of chromatin immunoprecipitation and next-generation gene sequencing (ChIP-seq). However, the process is tedious and requires material from up to one million cells to produce results.

Even so, this approach fails to deliver a conclusive picture.

“Using the older method, we can infer that two proteins might have a relationship because we can see that they bind to DNA at nearby locations,” Kopan says. “But we cannot see whether the two proteins are binding at the same time, or even within the same cell. So we cannot be confident that an actual relationship exists.”

NOTCH KNOWLEDGE

The new SpDamID tool builds from nearly two decades of study in Kopan’s lab to explore Notch, a critical molecule involved in tissue and organ development. When switched on, Notch binds to DNA—but only after linking first to a DNA-binding partner.

The new tool exploits this partnership process. Led by Hass, lab staff began splitting a well-known enzyme called DNA adenine methyltransferase (DAM). They connected one inactive half of DAM to one protein of interest, and the other half to another protein of interest.

Whenever the targeted proteins bind to DNA while in close proximity, or even when the proteins bind directly to each other, the reconnected DAM enzyme becomes active. This allows experts to mark each chromosome location where the two proteins interact.

This reaction occurs only when both proteins are active in the same cell and on the same strand of DNA. This eliminates nearly all the ambiguity from other methods over whether a relationship exists. The test also produces results from samples with as few as 10 cells.

EXPLORING APPLICATIONS

In Kopan’s lab, the SpDamID tool already has detected an interesting relationship between

Notch and the transcription factor Runx1, which could have implications for kidney development. The tool may also prove useful in exploring cancer, multiple sclerosis and other conditions.

Kopan has even been contacted by a plant biologist looking for an alternative to ChIP-seq.

So far, the team has fused the halves of SpDamID to 30 different transcription factor proteins, and documented the outcomes. Eventually, they hope to build a data library that covers all 1,400 known transcription factors.

While the new tool has a variety of potential uses, Kopan declines to speculate on the longer-term impact of SpDamID.

“We hope it will help a broad range of scientists,” he says. “But its value will last only until the next new tool comes along.”

Developmental Biology

RESEARCH & TRAINING DETAILS

Faculty	21
Joint Appointment Faculty	27
Research Fellows & Post Docs	23
Research Graduate Students	59
Total Annual Grant Awards	\$10.2M
Total Annual Industry Awards	\$129,895
Total Publications	54

Hass MR, Liow HH, Chen X, Sharma A, Inoue YU, Inoue T, Reeb A, Martens A, Fulbright M, Raju S, Stevens M, Boyle S, Park JS, Weirauch MT, Brent MR, Kopan R. SpDamID: Marking DNA Bound by Protein Complexes Identifies Notch-Dimer Responsive Enhancers. *Mol Cell*. 2015;59(4):685-697.



“This is the largest and most comprehensive study to assess the impact and risks of weight loss surgery in adolescents. Its findings add critical, objective information to an epidemic disease in the U.S.”

—Daniel von Allmen, MD



Stavra Xanthakos, MD, MS, (left), Thomas Inge, MD, PhD, and Michael Helmrath, MD, MS, (not shown) were among the leading co-authors of a study documenting powerful benefits resulting from bariatric surgery for obese teens.

Bariatric Surgery Improves Outcomes for Teens in Weight, Heart Health and Quality of Life

PUBLISHED ONLINE NOV. 6, 2015

The New England Journal of Medicine

Teenagers can be the biggest winners in life. By losing.

In the largest and most comprehensive analysis of its kind, researchers led by Cincinnati Children's found that adolescents who underwent bariatric weight-loss surgery won in three key ways.

They showed significant improvements in weight, cardiometabolic health, and weight-related quality of life. Cardiometabolic risk refers to someone's chances of developing heart disease, stroke or diabetes.

The study involved more than 80 researchers nationwide and showed that bariatric surgery reverses type 2 diabetes in a remarkable 95 percent of teens.

One more number of note: There are approximately 4.4 million severely obese children and adolescents in the U.S. An estimated 1,500 to 2,000 adolescents undergo surgical weight-loss procedures each year, and surgery in pre-adolescents is becoming more common.

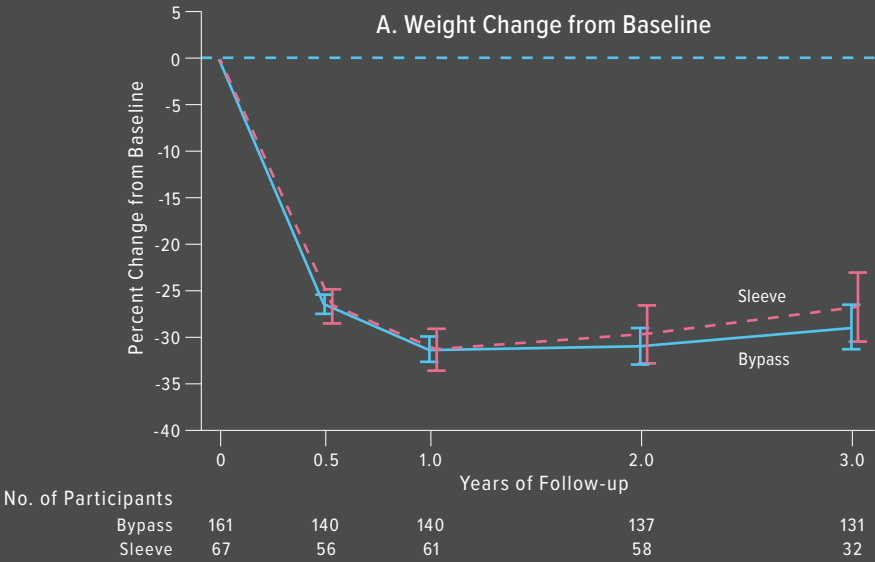
The study, published Nov. 6, 2015, in *The New England Journal of Medicine*, did not have the advantage of many precedents. Most prospective studies of bariatric surgery outcomes focus on adult cases.

What little research did exist on teens provided grim findings: only 2 percent of severely obese teenagers can lose weight and keep it off without surgery. Many who undergo surgery still struggled to get to and maintain a healthy weight.

For many obese teens, the path to adulthood is an emotional cul-de-sac. The more weight you gain, the worse you feel, and the more weight you gain. The authors noted that between 2003 and 2009, bariatric surgical cases among teens doubled nationally to 1,600.

"The remission rates for medical conditions such as diabetes and hypertension are greater than those we see in many studies of adults who had long-standing obesity before bariatric

Weight Changes and Prevalence of Dyslipidemia during the 3-Year Period after Bariatric Surgery



Panel A shows the modeled least-squares mean percent changes in weight from baseline at each study visit during the three years after Roux-en-Y gastric bypass surgery or vertical sleeve gastrectomy. The I bars represent 95 percent confidence intervals.

Bariatric Surgery Affected More Than Weight

Several co-existing conditions improved for many of the study participants.

At three years post-surgery:

74%

normalized
blood pressure

86%

resolved
abnormal kidney function

66%

normalized
lipid levels

19 out of 20

participants with Type 2 diabetes, median glycated hemoglobin dropped to 5.3%,
and median fasting glucose levels dropped to 88 mg/dl.

surgery,” says Thomas Inge, MD, PhD, the study’s principal investigator and lead author.

As Surgical Director of the Surgical Weight Loss Program for Teens at Cincinnati Children’s, Inge is convinced that early interventions are essential.

“If sustained,” he says, “the improvements seen in weight, blood sugar, kidney function, blood pressure, and lipid levels may translate into fewer strokes, heart attacks and other disabilities later in life.”

TYPE 2 DIABETES FADES, NORMAL KIDNEY FUNCTION RETURNS

The New England Journal publication coincided with the team’s presentation at The Obesity Society annual meeting in Los Angeles. The data for the study comes from the long-running Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) project. The consortium involves five clinical centers, led by Cincinnati Children’s.

The latest findings involved 242 severely obese adolescents, ages 13 to 19, who had an average, pre-surgery weight of 325 pounds. Three years after surgery, average weight had decreased by more than 90 pounds, or 27 percent.

In addition to the dramatic reversal of type 2 diabetes, 86 percent of patients saw a normalization of kidney function. Hypertension was corrected in 74 percent of cases. Lipid abnormalities were reversed in 66 percent.

Still, post-surgery life for teens brings many challenges.

DELAYING SURGERY CAN LIMIT THE POTENTIAL BENEFITS

Researchers found that half of participants had low iron stores three years after surgery, a 10-fold increase from pre-surgery. That makes monitoring of vitamin and iron supplementation crucial.

Also, 13 percent required additional abdominal surgery. The most common was gallbladder removal.

“We are also learning that once teens have crossed into these extremes of obesity, only 25

percent of them can achieve weights in the normal range after surgery,” says Michael Helmrath, MD, MS, Surgical Director of the Intestinal Rehabilitation Program. “And over half of them remain severely obese even after surgery.”

This means bariatric surgery needs to occur before teens reach the most extreme levels of obesity. Otherwise, the benefits may be limited.

Study co-author Stavra Xanthakos, MD, MS, is the Medical Director of the Surgical Weight Loss Program for Teens. She says pediatricians can use this study to help teens and families make treatment decisions.

“That’s especially important,” she says, “given that so many of us are now routinely caring for severely obese adolescents with significant health problems.”

General and Thoracic Surgery

RESEARCH & TRAINING DETAILS

Faculty	24
Joint Appointment Faculty	2
Research Fellows & Post Docs	8
Research Graduate Students	1
Total Annual Grant Awards	\$3.3M
Total Annual Industry Awards	\$157,307
Total Publications	90

Inge TH, Courcoulas AP, Jenkins TM, Michalsky MP, Helmrath MA, Brandt ML, Harmon CM, Zeller MH, Chen MK, Xanthakos SA, Horlick M, Buncher CR, Teen LC. Weight Loss and Health Status 3 Years after Bariatric Surgery in Adolescents. *N Engl J Med.* 2016;374(2):113-123.





Our 2016 Scientific Achievements

Our growing team of scientists, based in more than 50 research divisions and institutes, produced more than 2,200 peer-reviewed journal articles, book chapters and other publications in FY2016. The following pages feature the most significant publication from each of our research divisions.

HPV Vaccine Visits Provide Key Moment for Education



Tanya Mullins, MD, MS



Jessica Kahn, MD, MPH

PUBLISHED JULY 31, 2015

Vaccine

Clinicians have a “golden moment for education” of teen-age girls and their mothers during a girl’s first vaccination against the sexually transmitted human papilloma virus (HPV).

A team from the Division of Adolescent and Transition Medicine interviewed 25 teen girls and their mothers four times over 30 months after a girl’s first HPV vaccine at age 11-12. The researchers were interested in determining whether receiving the vaccine would improve understanding of other STD risks or affect sexual activity. Their findings were published July 31, 2015, in *Vaccine*.

Although HPV knowledge was poor at baseline, researchers found that most girls developed accurate HPV risk perceptions by 30 months. However, only half developed accurate risk perceptions about other sexually transmitted diseases (STDs).

Those who were increasingly knowledgeable about HPV were better able to articulate other STD risks and less likely to initiate sexual activity. The majority of teen girls also thought practicing safer sex was still important after vaccination, regardless of their knowledge level, risk perceptions, or sexual experience.

The initial vaccine visit, not follow-up booster visits, proved to be the primary opportunity to provide accurate information about infection risks and safer sex.

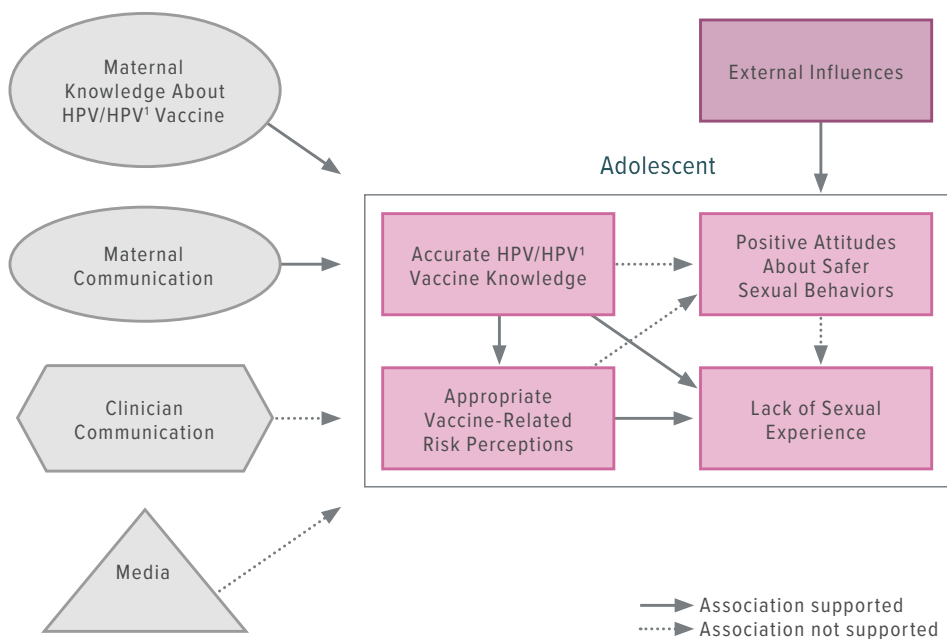
“Knowledge is such an incredible tool for understanding risk perceptions about safer sex,” says Tanya Mullins, MD, MS. “Most of the knowledge gained after that first vaccine visit was from outside the clinical setting—from the school or from moms.”

Mullins says the study should assure clinicians that their discussions about vaccines and STDs with teen girls have an impact. “However, we can do better, because there are girls who aren’t hearing the information at that first visit or who aren’t internalizing it.”

RESEARCH & TRAINING DETAILS

Faculty	16
Joint Appointment Faculty	2
Research Graduate Students	3
Total Annual Grant Awards	\$1.9M
Total Publications	60

Mullins TL, Widdice LE, Rosenthal SL, Zimet GD, Kahn JA. Risk perceptions, sexual attitudes, and sexual behavior after HPV vaccination in 11-12 year-old girls. *Vaccine*. 2015;33(32):3907-3912.



This diagram demonstrates the factors that affect accurate adolescent knowledge about human papilloma virus (HPV), the HPV vaccine, and vaccine-related risk perceptions.

Mucosal Mast Cells Play Role in Severe Allergic Reactions



Yui-Hsi Wang, PhD

RESEARCH & TRAINING DETAILS

Faculty	16
Joint Appointment Faculty	2
Research Fellows and Post Docs	8
Research Graduate Students	6
Total Annual Grant Awards	\$7.6M
Total Annual Industry Awards	\$1.M
Total Publications	50

Chen CY, Lee JB, Liu B, Ohta S, Wang PY, Kartashov AV, Mugge L, Abonia JP, Barski A, Izuhara K, Rothenberg ME, Finkelman FD, Hogan SP, Wang YH. Induction of Interleukin-9-Producing Mucosal Mast Cells Promotes Susceptibility to IgE-Mediated Experimental Food Allergy. *Immunity*. 2015;43(4):788-802.

PUBLISHED SEPT. 22, 2015

Immunity

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

This key finding, from a mouse study led by Yui-Hsi Wang, PhD, appeared online Sept. 22, 2015 in the journal *Immunity*. Insights from the study eventually could lead to a blood test to identify children at highest risk of anaphylactic shock triggered by the immune antibody IgE (immunoglobulin E).

MMC9 cells produce large amounts of interleukin 9 (IL-9), which amplifies 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.”

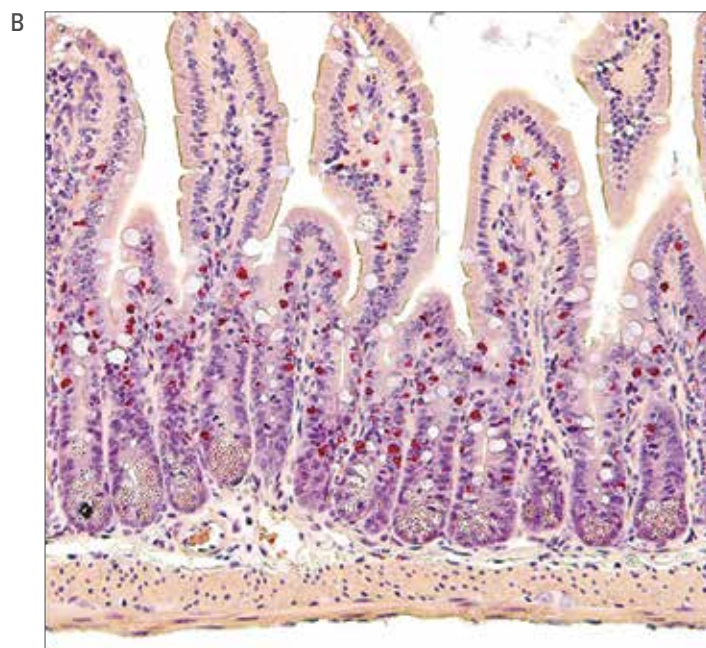
Peanuts, shellfish and a host of other foods can prompt the immune systems of some children to surge out of control. Without immediate intervention, the reaction can lead to diarrhea, hypothermia, respiratory distress, and shock.

About 40 percent of children have some IgE-associated food sensitivity, but only 8 percent of those children develop the severe reactions that can lead to shock, Wang says.

To verify that MMC9 cells were fueling severe allergic reactions, researchers treated the mice with an antibody that eliminated the cells. This resulted in decreased food allergy symptoms. When the team transferred MMC9 cells back into the same mice, the animals resumed exhibiting symptoms.

Researchers further linked this pathway to humans by analyzing small intestine biopsy samples from food allergy patients. The team found significantly increased expression of the IL-9 genetic transcript and other related transcripts.

Now the researchers are searching for the human equivalent of the MMC9 cells. If successful, their work ultimately may improve treatments to control dangerous food allergies.



A: This electron microscope image depicts a mucosal mast cell (MMC9).
B: These cells can secrete prodigious amounts of IL-9, which fueled intestinal allergy reactions shown here in mice.

Team Unlocks Connection Between Genetic Variants and Postoperative Morphine-induced Respiratory Depression



Senthilkumar Sadhasivam,
MD, MPH



Vidya Chidambaran, MD

RESEARCH & TRAINING DETAILS

Faculty	58
Joint Appointment Faculty	2
Research Fellows & Post Docs	9
Research Graduate Students	6
Total Annual Grant Awards	\$2.7M
Total Annual Industry Awards	\$151,890
Total Publications	65

Chidambaran V, Venkatasubramanian R, Zhang X, Martin LJ, Niu J, Mizuno T, Fukuda T, Meller J, Vinks AA, Sadhasivam S. ABCC3 genetic variants are associated with postoperative morphine-induced respiratory depression and morphine pharmacokinetics in children. *Pharmacogenomics J.* 2016 Jan 26. [Epub ahead of print]

PUBLISHED ONLINE JANUARY 26, 2016
The Pharmacogenomics Journal

Respiratory depression is among the most serious side effects of morphine-induced anesthesia. Now, researchers have found that genetic variants in children are crucial to ensuring safer, shorter post-operative stays.

The variants are in a liver transporter gene called ABCC3. This gene facilitates hepatic morphine metabolite efflux, the mechanism that allows morphine and its active metabolite to dissipate throughout the body.

The study, published in *The Pharmacogenomics Journal*, involved 316 children undergoing tonsillectomy.

The team found that children with these variants and respiratory depression had postoperative stays about three times longer than children without the variants. These are the first reports to show a direct association of ABCC3 variants with opioid-related respiratory depression.

Senthilkumar Sadhasivam, MD, MPH, and Vidya Chidambaran, MD, both of the Division of Anesthesia, led the study.

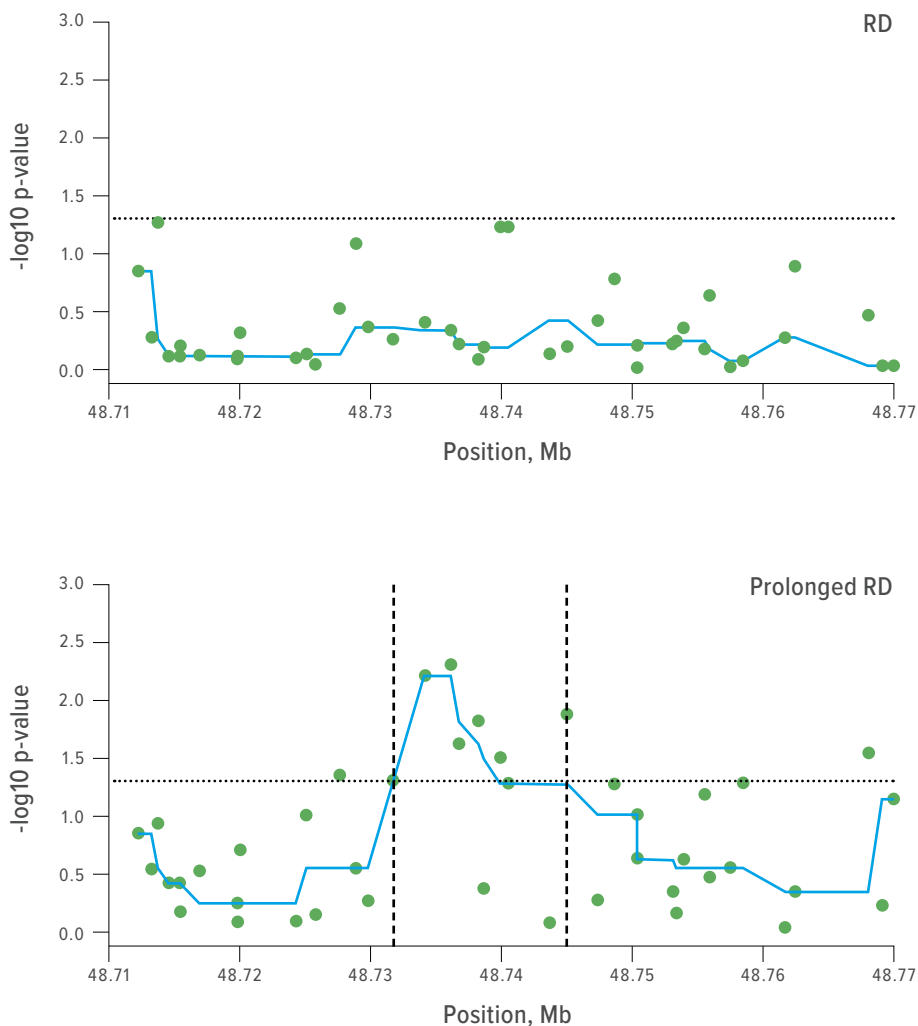
“If we can routinely do ABCC3 genotyping preoperatively,” Sadhasivam says, “we can reliably identify at-risk children and tailor their pain management to minimize their postoperative risk.”

For example, a genetic screening test could help guide perioperative strategies, including the possible use of fentanyl as an alternative to morphine.

The next steps for this research have already begun. The biotech company Assurex has licensed the team’s intellectual property, including associations with ABCC3 variants.

“We are excited that this discovery would come to clinical practice sooner because of this commercialization agreement,” Sadhasivam says.

Meanwhile, the team is working to develop clinical decision algorithms based on multiple genes to improve predictive reliability.



Researchers plotted the $-\log_{10}$ (p-values) of the single SNP association tested in additive models. The dotted reference lines show the $-\log_{10}$ (p-value of 0.05) level. Several ABCC3 SNPs between the vertical lines show significant association between prolonged post-operative stay and respiratory depression (RD). The p-values were smoothed using a running median represented by the blue line in both plots. The Y axis shows the $-\log_{10}$ p-values and the X axis shows the chromosomal positions of the ABCC3 polymorphisms (SNPs) on Chromosome 17.

Pollution-Related Asthma Response in African American Children Traced to TET1 Gene



Hong Ji, PhD

PUBLISHED MARCH 2016

Journal of Allergy and Clinical Immunology

Diesel exhaust particulates change the expression of the TET1 gene in airway epithelial cells, which may shed new light on why higher rates of asthma affect African American children.

This finding, published in March 2016 in the *Journal of Allergy and Clinical Immunology*, provides evidence that supports a long-suspected possible cause of asthma and the role played by traffic-related air pollution (TRAP).

“Our study demonstrated for the first time that DNA methylation at the TET1 promoter is associated with childhood asthma in African Americans, and methylation at the same CpG site was significantly associated with current exposure to TRAP,” says Hong Ji, PhD, lead author.

Under the direction of Gurjit (Neeru) Khurana Hershey, MD, PhD, Ji worked with colleagues in Asthma Research, Human Genetics and Biostatistics and Epidemiology.

The team studied nasal epithelial cells of African American children for DNA-derived methylation levels of the TET1 gene. They compared children with asthma against non-asthmatic siblings. They also overlaid the results with data about TRAP exposure.

The study identified TET1 and associated TET enzymes as possible direct players in the development of asthma. The team also observed that diesel exhaust particulates change the expression of the TET1 gene in airway epithelial cells. Specifically, asthma was significantly associated with both a loss of TET1 promoter methylation and increased levels of global 5-hydroxymethylcytosine (5-hmC).

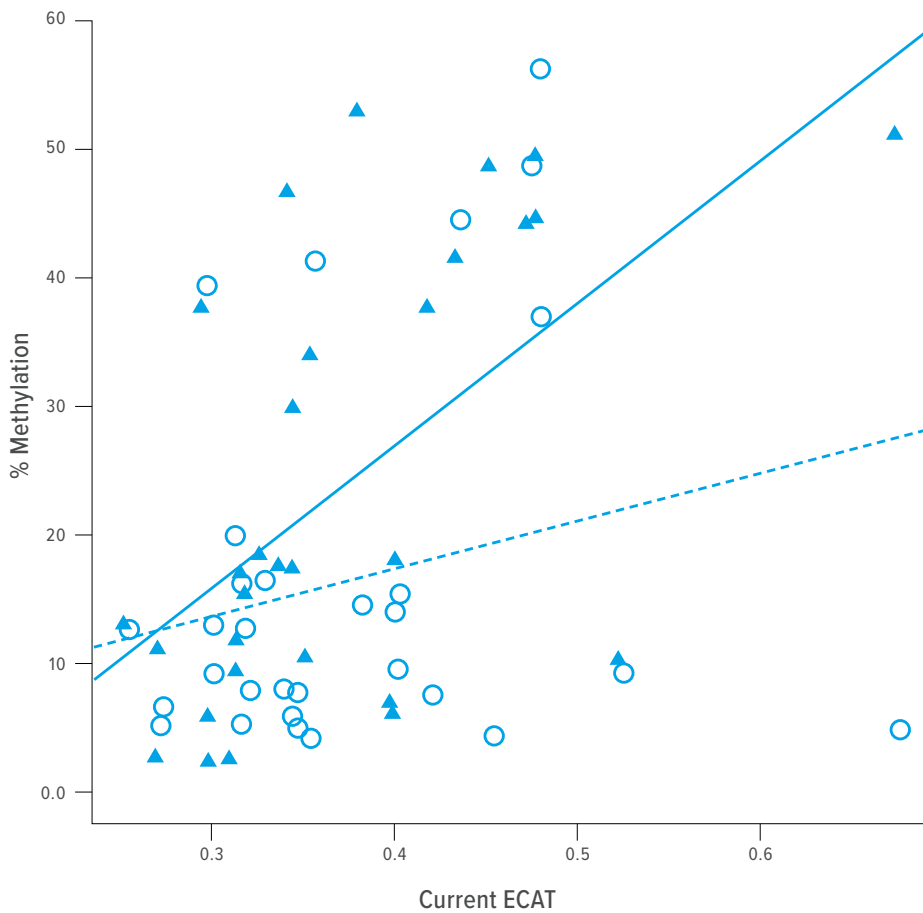
The study adds to the large role TET1 already plays in human development. Other studies have linked the gene to memory, brain function, leukemia, and more, Ji says.

Armed with new understanding of asthma’s epigenetic underpinnings, Ji says researchers can begin using animal models to learn more about how TET1 and other epigenetic enzymes affect asthma development. Eventually, this line of research could lead to new therapies and treatments.

RESEARCH & TRAINING DETAILS

Faculty	5
Research Fellows & Post Docs	6
Research Graduate Students	1
Total Annual Grant Awards	\$4M
Total Publications	23

Somineni HK, Zhang X, Biagini Myers JM, Kovacic MB, Ulm A, Jurcak N, Ryan PH, Khurana Hershey GK, Ji H. Ten-eleven translocation 1 (TET1) methylation is associated with childhood asthma and traffic-related air pollution. *J Allergy Clin Immunol.* 2016;137(3):797-805 e795.



This chart illustrates the influences of traffic-related air pollution (TRAP) on cg23602092 methylation and the association between cg23602092 methylation and asthma. Control subjects appear as solid triangles and asthmatic patients appear as open circles. The solid line shows the relationship between TRAP exposure (current ECAT value) and methylation for control subjects. The dashed line shows the relationship for asthmatic patients.

Symptoms of ‘Sluggish Cognitive Tempo’ Differ from ADHD, Deserve Further Study



Stephen Becker, PhD

PUBLISHED MARCH 2016

Journal of the American Academy of Child and Adolescent Psychiatry

Since the 1980s, behavioral medicine specialists have debated whether a set of attention-related difficulties in children—known as “sluggish cognitive tempo” (SCT)—were part of attention-deficit/hyperactivity disorder (ADHD).

Stephen Becker, PhD, a clinical psychologist in Behavioral Medicine and Clinical Psychology, conducted a meta-analysis of 73 SCT studies covering 19,000 participants. His team’s study concludes that “at least a subset of SCT symptoms is statistically distinct from the ADHD symptom dimensions and inattention specifically.”

Unlike overactive children with ADHD, the estimated 5 percent of children with SCT behaviors tend to be sluggish, underactive, slow processors. They are often described as drowsy, spacy, or “in a fog.” They are daydreamers who get lost in their thoughts or stare blankly into space, Becker says.

“SCT is a very untapped area of research, and increasingly study after study shows that these symptoms are directly related to issues that matter, issues we care about in children: academic function, relationships with peers, sleep functioning,” Becker says. “This analysis is the strongest evidence to date to show that the attention-related symptoms in this construct are not the same thing as ADHD. They’re something different, and they’re significantly associated with impairment.”

Further studies could explore:

- SCT’s impact on academic performance
- The potential benefits of social skills training
- And whether treatments other than stimulants are better suited for children with SCT behaviors

“With SCT, we are where ADHD was 30 to 40 years ago,” Becker says. “As research unfolds, we hope to have a better idea of what these symptoms mean for assessment and treatment.”

RESEARCH & TRAINING DETAILS

Faculty	49
Joint Appointment Faculty	2
Research Fellows & Post Docs	6
Research Graduate Students	58
Total Annual Grant Awards	\$9.4M
Total Publications	142

Becker SP, Leopold DR, Burns GL, Jarrett MA, Langberg JM, Marshall SA, McBurnett K, Waschbusch DA, Willcutt EG. The Internal, External, and Diagnostic Validity of Sluggish Cognitive Tempo: A Meta-Analysis and Critical Review. *J Am Acad Child Adolesc Psychiatry*. 2016;55(3):163-178.

Sluggish Cognitive Tempo (SCT) Construct

Item Content	Mean factor loading on an SCT factor
Sluggish	0.80
Tired/lethargic	0.80
Slow thinking/processing	0.80
Loses train of thought/cognitive set	0.79
Sleepy/drowsy	0.79
Spacey	0.78
In a fog	0.77
Underactive/slow moving	0.77
Daydreams	0.75
Lost in thoughts	0.75
Stares blankly	0.74
Easily confused	0.74
Apathetic/unmotivated	0.72
Absentminded	0.61
Slow work/task completion	0.59
Low initiative and persistence	0.50
Poor listening/difficulty with instructions	0.50
Easily bored	0.38

Note. The 13 items in bold were identified in this meta-analytic study as optimal SCT items that are separate from ADHD symptoms of inattention (mean factor loading >0.70).

How Machine Learning Can Make Clinical Trials More Successful



Yizhao Ni, PhD

RESEARCH & TRAINING DETAILS

Faculty	13
Joint Appointment Faculty	11
Research Fellows & Post Docs	1
Research Graduate Students	23
Total Annual Grant Awards	\$5.8M
Total Publications	55

Ni Y, Beck AF, Taylor R, Dyas J, Solti I, Grupp-Phelan J, Dexheimer JW. Will they participate? Predicting patients' response to clinical trial invitations in a pediatric emergency department. *J Am Med Inf Assoc* 2016:ocv216.

PUBLISHED APRIL 27, 2016
Journal of the American Medical Informatics Association

Scientists are teaching computers how to predict whether people will agree to participate in clinical trials. “Challenges with patient recruitment for clinical trials are a major barrier to timely and efficient translational research,” says Yizhao Ni, PhD, an instructor in the Division of Biomedical Informatics. “The ultimate goal of our research is to increase participation in clinical trials, and to help ensure that studies can be completed with meaningful data.”

Ni was lead author of a study published April 27, 2016, in the *Journal of the American Medical Informatics Association* that details the value of machine learning as a potential recruitment aid.

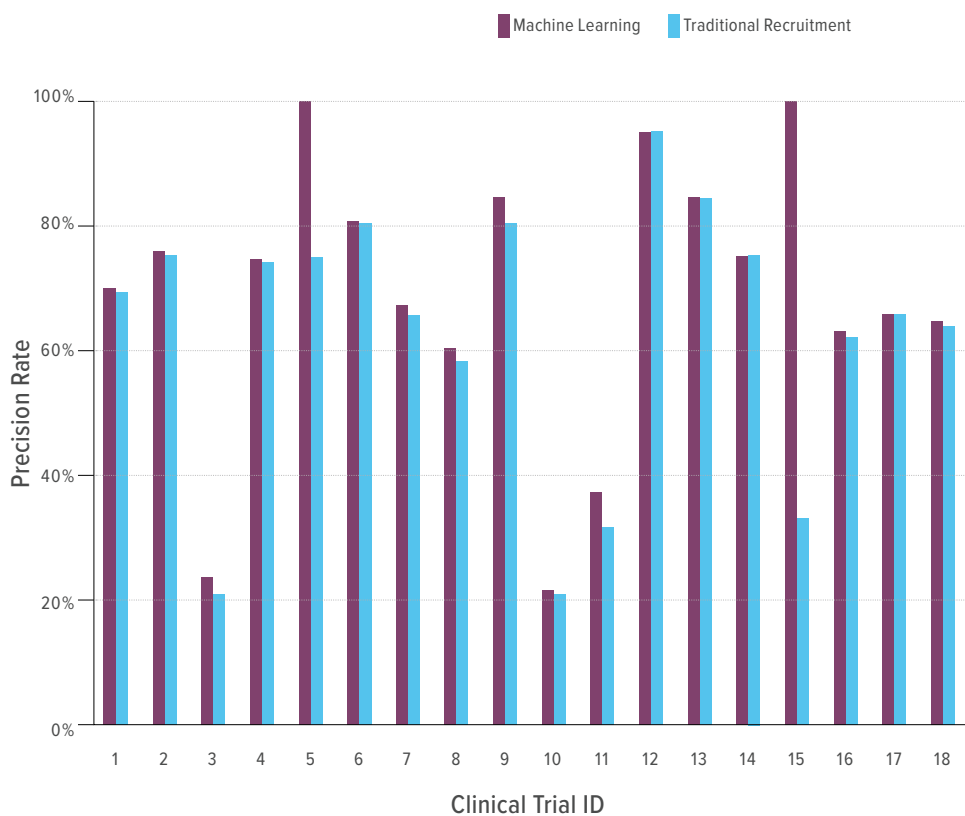
Ni and colleagues gathered demographic information from thousands of emergency department patients and families who were invited to join 18 studies over a three-year period. They also assembled clinical trial data about the complexity and time commitments involved.

The team’s new algorithm had a 72 percent accuracy rate at predicting which patients would agree to join a study. The actual rate, using traditional practices, was 60 percent.

The machine learning algorithm adjusted how to weigh factors including age, race, education, socioeconomic level, attitudes about medical research, and more. It ignored assumptions and biases that might have existed among staff recruiters.

It may be possible to push the algorithm’s accuracy beyond 72 percent, Ni says. However, a major challenge will be developing efficient ways to gather the data that automated algorithms need in real time. It remains difficult to process recruitment information in busy medical clinic environments.

Even so, by removing biases, machine learning algorithms eventually could help clinical research coordinators use the data they have to become more effective at matching patients with appropriate clinical studies, Ni says.



This chart compares the accuracy of machine learning algorithms vs. traditional recruitment at predicting whether families would agree to participate in clinical trials.

Community-Based Approach Improves Retention in Home Visiting Programs



Ted Folger, PhD



Robert Ammerman, PhD

RESEARCH & TRAINING DETAILS

Faculty	21
Joint Appointment Faculty	14
Research Fellows & Post Docs	2
Research Graduate Students	10
Total Annual Grant Awards	\$7.3M
Total Publications	168

Folger AT, Brentley AL, Goyal NK, Hall ES, Sa T, Peugh JL, Teeters AR, Van Ginkel JB, Ammerman RT. Evaluation of a Community-Based Approach to Strengthen Retention in Early Childhood Home Visiting. *Prev Sci.* 2016;17(1):52-61.

PUBLISHED JANUARY 2016
Prevention Science

Home visiting programs, known to support positive parenting and stress reduction during early child development, often face challenges in high-risk neighborhoods.

Families tend to be low-income. They move a lot. They often endure numerous crises, making it difficult for home visitors to sustain relationships.

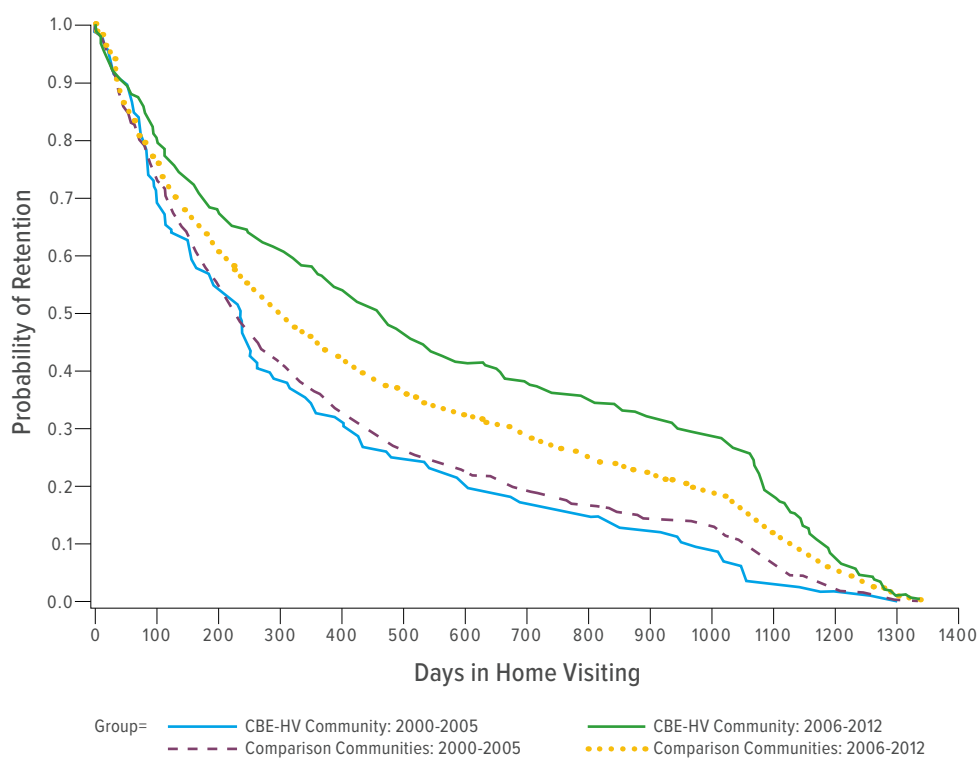
A study by the Division of Biostatistics and Epidemiology, in collaboration with Every Child Succeeds, finds that explicitly designed community-based enrichment approaches can boost parental engagement and increase retention in home visiting programs. The findings appeared January 2016 in *Prevention Science*.

The program in Cincinnati’s low-income Avondale neighborhood was designed with involvement from Avondale community, faith-based and business leaders, says epidemiologist and lead author Ted Folger, PhD. Starting in 2006, participating families received access to child care to attend regular support groups for mothers and fathers and a weekly free “pantry” to supply needed diapers, clothing and developmental toys for children. The program also hired neighborhood mothers to serve as community liaisons.

Compared to families in other high-risk Cincinnati neighborhoods, the Avondale families experienced on average 166 more enrolled days and seven additional home visits. The Avondale program also reported higher retention rates at 12 months (55 percent vs. 41 percent) and at 24 months (33 percent vs. 24 percent).

“This is about developing community-level influences that improve outreach and ensure a more optimal level and duration of support for the developing child,” Folger says. “If we can improve community-level engagement and support, we have a better chance of family buy-in and success.”

Further studies will examine how the community-based approach affects other measures of child health, safety and development.



This chart shows the probability of home visiting retention for mothers in the Community-Based Enrichment—Home Visitation (CBE-HV) group vs. comparison communities.

Vismodegib Shows Promise in Recurrent Medulloblastoma Sonic Hedgehog Subgroup



Maryam Fouladi, MD, MSc

The Cancer and Blood Diseases Institute (CBDI) includes the Divisions of Bone Marrow Transplant and Immune Deficiency, Experimental Hematology, Hematology, and Oncology

INSTITUTE RESEARCH & TRAINING DETAILS

Faculty	81
Joint Appointment Faculty	23
Research Fellows & Post Docs	38
Research Graduate Students	31
Total Annual Grant Awards	\$20M
Total Annual Industry Awards	\$4.6M
Total Publications	212

Robinson GW, Orr BA, Wu G, Gururangan S, Lin T, Qaddoumi I, Packer RJ, Goldman S, Prados MD, Desjardins A, Chintagumpala M, Takebe N, Kaste SC, Rusch M, Allen SJ, Onar-Thomas A, Stewart CF, Fouladi M, Boyett JM, Gilbertson RJ, Curran T, Ellison DW, Gajjar A. Vismodegib Exerts Targeted Efficacy Against Recurrent Sonic Hedgehog-Subgroup Medulloblastoma: Results From Phase II Pediatric Brain Tumor Consortium Studies PBTC-025B and PBTC-032. *J. Clin. Oncol.* 2015;33(24):2646-2654.

PUBLISHED AUG. 20, 2015
Journal of Clinical Oncology

A drug that has helped some people with basal cell carcinoma also shows promise as an improved therapy for a subgroup of people with recurrent medulloblastomas.

Vismodegib provided longer periods of progression-free survival (PFS), but only when tumors belonged to a sonic hedgehog molecular subgroup (SHH-MB), according to findings from two phase II Pediatric Brain Tumor Consortium clinical trials.

Cincinnati Children’s brain tumor expert Maryam Fouladi, MD, MSc, was among the leading co-authors.

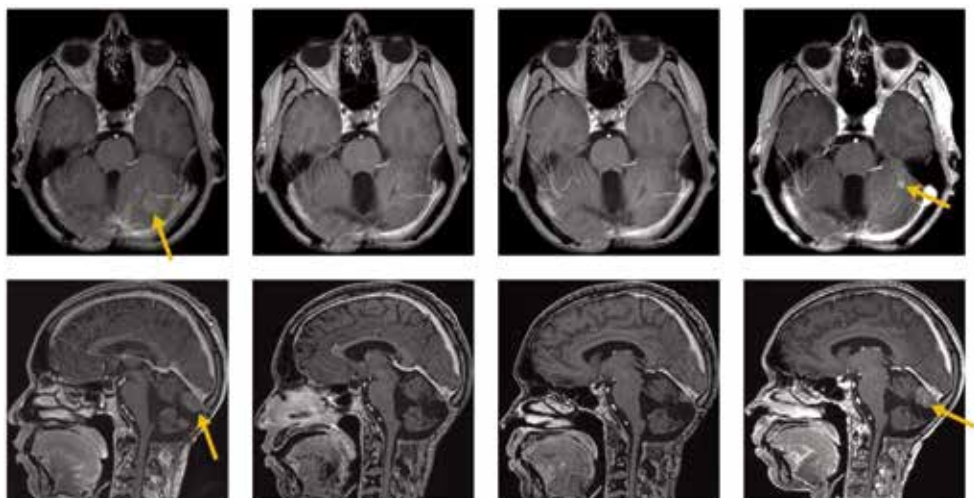
The combined study involved 43 adult and pediatric patients with recurrent medulloblastomas. Investigators conducted brain scans, gene sequencing tests and drug activity evaluations as participants received the drug.

Disease progression ultimately occurred in all patients. However, prolonged disease stabilization occurred in 41 percent of patients in the SHH-MB subgroup. The longest progression-free periods lasted from about six months to more than 15 months.

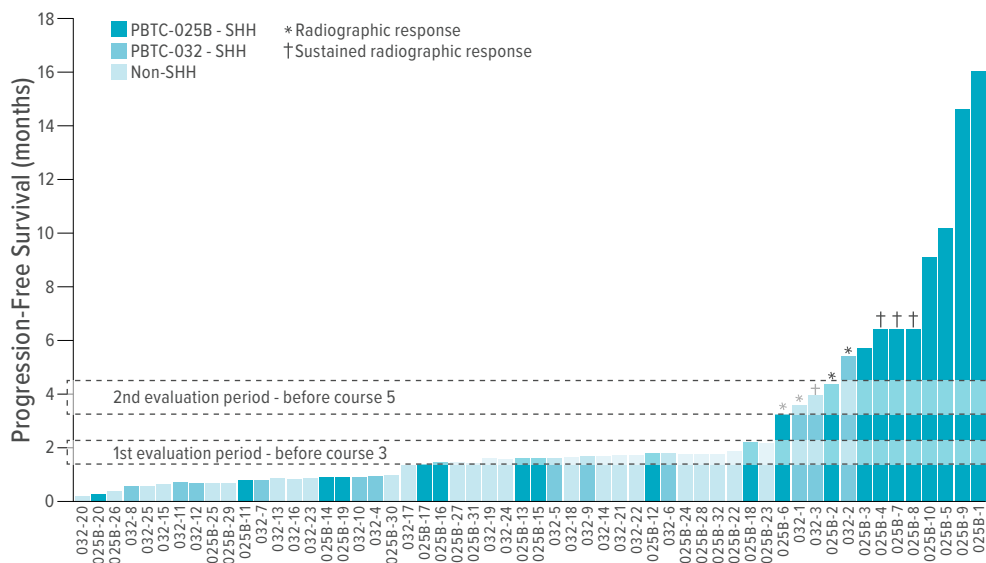
“This finding is significant because the SHH subgroup accounts for about 30 percent of all medulloblastomas,” Fouladi says. “However, much more investigation is needed to address the challenges that also emerged in this study.”

While the drug showed benefit for some adult patients and one child, this study lacked enough children with SHH tumors to make conclusions about pediatric benefit. In recent years, experts have learned that adult-onset medulloblastomas are much more likely to be in the SHH subgroup.

Even for those who did benefit, tumor growth ultimately resumed. Strategies to overcome drug resistance are essential. The study also underscores the importance of complete molecular profiling of medulloblastomas. Drugs such as vismodegib will live up to their promise only if their use focuses on precisely targeted populations, the study authors say.



These magnetic resonance images show responses in two patients with recurrent sonic hedgehog–subgroup medulloblastoma (MB) treated with vismodegib. Images were obtained at the start of therapy and at 2, 4, and 6 months after. Gold arrows indicate recurrent lesions. After initial response, MB recurs locally.



This bar graph depicts time to disease progression. Only patients with sonic hedgehog subgroup medulloblastoma (SHH-MB) who were enrolled onto PBTC-025B (blue shades) or PBTC-032 (light blue shades) remained progression free until second evaluation period.

Two-Step Gene Therapy Shows Early Promise in Treating High-Grade Gliomas



Qing Richard Lu, PhD

INSTITUTE RESEARCH & TRAINING DETAILS

Faculty	81
Joint Appointment Faculty	23
Total Annual Grant Awards	\$20M
Total Annual Industry Awards	\$4.6M
Total Publications	212

Lu F, Chen Y, Zhao C, Wang H, He D, Xu L, Wang J, He X, Deng Y, Lu EE, Liu X, Verma R, Bu H, Drissi R, Fouladi M, Stemmer-Rachamimov AO, Burns D, Xin M, Rubin JB, Bahassi el M, Canoll P, Holland EC, Lu QR. Olig2-Dependent Reciprocal Shift in PDGF and EGF Receptor Signaling Regulates Tumor Phenotype and Mitotic Growth in Malignant Glioma. *Cancer Cell*. 2016;29(5):669-683.

PUBLISHED MAY 9, 2016
Cancer Cell

Words like “victory” rarely get used when talking about treatments for aggressive high-grade glioma and glioblastoma. The conversation more commonly turns to a sad prognosis focused on how long a child has to live.

However, scientists in our Cancer and Blood Diseases Institute have scored an early-stage research win.

In a study published in May 2016, scientists tested a form of “suicide gene therapy,” an approach that blocks glioma formation by eliminating Olig2-producing tumor cells. In mouse models, the team shut down Olig2, a gene long implicated in forming high-grade gliomas. This changed the tumors’ cellular makeup, making them vulnerable to follow-up treatment.

This was the first blow in a one-two punch.

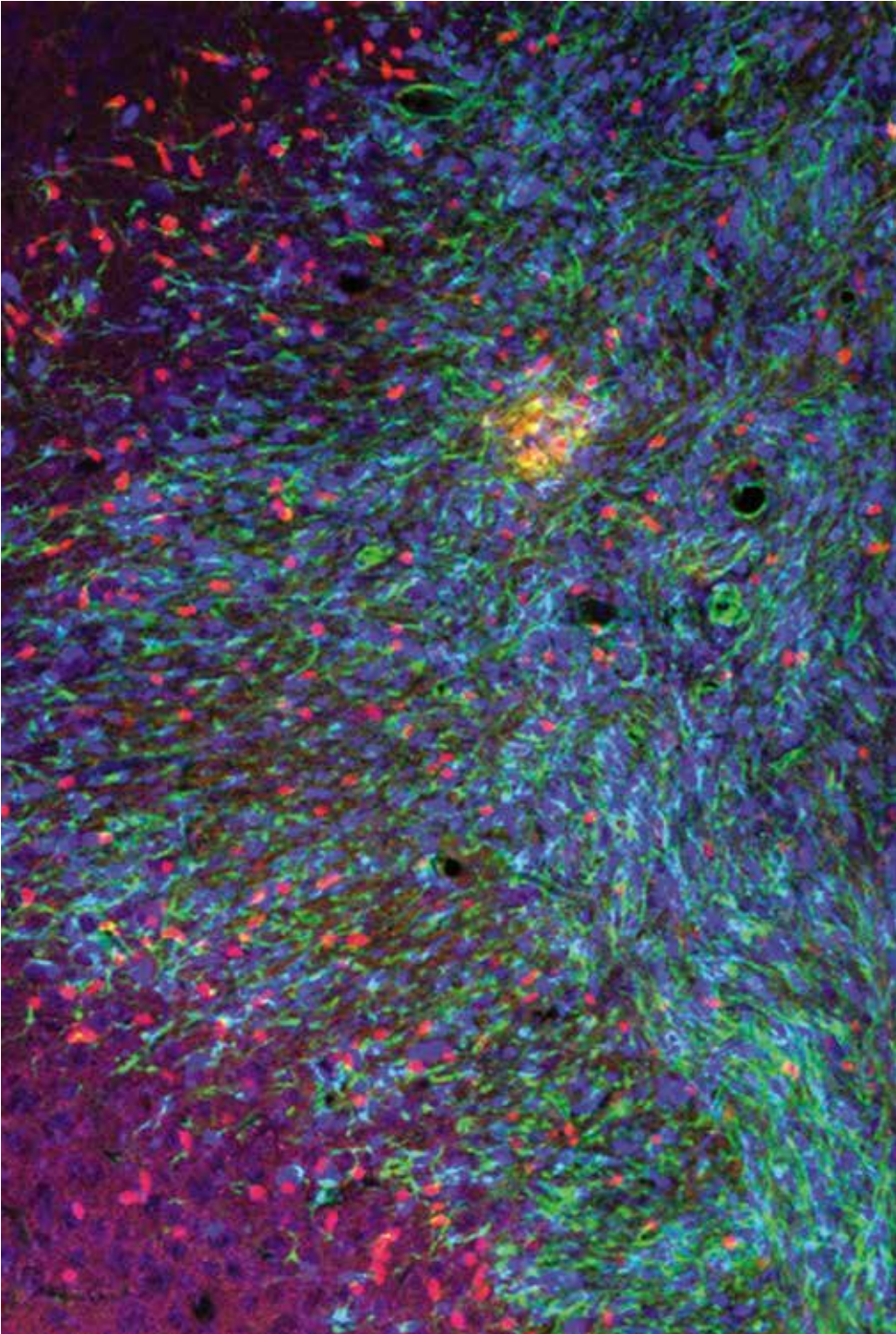
“By inhibiting Olig2 in tumor-forming cells, we were able to change the tumor cells’ makeup and sensitize them to targeted molecular treatment. This suggests a proof-of-principle for stratified therapy in distinct subtypes of malignant gliomas,” says Qing Richard Lu, PhD, lead investigator.

Once altered, the proneural cancer cells behaved more like astrocytes, which produce high levels of epidermal growth factor receptor (EGFR). This protein is a common target for effective chemotherapies against other types of cancer.

Using the drug gefitinib to block EGFR in the mice, Lu and colleagues halted the brain cancers.

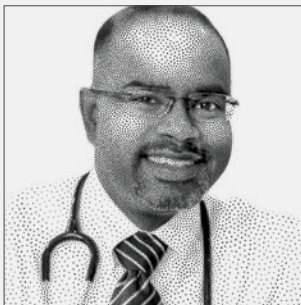
Translating this finding into a human clinical trial will require much more study and testing. However, the progress was significant enough to attract a commentary written by Rebecca Ihrie, PhD, and Nalin Leelatian, MD, of Vanderbilt University.

“Intriguingly (the study) provides insight into an experimental paradigm that enables further exploration of how tumor phenotypes may evolve during treatment,” they wrote. The findings represent “exciting steps toward identifying, restricting, and killing elusive cell populations.”



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

Interferon Shows No Benefit in EURAMOS-1 Trial



Rajaram Nagarajan, MD, MS

INSTITUTE RESEARCH & TRAINING DETAILS

Faculty	81
Joint Appointment Faculty	23
Total Annual Grant Awards	\$20M
Total Annual Industry Awards	\$4.6M
Total Publications	212

Bielack SS, Smeland S, Whelan JS, Marina N, Jovic G, Hook JM, Krailo MD, Gebhardt M, Papai Z, Meyer J, Nadel H, Randall RL, Deffenbaugh C, Nagarajan R, Brennan B, Letson GD, Teot LA, Goorin A, Baumhoer D, Kager L, Werner M, Lau CC, Sundby Hall K, Gelderblom H, Meyers P, Gorlick R, Windhager R, Helmke K, Eriksson M, Hoogerbrugge PM, Schomberg P, Tunn PU, Kuhne T, Jurgens H, van den Berg H, Bohling T, Picton S, Renard M, Reichardt P, Gerss J, Butterfass-Bahloul T, Morris C, Hogendoorn PC, Seddon B, Calaminus G, Michelagnoli M, Dhooge C, Sydes MR, Bernstein M, EUROMOS-1 investigators. Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial. *J. Clin. Oncol.* 2015;33(20):2279-2287.

PUBLISHED JULY 10, 2015
Journal of Clinical Oncology

Adding pegylated interferon to post-surgery maintenance therapy for people with osteosarcoma showed no clear benefit beyond existing standard chemotherapy, according to recent findings from the ongoing EURAMOS-1 clinical trial.

Rajaram Nagarajan, MD, MS, Clinical Director for Oncology, was among the leading co-authors on the paper, which reports results from one of multiple studies under way through a large-scale, international clinical trial group. Details were published in July 2015 in the *Journal of Clinical Oncology*.

The European and American Osteosarcoma Study Group (EURAMOS) was founded in 2001 to improve survival rates for the most common form of bone cancer affecting children. The group’s first study, EURAMOS-1, was launched in 2005.

Cincinnati Children’s is a member of the Children’s Oncology Group (COG), one of four major pediatric oncology groups involved in EURAMOS. Nagarajan helped develop the Quality of Life Study component of the trial. Analysis continues for those results.

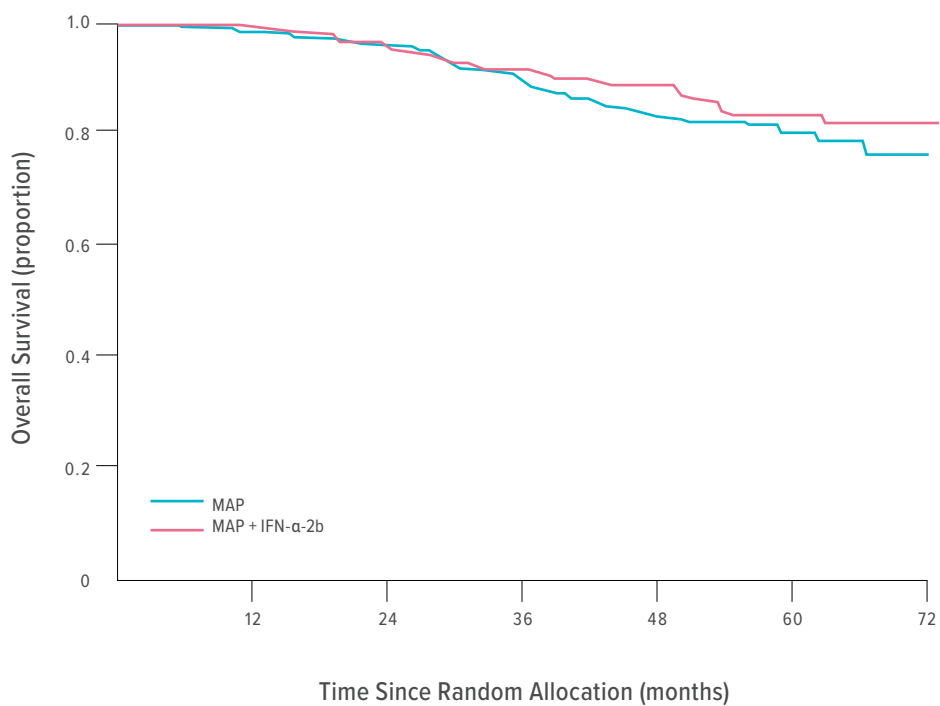
With more than 2,200 patients registered from more than 300 medical centers, EURAMOS is the largest osteosarcoma study ever conducted. The study involved 716 patients.

The team found that 77 percent of patients receiving pegylated interferon alfa-2b (IFN- α -2b) survived three years with no further cancer events, compared to 74 percent without adding interferon. The difference was not statistically significant.

“No change in practice is indicated by these data,” authors wrote.

Nagarajan says the study proves that a large, international collaboration can produce useful results, which builds a foundation for future clinical trials.

“Though these results were negative, it helped answer the question of whether interferon was beneficial,” he says. “Now, focus can be placed on other therapeutic modalities and drugs.”



This graph shows minimal difference between overall survival rates for people with osteosarcoma when treated with MAP chemotherapy (methotrexate, doxorubicin and cisplatin) versus receiving MAP plus interferon therapy.

Mimics of MicroRNA-130b May Hold a Key to Blocking Lupus-Related Kidney Damage



Nan Shen, MD



John Harley, MD, PhD

RESEARCH & TRAINING DETAILS

Faculty	11
Joint Appointment Faculty	3
Research Fellows & Post Docs	8
Research Graduate Students	12
Total Annual Grant Awards	\$5.8M
Total Publications	40

Zhou S, Shen N. MicroRNA-130b Ameliorates Murine Lupus Nephritis Through Targeting the Type I Interferon Pathway on Renal Mesangial Cells. *Arthritis Rheumatol.* 2016;68(9):2232-2243.

PUBLISHED APRIL 25, 2016
Arthritis & Rheumatology

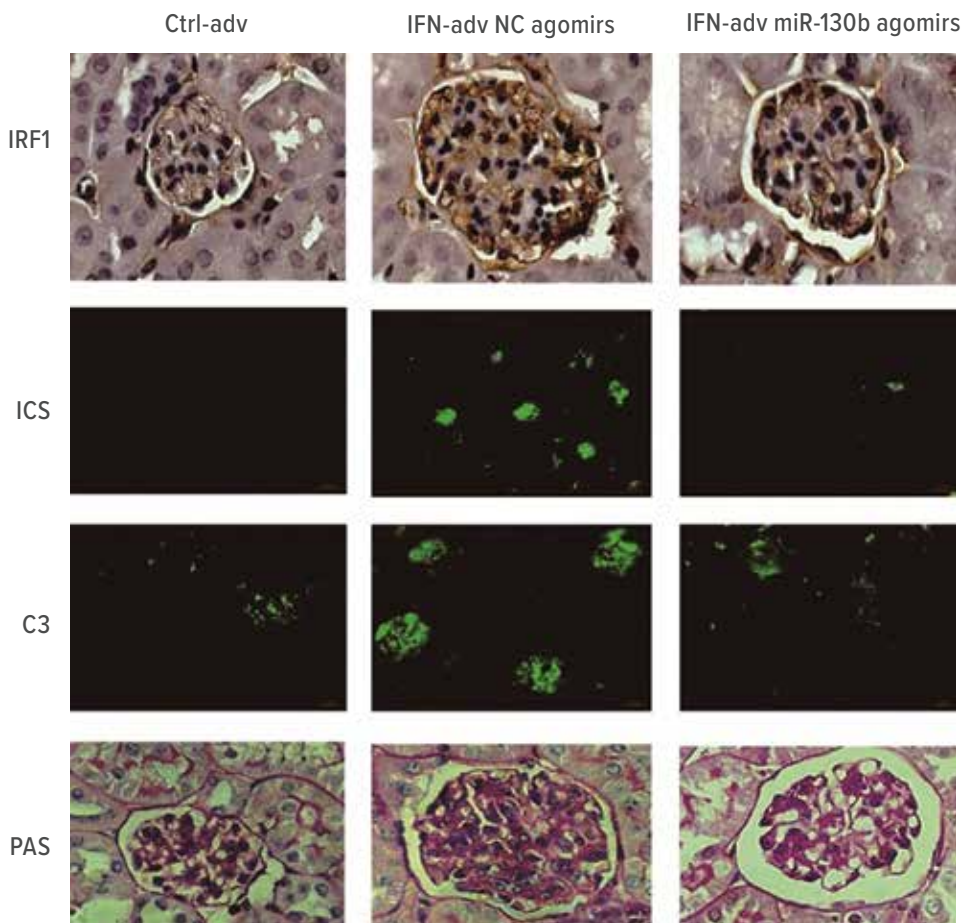
Experts have known for some time that Type I interferon (IFN) plays a critical role in the progression of lupus nephritis (LN), a dangerous complication that affects as many as 60 percent of people with lupus at some point in their lives. Now, a team of scientists from Cincinnati Children’s and several institutions in China has tracked down a specific microRNA that controls the IFN pathway in renal cells. Their findings appear in the April 2016 issue of *Arthritis & Rheumatology*.

Their analysis shows that microRNA-130b (miR-130b) is under-expressed in kidney tissues of patients and lupus-prone mice. This under-expression correlates with heightened abnormal activation of the IFN response in LN patients. Overexpression of a synthetic mimic of miR-130b in mice reduced kidney damage. Testing found decreased proteinuria, lower levels of immune complex deposition, and lack of glomerular lesions.

“Showing that manipulating this novel disease pathway regulator is possible is an important first step toward developing new, potentially life-saving treatments for people with lupus,” says John Harley, MD, PhD, Director of the Center for Autoimmune Genomics and Etiology (CAGE).

Currently, doctors use corticosteroids, immune-suppressing agents and other drugs to control LN. However, these drugs pose serious side-effect risks. A new option would be welcome because even with treatment, some patients develop kidney failure and require dialysis and/or a kidney transplant to survive.

To advance these findings, Harley and colleagues plan to evaluate this and other mimics and antagonists of miRNAs for their impact on the processes that lead to lupus and LN.



These images show the deposition of immune complexes and the complement protein C3, as analyzed by immunofluorescence. PAS-stained kidney sections were analyzed for renal lesion scores, which showed that miR-130b agomir ameliorated interferon- α -accelerated lupus nephritis (LN) in mice.

Computer Models Combine Growth and Disease Patterns with Real-Time Patient Data for Precision Drug Dosing



Alexander Vinks, PharmD, PhD



Tsuyoshi Fukuda, PhD

RESEARCH & TRAINING DETAILS

Faculty	4
Joint Appointment Faculty	3
Research Fellows & Post Docs	7
Research Graduate Students	1
Total Annual Grant Awards	\$77,445
Total Annual Industry Awards	\$282,532
Total Publications	27

Vinks AA, Emoto C, Fukuda T. Modeling and simulation in pediatric drug therapy: Application of pharmacometrics to define the right dose for children. *Clin Pharmacol Ther.* 2015;98(3):298-308.

PUBLISHED SEPT. 2015

Clinical Pharmacology & Therapeutics

Computer models maintained by Cincinnati Children's pharmacology researchers now use real-time patient data to give pediatricians worldwide better information on ideal drug dosing strategies for children.

These new models, described in the September 2016 issue of *Clinical Pharmacology & Therapeutics*, work effectively whether the patients are tiny premature infants, rapidly growing toddlers, or adolescents.

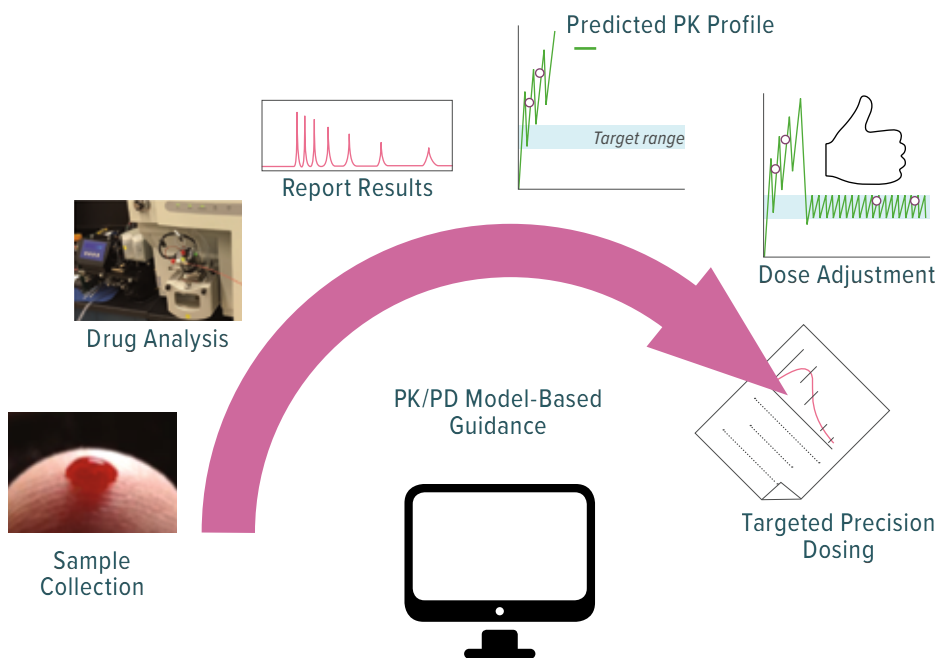
Alexander Vinks, PharmD, PhD, Director, Clinical Pharmacology, worked with colleagues Tsuyoshi Fukuda, PhD, and Chie Emoto, PhD, to describe how computer modeling applies to pharmacokinetics (how a drug moves within a body) and to pharmacodynamics (how a drug affects the body).

"This approach is very different from the current paradigm where for most drugs, we give incremental doses but don't have easy markers that we can use to tailor doses over time," Vinks says. "With pharmacokinetics modeling, we can track how growth spurts reflect on the behavior of the drug in the child, capture these growth patterns in computer models, and turn that into management information to predict effective doses."

The computer models serve as a "flight control center" that can allow doctors to adjust doses according to population-based models and real-time patient data. Such data can include age, gender, body weight, diagnosis, genotype, organ function, race, ethnicity, blood concentration levels, and enzyme functions.

Modeling also can support clinical study design and regulatory approval, processes still based on standard doses, safety and efficacy in average patients, Vinks says.

Eventually, he predicts that rising use of improved computer models will help produce "a new cadre of investigators well versed in pediatric clinical pharmacology, pharmacokinetics and pharmacogenetics."



Cela1 Protein Plays a Key Role in Postnatal Lung Development



Brian Varisco, MD

PUBLISHED OCTOBER 2015
The FASEB Journal

Even though lung biologists have a relatively deep understanding of the molecular mechanisms that regulate embryonic and fetal lung development, they understand less about the development and growth of the postnatal lung.

A study led by Brian Varisco, MD, identified a role for chymotrypsin-like elastase 1 (Cela1) protein in remodeling lung elastin in a stretch-dependent manner. Protein-level expression of Cela1 had previously been demonstrated only in the pancreas. The findings appeared October 2015 in *The FASEB Journal*.

Knowing that the postnatal lung is constantly exposed to cyclic stretch, the team used normal mouse lung development, the mouse pneumonectomy model of lung regeneration, and living mouse lung sections to test whether the expression and binding of Cela1 were stretch-dependent.

Among the results: Cela1 protein increased 176-fold during lung development, and an additional three-fold during lung regeneration. Stretch increased Cela1 binding to lung elastin by 46 percent. This binding occurred in areas of increased elastin remodeling.

Cela1 also was expressed in a subset of lung cells that reside in regions where multiple airspace walls come together. This indicates that Cela1 may play an important postnatal role in stretch-dependent remodeling of the peripheral lung.

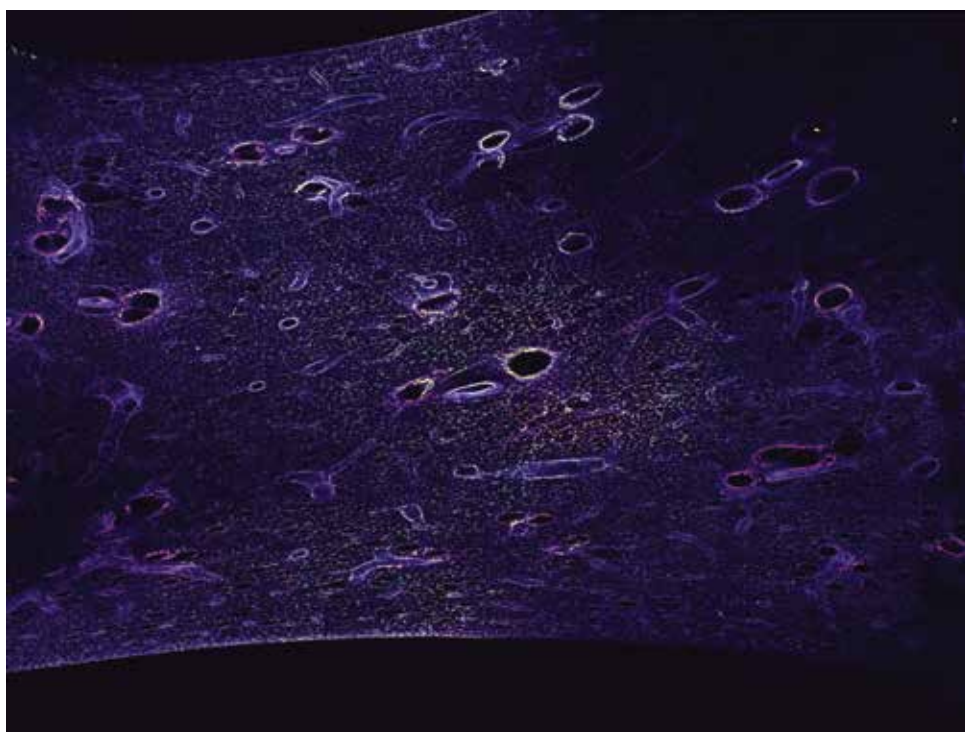
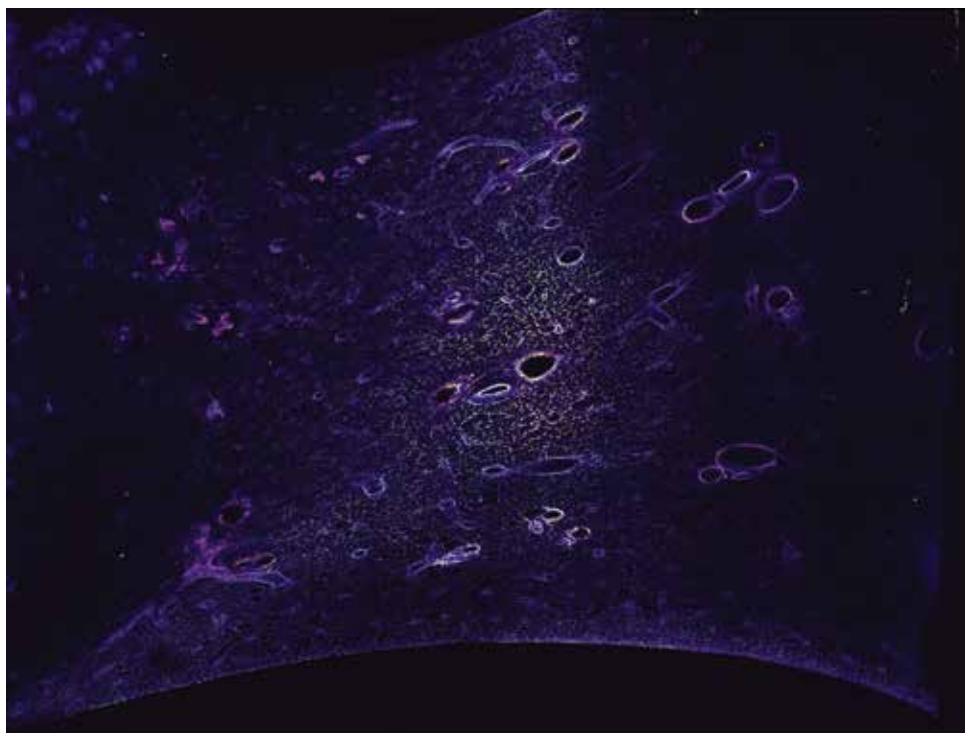
The team also found that the protease of Cela1 is neutralized by the Serpina1 (a-1-antitrypsin), a protein-coding gene associated with progressive emphysema. Thus, Cela1 may play a role in distal lung development and regeneration as well as in the airspace destruction triggered by alpha-1-antitrypsin deficiency.

Says Varisco: “These findings may lead to novel therapies targeting Cela1 in diseases of congenital or acquired distal airspace simplification.”

RESEARCH & TRAINING DETAILS

Faculty	13
Total Annual Grant Awards	\$2.6M
Total Annual Industry Awards	\$85,000
Total Publications	49

Joshi R, Liu S, Brown MD, Young SM, Battie M, Kofron JM, Xu Y, Weaver TE, Apsley K, Varisco BM. Stretch regulates expression and binding of chymotrypsin-like elastase 1 in the postnatal lung. *FASEB J.* 2016;30(2):590-600.



These before and after images of postnatal lung development in mice illustrate how Ccl1 binding and elastase activity increased with stretch.

Rising Sedation Use by Pediatric Dentists Reflects Changing Expectations



Stephen Wilson, DMD, PhD

PUBLISHED MARCH-APRIL 2016

Pediatric Dentistry

Sedation use is rising, especially among dentists working with school-aged children. Meanwhile, restraint use is declining.

These are some of the trends in pediatric dentistry detailed by a 25-year follow-up survey of members of the American Academy of Pediatric Dentistry (AAPD).

Stephen Wilson, DMD, PhD, recently retired Director of the Division of Dentistry, and Rutgers University professor emeritus Milton Houpt, DDS, PhD, examined findings from 1,642 responses to a 2010 AAPD survey. They compared the data to surveys conducted in 1985, 1991, 1995 and 2000.

Pediatric dentists still rely primarily on benzodiazepines and nitrous oxide to sedate their young patients. The use of restraints has steadily declined.

The most frequently used benzodiazepine has been diazepam (Valium). Other sedatives, used with or without nitrous oxide, have included midazolam (Versed), hydroxyzine (Vistaril) and choral hydrate.

The authors report an increase in sedation use by dentists in practice less than five years and more than 20 years, as well as regional variations. The highest rates of sedation occurred in the Southeast, with growing rates in the West, declining rates in the Midwest and stable rates in the Northeast.

Over the last two decades, sedation rates have declined for preschool-aged children, but have risen among the school-aged. Dentists indicating a rising use of sedatives say they: a) felt children needed sedation, b) were prepared to provide sedation, or c) found general anesthesia more difficult.

The increase reflects, in part, new sedation-related training requirements. However, other social factors also play a role.

“I think it’s a function of how our society is changing,” Wilson says. “Today’s parents don’t want their children to feel the discomfort of dental procedures.”

RESEARCH & TRAINING DETAILS

Faculty	7
Joint Appointment Faculty	1
Total Publications	4

Wilson S, Houpt M. Project USAP 2010: Use of Sedative Agents in Pediatric Dentistry—a 25-year Follow-up Survey. *Pediatr Dent*. 2016;38(2):127-133.

How Patients Are Monitored

Monitoring Method	% of practitioners who use sedation					
	1985 (N=1,003)	1991 (N=1,043)	1995 (N=1,138)	2000 (N=1,328)	2010 (N=1,066)	2010 (N=903)
Evaluate color	98	98	99	82	89	88
Use of precordial stethoscope	35	54	60	41	36	52
Monitor pulse	58	93	60	54	73	82
Monitor respiration	76	80	87	47	54	67
Monitor blood pressure	18	34	82	28	48	63
Use a pulse/oximeter	0	69	87	80	90	97
Use a capnography	0	0	2	4	5	12

Number and Percentage of Respondents Indicating Use of Regimens Across Percentage Distribution of Their Patient Pool

Regimen	N*	5-20†	21-40	41-60	61-80	>80
Diazepam and nitrous	361	67‡	11	5	5	11
Midazolam oral and nitrous	284	57	13	9	5	16
Hydroxyzine and nitrous	256	42	13	10	12	23
Chloral hydrate hydroxyzine and nitrous	238	34	7	13	11	35
Diazepam	195	70	9	6	2	14
Meperidine promethazine and nitrous	190	18	11	12	16	44
Hydroxyzine alone	184	48	10	4	8	30
Chloral hydrate meperidine and hydroxyzine	146	23	10	14	19	34
Chloral hydrate and nitrous	131	44	8	10	10	28
Chloral hydrate and hydroxyzine	104	39	10	13	12	27
Chloral hydrate alone	102	45	13	6	10	26
Midazolam nasal and nitrous	87	69	8	3	3	16
Midazolam meperidine and hydroxyzine	78	62	18	4	8	9
Meperidine and promethazine	62	37	11	10	6	35
Chloral hydrate promethazine and nitrous	54	43	24	13	9	11
Meperidine with nitrous	52	48	13	6	15	17
Chloral hydrate and promethazine	24	63	17	8	8	4
Meperidine	16	69	6	6	0	19

*Number of respondents reporting use of listed drug regimen.

†List of response categories in the survey of % of patients in respondent's practice.

‡% of sedated patients who receive listed drug regimen in their practice by response categories (e.g., in the first cell labeled 67, the interpretation is that 67 of 361 respondents indicated they use diazepam and nitrous for 1-20 of their patient pool).

Biological Response Modifiers Have Uses Beyond Psoriasis for Children and Adolescents



Kara Shah, MD, PhD



Fernanda Bellodi Schmidt, MD

PUBLISHED ONLINE NOV. 26, 2015

Pediatric Dermatology

An extensive medical literature review reveals an expanding role for biologic response modifiers in treating inflammatory dermatologic disorders other than psoriasis in children and adolescents.

The report, published in *Pediatric Dermatology*, was led by Kara Shah, MD, PhD, Director, Division of Dermatology; and Fernanda Bellodi Schmidt, MD, Clinical Director.

Previous studies indicate that biologics pose fewer safety risks than traditional immune-suppressing agents. However, doctors have limited experience treating children with biologics because most of the conditions studied are relatively rare and the drugs were developed for adults.

This study examined treatment regimens, doses, side effects and responses among children treated with etanercept, infliximab, ustekinumab, omalizumab and rituximab.

Their review found potential off-label uses for biologics including: omalizumab for atopic dermatitis; etanercept and other TNF- α antagonists for pyoderma gangrenosum and hidradentitis suppurativa (HS); and rituximab for autoimmune bullous diseases.

Since the study was published in print in early 2016, adalimumab has been approved for HS treatment in adults. Phase 2 clinical trials are evaluating the use of topical tofacitinib and injectable secukinumab and tralokinumab for alopecia areata in adults. Work continues to develop a biologic response modifier for severe atopic dermatitis.

“The hope is to raise awareness for other dermatologic conditions that also can benefit from treatment with biologics,” Schmidt says. “New and promising therapies are undergoing studies in adults. Further studies will be needed to investigate how children respond to these drugs.”

RESEARCH & TRAINING DETAILS

Faculty	3
Total Publications	2

.....

Bellodi-Schmidt F, Shah KN. Beyond Psoriasis: Novel Uses for Biologic Response Modifiers in Pediatric Dermatology. *Pediatr Dermatol*. 2016;33(1):18-27.



Some off-label uses of biologic response modifiers show promise for treating children with dermatologic conditions, including: omalizumab for atopic dermatitis (A); etanercept and other TNF- α antagonists for pyoderma gangrenosum (B); and rituximab for autoimmune bullous diseases (C).

Medication Use Patterns in Down Syndrome Change as Children Age, Develop



Julia Anixt, MD

PUBLISHED OCTOBER 2015

Journal of Developmental and Behavioral Pediatrics

Specialists who treat children and teens with Down syndrome sometimes encounter “diagnostic overshadowing,” a tendency to attribute a child’s behavior problems to the syndrome, rather than other common conditions.

Now a study that followed hundreds of children with Down syndrome has found that medication use over time follows the same patterns and levels of severity of common neurobehavioral problems reported across the age span.

The study reviewed electronic medical records of 832 patients covering 5,324 visits. Researchers tracked the use of central nervous system (CNS) stimulants, selective serotonin re-uptake inhibitors (SSRI), atypical antipsychotics (AAP), and alpha adrenergic agonists (AAG).

In general, children ages 12-21 were 25 percent more likely to be taking at least one medication compared to children ages 5-11 (17 percent). With each year of age, children aged 5-11 years showed rising odds of receiving stimulants. Typically, the drugs were used to treat attention and hyperactivity problems.

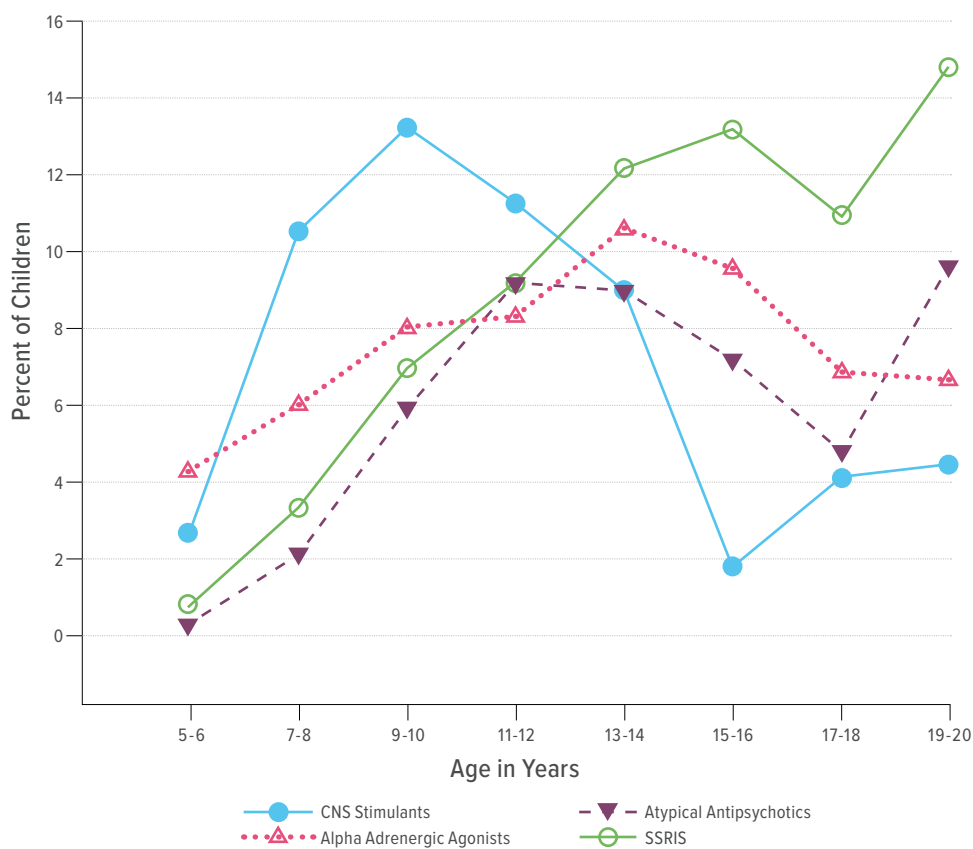
In children 12 and older, stimulant use decreased. However, prescription rates for SSRI and AAP medications were much higher than the younger group. Typically, doctors prescribed these medications to treat anxiety, depression, and other severe behavior problems.

“The pattern of medicine use seemed consistent with the types of problems we see clinically,” says Julia Anixt, MD, co-author of the study. “Behavior issues can become more complicated as children with Down syndrome age, and families may be more comfortable using medication to treat behavior problems in adolescents than in younger children.”

RESEARCH & TRAINING DETAILS

Faculty	18
Joint Appointment Faculty	1
Research Fellows & Post Docs	2
Total Annual Grant Awards	\$2.4M
Total Publications	26

Downes A, Anixt JS, Esbensen AJ, Wiley S, Meinzen-Derr J. Psychotropic Medication Use in Children and Adolescents With Down Syndrome. *J Dev Behav Pediatr.* 2015;36(8):613-619.



This figure shows the rates of medication use among children with Down syndrome, by age and category of medication.

Checklist, Video Laryngoscope and Experience Improve the Success of Rapid Sequence Intubation in Children



Benjamin Kerrey, MD



Srikant Iyer, MD, MPH

RESEARCH & TRAINING DETAILS

Faculty	46
Joint Appointment Faculty	3
Total Annual Grant Awards	\$2.8M
Total Publications	105

Kerrey BT, Mittiga MR, Rinderknecht AS, Varadarajan KR, Dyas JR, Geis GL, Luria JW, Frey ME, Jablonski TE, Iyer SB. Reducing the incidence of oxyhaemoglobin desaturation during rapid sequence intubation in a paediatric emergency department. *BMJ Qual Saf.* 2015;24(11):709-717.

PUBLISHED JULY 2015

BJM Quality & Safety Online First

The challenge of performing rapid sequence intubation in a pediatric emergency department is complicated by its relative rare use and a resulting lack of experience with the procedure by the care providers who must perform it.

However, a multi-year research effort led by the Division of Emergency Medicine demonstrates success at improving outcomes, according to a study published in July 2015 in *BJM Quality & Safety Online First*.

The project began with videotape analysis of intubations from 2009-2010. The team identified key factors associated with performance gaps, including oxyhemoglobin desaturation in 33 percent of cases and frequent prolonged laryngoscopy attempts.

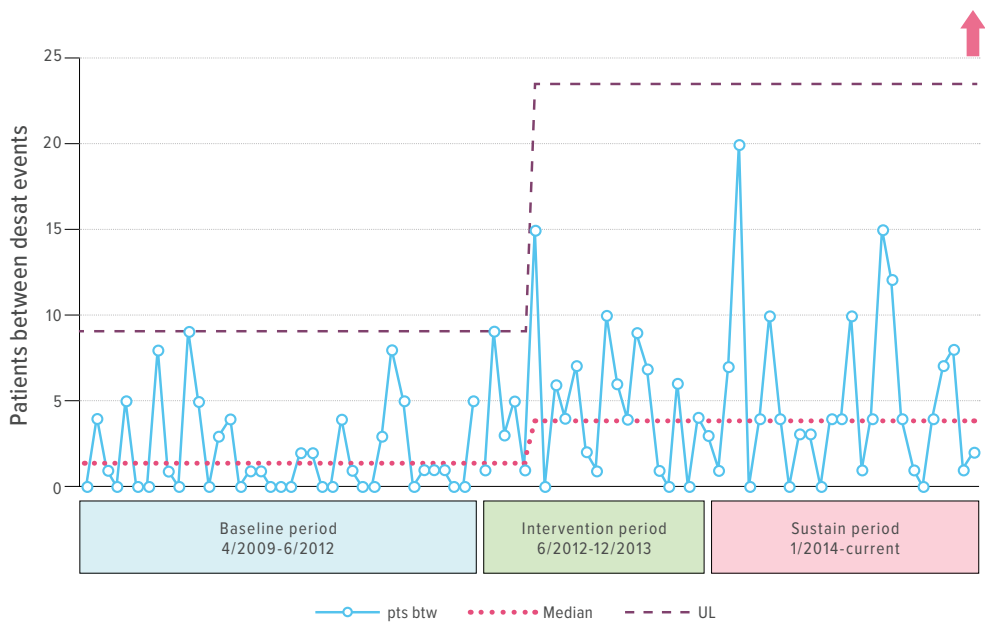
In 2012, an improvement initiative developed interventions to enhance safety and reliability. They included providing attending staff with a detailed checklist of specific intubation steps, use of a video laryngoscope, and restricting the procedure to more experienced providers.

Attending physicians Benjamin Kerrey, MD, and Srikant Iyer, MD, MPH, led an analysis of the changes, based on 75 videotaped intubations in 2015-2016. The team reports the near elimination of esophageal intubations and a reduction in children experiencing oxygen desaturation from 33 percent to 16 percent.

Now Kerrey is working with other institutions interested in adopting the Cincinnati-developed program.

“In a four-year period, we went from knowledge discovery through improvement and now into sustainability,” Kerrey says. “With safety as our focus, we reduced the rate of desaturation and got better at the procedure.”

Number of patients (undergoing RSI) between desaturation events



This statistical process control chart (G-chart) shows changes in the rate of oxyhaemoglobin desaturation during rapid sequence intubation.

Novel Genetic Mutation Linked to Rare Form of Short Stature



Andrew Dauber, MD, MMSc



Vivian Hwa, PhD

RESEARCH & TRAINING DETAILS

Faculty	17
Joint Appointment Faculty	3
Research Fellows & Post Docs	3
Total Annual Grant Awards	\$1.4M
Total Annual Industry Awards	\$169,754
Total Publications	56

Dauber A, Munoz-Calvo MT, Barrios V, Domene HM, Klopperpris S, Serra-Juhe C, Desikan V, Pozo J, Muzumdar R, Martos-Moreno GA, Hawkins F, Jasper HG, Conover CA, Frystyk J, Yakar S, Hwa V, Chowen JA, Oxvig C, Rosenfeld RG, Perez-Jurado LA, Argente J. Mutations in pregnancy-associated plasma protein A2 cause short stature due to low IGF-I availability. *EMBO Mol Med.* 2016;8(4):363-374.

PUBLISHED MARCH 2016
EMBO Molecular Medicine

A team of international researchers, led by Andrew Dauber, MD, MMSc, Director of the Cincinnati Center for Growth Disorders, has identified a new genetic mutation linked to a rare form of short stature in children.

The discovery gives endocrinologists around the world a new diagnosis to consider in children who present with idiopathic short stature, even in the presence of elevated concentrations of the insulin-like growth hormone IGF-I and IGFBP-3.

“This is essentially a mutation that affects the bioavailability and activity of IGF-1,” Dauber says.

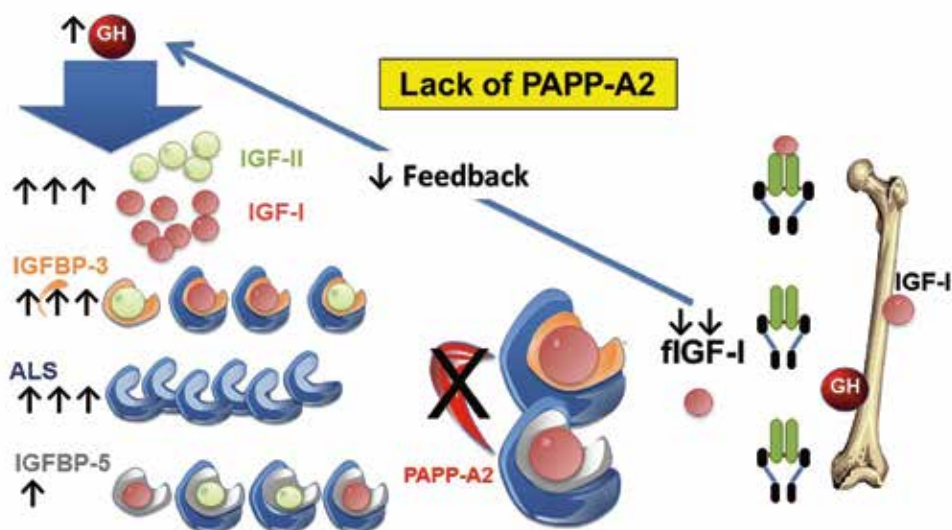
Dauber and co-researcher Vivian Hwa, PhD, worked with experts from Spain, Argentina, Denmark and throughout the U.S. to track down and study five children from two families that have the rare mutation. Their study appears in the March 2016 issue of *EMBO Molecular Medicine*.

In addition to short stature, these children exhibited small chins, mild microcephaly, longer fingers and toes, and elevated levels of IGF-1, ALS and IGFBP-3.

Using whole exome analysis, the team detected a loss-of-function mutation in the pregnancy-associated plasma protein A2, PAPP-A2. This mutation inhibits the body’s ability to cleave two of six specific IGF binding proteins, IGFBP-3 and -5, both of which are critical for the release of IGF-I for normal growth and development.

“These patients provide important insights into the regulation of longitudinal growth in humans, documenting the critical role of PAPP-A2 in releasing IGF-I from its binding proteins,” the authors wrote.

Dauber says the findings, duplicated in mouse models, also “indicate that understanding PAPP-A2 regulation and function will have important implications in both the clinical diagnosis of growth retardation and other areas of IGF-1 biology,” including insulin resistance, glucose control, cancer and longevity.



This illustration depicts the mechanism underlying growth failure due to lack of PAPP-A2. An increased formation of ternary complexes, due to decreased proteolysis subsequent to the lack of PAPP-A2 activity, results in reduced concentrations of fIGF-I in serum and most likely at specific target tissues. This also decreases the negative feedback effect of IGF-I on growth hormone (GH) production, contributing to increased circulating concentrations of GH. Increased serum GH concentrations cause increased IGF-I, IGFBP-3, and ALS concentrations. The increased levels of IGFBP-3 and ALS in turn contribute to further ternary complex formation and an increase in total IGF-I and IGF-II concentrations.

Quality Improvement Strategies Improve Adherence With Well Child Care Goals



Neera Goyal, MD, MSc

PUBLISHED DEC. 15, 2015
Child Abuse & Neglect

The same quality improvement strategies that have improved hospital care can also optimize the effectiveness of home visiting programs.

The study, published Dec. 15, 2015, in *Child Abuse & Neglect*, examined curriculum planning, visitor training, continuous program improvements, and family progress monitoring initiatives. These efforts increased adherence with recommended well-child care goals from 58 percent at baseline to 85 percent after three years, according to study author Neera Goyal, MD, MSc, Every Child Succeeds team member and attending physician in the Division of Neonatology.

The study tracked quality improvement cycles conducted at three agencies involving 18 home visitors and 139 families with infants under 6 months. Every Child Succeeds then helped implement best practices in programs located in seven counties in southwestern Ohio and Northern Kentucky.

In addition to informing parents about nutrition, child development, and community resources, Every Child Succeeds urges that infants complete at least three well-child visits by age 6 months.

“The real impact is to demonstrate the importance of ongoing, structured quality improvement efforts,” Goyal says. “Quality improvement is a widely accepted strategy in healthcare settings, but not necessarily in the home visiting arena. This represents a helpful model that can be used by other home visiting programs.”

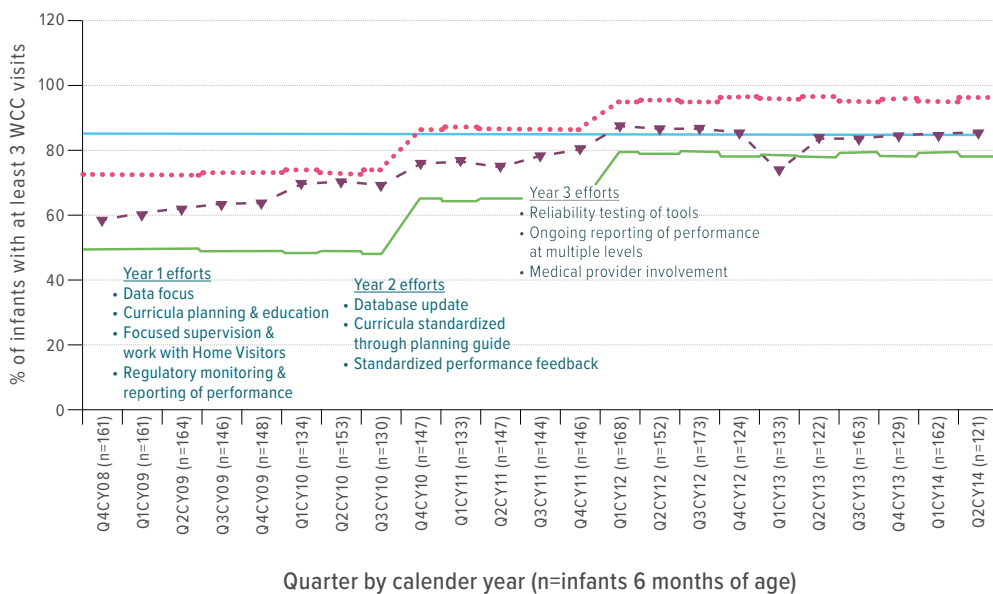
The findings also address funding requirements in the Affordable Care Act and other, more stringent requirements for home visiting programs. The shared information flowing from these initiatives could represent “a new frontier of cooperation between home visiting programs and primary medical centers,” Goyal says.

RESEARCH & TRAINING DETAILS

Faculty	1
Joint Appointment Faculty	1
Research Fellows & Post Docs	2
Total Publications	6

Goyal NK, Ammerman RT, Massie JA, Clark M, Van Ginkel JB. Using quality improvement to promote implementation and increase well child visits in home visiting. *Child Abuse Negl.* 2016;53:108-117.

Well child care (WCC) visits in first 6 months



This chart shows the impact of curricula planning, regular monitoring, focused supervision and other quality improvement interventions on the percentage of infants receiving three well-child visits within six months of birth.

Novel Bile Acid Drug Halts Progression of Sclerosing Cholangitis in Mice



Alexander Miethke, MD

RESEARCH & TRAINING DETAILS

Faculty	38
Joint Appointment Faculty	2
Research Fellows & Post Docs	10
Research Graduate Students	13
Total Annual Grant Awards	\$9.1M
Total Annual Industry Awards	\$100,997
Total Publications	142

Miethke AG, Zhang W, Simmons J, Taylor AE, Shi T, Shanmukhappa SK, Karns R, White S, Jegga AG, Lages CS, Nkinin S, Keller BT, Setchell KD. Pharmacological inhibition of apical sodium-dependent bile acid transporter changes bile composition and blocks progression of sclerosing cholangitis in multidrug resistance 2 knockout mice. *Hepatology*. 2016;63(2):512-523.

PUBLISHED FEBRUARY 2016

Hepatology

An experimental compound shows promising signs in mouse models of halting the progression of primary sclerosing cholangitis (PSC), a potentially fatal liver condition that affects about one in 100,000 children in the U.S.

The study, published in February 2016 in *Hepatology*, was led by Alexander Miethke, MD, Division of Pediatric Gastroenterology, Hepatology and Nutrition.

The study reports success with SC-435, a compound that inhibits the action of apical sodium-dependent bile acid transporter (ASBT). SC-435 prevents circulation of toxic bile acids that can lead to bile duct damage in the liver.

The research team started with a line of drug-resistant knockout mice. They fed the mice for two weeks with chow containing SC-435, then tracked bile acid and phospholipid levels.

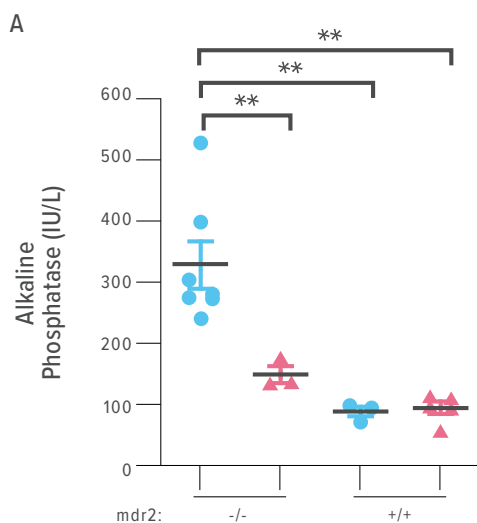
The experimental bile acid therapy was developed by Lumena Pharmaceutical Inc. It has been tested at Cincinnati Children's for a variety of cholestatic liver diseases.

"Treatment with SC-435 has a dramatic effect, not simply by reducing liver biochemistries like plasma levels for ALT or bilirubin, but also by actually halting progression of the disease," Miethke says. "Untreated mice progressed rapidly to fibrosis, exhibited classic signs of liver inflammation and bile duct damage and lost weight. Treated mice had nearly normal livers, did not develop fibrosis and gained weight."

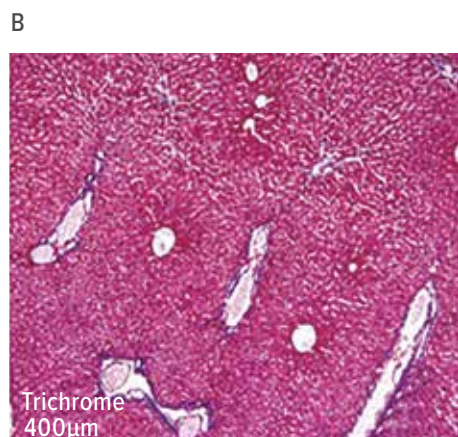
The finding, he says, can serve as a pre-clinical model to pursue clinical studies in children with PSC.

"There is no other treatment for this condition except liver transplantation. Even if transplanted, these children have a small risk for recurrence of the disease," Miethke says.

Replicating the success of SC-435 treatment in humans, he says, "would be quite amazing, especially if it shows that delivering the treatment early in the disease can prevent the progression of fibrosis."



A: This chart compares ALP levels in four groups of mice. Body weights were recorded throughout the 14 days of intervention. ALP levels were determined on blood sampled by cardiocentesis on DOT 14.

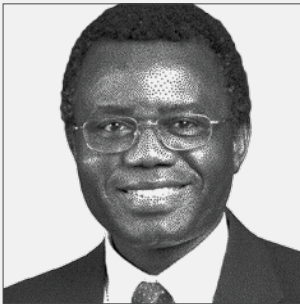


B: This section from a paraffin-embedded liver sample obtained from mdr2^{-/-} mice on DOT 14 was subjected to H&E and trichrome staining. Components of sclerosing cholangitis score (inflammation, ductal proliferation, necrosis, and fibrosis) were analyzed on a 1-41 scale.

Vitamin D Deficiency Impacts PICU Outcomes in India



Mark Steinhoff, MD



Adekunle Dawodu, MBBS

RESEARCH & TRAINING DETAILS

Faculty	3
Joint Appointment Faculty	5
Total Annual Grant Awards	\$774,778
Total Publications	5

Ebenezer K, Job V, Antonisamy B, Dawodu A, Manivachagan MN, Steinhoff M. Serum Vitamin D Status and Outcome among Critically Ill Children Admitted to the Pediatric Intensive Care Unit in South India. *Indian J Pediatr.* 2016;83(2):120-125.

PUBLISHED ONLINE JULY 19, 2015
Indian Journal of Pediatrics

When researchers analyzed the conditions of critically ill patients at a pediatric hospital in South India, they found a common thread between severity of illness and the need for mechanical ventilation.

The children were deficient in vitamin D. It was the first study of its kind to examine the association between vitamin D status and how children fare in the PICU.

Low serum 25(OH) D level was also connected to the use of vasocompressors, which increase blood pressure and are typically used to treat hypertension in critically ill patients.

The study was led by senior author Mark Steinhoff, MD, Director of Global Child Health, and included Adekunle Dawodu, MBBS, Director of International Patient Care and Education.

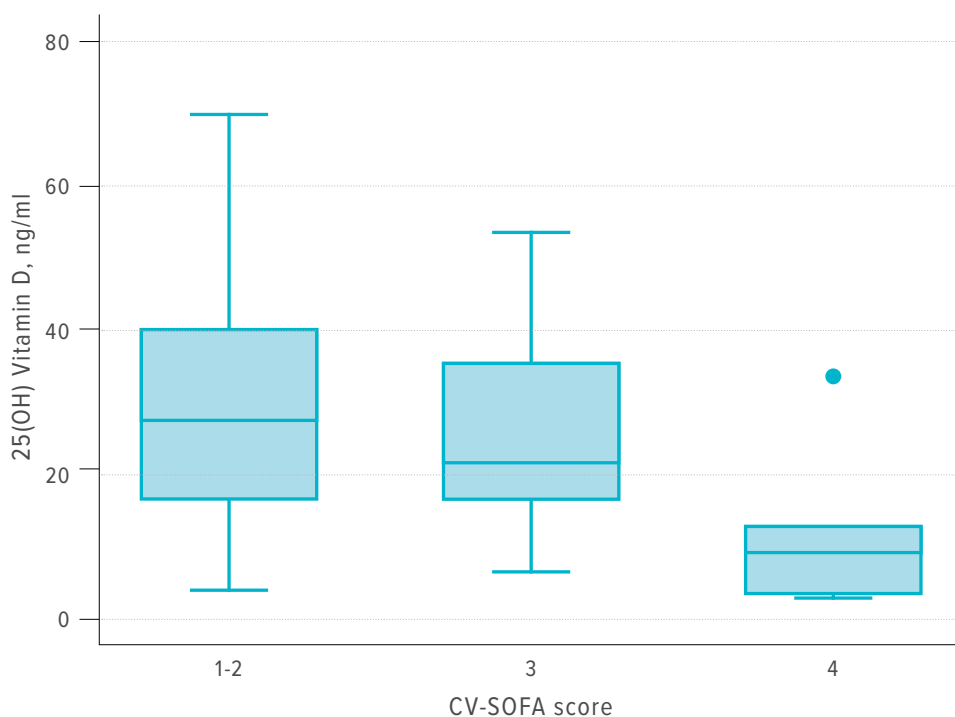
Vitamin D deficiency affects 75 to 90 percent of Indian children. Factors include the lack of vitamin D-fortified foods and lower levels of skin exposure to the sun.

“They have chronic illness which may be associated with low vitamin D,” Dawodu says. “Vitamin D deficiency also may be associated with the severity of illness among critically ill children.”

The team examined 54 such children, nearly 40 percent of whom were infants. The three most common reasons for their hospitalization were shock (31 percent), central nervous system conditions (23 percent) and respiratory illnesses (21 percent).

Vitamin D was once only related to bone health and calcium homeostasis, but scientists have discovered that most tissues and cells have vitamin D receptors, and that vitamin D impacts cardiovascular function, innate immunity, and cell growth and proliferation.

The authors urged that additional studies should examine the association of vitamin D and mortality rates, and that “prospective evaluations of the effect of vitamin D supplementation among critically ill children warrant urgent study.”



This figure shows the correlation between lower vitamin D levels and treatment by the use of a vasopressor, a class of drugs that induce vasoconstriction in blood vessels, which increases blood pressure. It is a common treatment for hypotension, particularly in critically ill patients in PICU.



Dr. Kala Ebenezer, at left, of Christian Medical College Hospital in Vellore, India, visits the team at Cincinnati Children's Division of Global Child Health. Mark Steinhoff, MD, the division's Director, is second from the right. The study on the correlation between vitamin D status and PICU outcomes was conducted at CMC Hospital.

BMIz Scores May Help Predict Carotid Artery Thickening, but Other Common Heart Disease Risk Factors Do Not



Elaine Urbina, MD, MS



Amy Shah, MD, MS

INSTITUTE RESEARCH & TRAINING DETAILS

Faculty	60
Joint Appointment Faculty	2
Research Fellows & Post Docs	22
Research Graduate Students	11
Total Annual Grant Awards	\$12.7M
Total Annual Industry Awards	\$719,459
Total Publications	233

Shah AS, Dabelea D, Fino NF, Dolan LM, Wadwa RP, D'Agostino R Jr, Hamman R, Marcovina S, Daniels SR, Urbina EM. Predictors of Increased Carotid Intima-Media Thickness in Youth With Type 1 Diabetes: The SEARCH CVD Study. *Diabetes Care*. 2016 Mar;39(3):418-25.

PUBLISHED MARCH 2016

Diabetes Care

When obesity gets worse for teens with type 1 diabetes, their carotid arteries get thicker and their risk of suffering a heart attack or stroke later in life rises.

However, other known heart disease risk factors, including smoking, high blood pressure and high hemoglobin A1c levels, do not appear to impact carotid artery thickness.

These findings underscore Body Mass Index Z-scores (BMIz), as a potentially modifiable risk factor for heart disease for children with type 1 diabetes. Unlike standard BMI measures for adults, BMIz scores show how body mass deviates from the norm as children grow.

"We found body mass index emerged as the only factor associated with a thicker carotid artery," says senior author, Elaine Urbina, MD, MS, Director of Preventive Cardiology at the Heart Institute. "This suggests that considerably more study is needed to fully understand the connections between childhood diabetes and heart disease."

Urbina, first author Amy Shah, MD, MS, in the Division of Endocrinology, and several colleagues in the SEARCH for Diabetes in Youth Study evaluated 298 children with type 1 diabetes to measure how heart disease risk factors changed over five years. The team evaluated BMIz, lipids, blood pressure, hemoglobin A1c, and smoking status. They also used ultrasound to measure the carotid artery.

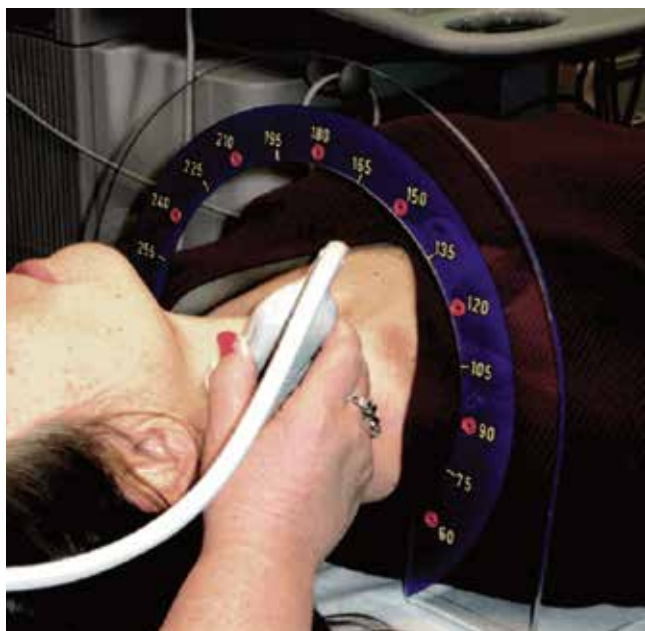
After five years, 53 percent of participants showed signs of two or more heart disease risk factors, a clear increase over baseline. The one change that showed statistically significant impact: 34 percent of children demonstrated high BMIz scores after five years, up from 27 percent when the study began.

Previous studies led by Urbina and Shah established that youths with type I diabetes can show surprising early signs of atherosclerosis. "Our new findings indicate that controlling obesity may be one of the most impactful approaches for minimizing heart disease risk for these children," Shah says.

A



B



A: An ultrasound image detects carotid artery thickening in a teen with type 1 diabetes. A study published in *Diabetes Care* reports that elevated BMIz scores were the only one of several cardiovascular risk factors that were associated with carotid artery thickening.

B: This image illustrates the ultrasound testing method used in the study.

Early Success for Replacement Valves That Can Grow With a Child



Farhan Zafar, MD



David Morales, MD

INSTITUTE RESEARCH & TRAINING DETAILS

Faculty	60
Joint Appointment Faculty	2
Total Annual Grant Awards	\$12.7M
Total Annual Industry Awards	\$719,459
Total Publications	233

Zafar F, Hinton RB, Moore RA, Baker RS, Bryant R, 3rd, Narmoneva DA, Taylor MD, Morales DL. Physiological Growth, Remodeling Potential, and Preserved Function of a Novel Bioprosthetic Tricuspid Valve: Tubular Bioprosthesis Made of Small Intestinal Submucosa-Derived Extracellular Matrix. *J Am Coll Cardiol*. 2015;66(8):877-888.

PUBLISHED AUG. 25, 2015

Journal of the American College of Cardiology

When small children need heart valve replacements, they often require multiple operations because the artificial valves they receive cannot grow. Soon, there may be a solution to this challenge.

A study led by Farhan Zafar, MD, and David Morales, MD, Director of Congenital Heart Surgery, Heart Institute, reports early success in animal models with a new heart valve that actually does grow.

The study team evaluated a tricuspid valve made of small intestinal submucosa-derived extracellular matrix (SIS-ECM). Results appeared Aug. 25, 2015, in the *Journal of the American College of Cardiology*.

This special tissue, made by Georgia-based CorMatrix Cardiovascular, has been used as a patch in various tissue repairs. This was one of its first uses as a replacement valve.

Surgeons placed the new valves in eight lambs, then evaluated outcomes three months and eight months later.

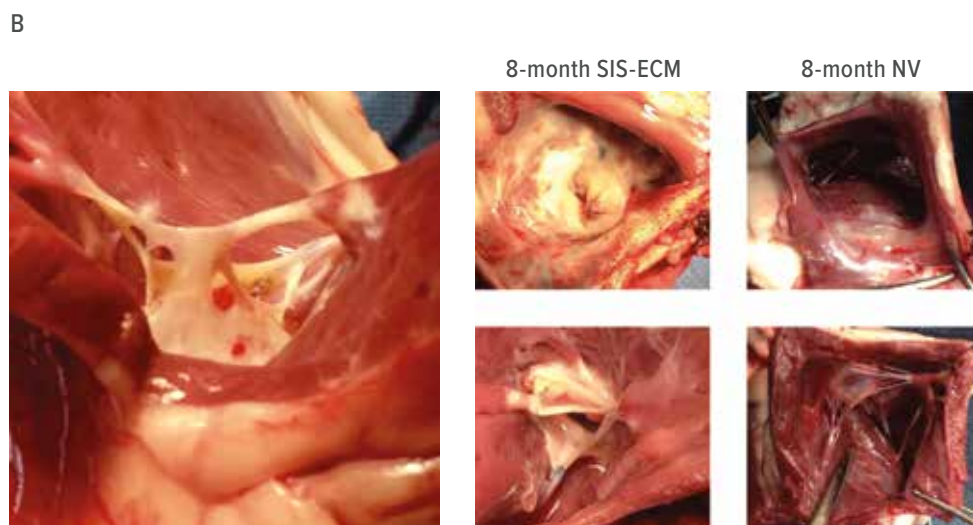
On average, the lambs tripled their weight while their replaced heart valves grew 50 percent in diameter. This expansion was similar to natural growth. Valves in seven animals functioned normally, one developed a malfunction.

The study indicates that the valves grew as resident mesenchymal cells migrated into the bio-scaffold.

The valves functioned without inflammation or calcification. They also outperformed standard prosthetic valves placed in other lambs, which showed signs of stenosis.

“This growth characteristic is vital for pediatric patients,” Morales says. “Many surgeons implant oversized valves in an attempt to accommodate for this problem. However, patient-to-valve size mismatch often leads to its own complications.”

Some young adults already have received SIS-ECM valves on a “compassionate use” basis, and early outcomes have been promising. This clinical use and the research here led to the U.S. Food and Drug Administration approving an IDE clinical trial in children and adults. Cincinnati Children’s is the first to enroll a pediatric patient in the study.



In graph (A) lambs tripled their weight over the study period with a corresponding, appropriate increase in a tubular tricuspid valve made from small intestinal submucosa-derived extracellular matrix (SIS-ECM). Visual examination (B) indicated that SIS-ECM valves appeared similar to native valves (NV). This valve displays signs of chord formation, tendons that connect the valve to heart muscle.

Recognizing the ‘Family Voice’ Can Smooth Transitions from Hospital to Home



Samir Shah, MD, MSCE



Jeffrey Simmons, MD, MSc

RESEARCH & TRAINING DETAILS

Faculty	38
Joint Appointment Faculty	7
Total Annual Grant Awards	\$1.3M
Total Annual Industry Awards	\$2,500
Total Publications	75

Solan LG, Beck AF, Brunswick SA, Sauers HS, Wade-Murphy S, Simmons JM, Shah SS, Sherman SN, Group HOS. The Family Perspective on Hospital to Home Transitions: A Qualitative Study. *Pediatrics*. 2015;136(6):e1539-1549.

PUBLISHED DECEMBER 2015
Pediatrics

“Overwhelmed.” “I just can’t do it.” “Way too much.” “Confused.” “Exhausted.” “Scared to leave the hospital.” “How do I know?....”

Medical professionals know the transition from hospital to home for a sick child can be stressful for parents and caregivers—and that stress can negatively impact patient outcomes and recovery.

The Hospital-to-Home Outcomes (H2O) study conducted detailed focus groups with 61 caregivers within 30 days of a child’s release. Researchers gained compelling insights into common at-home challenges.

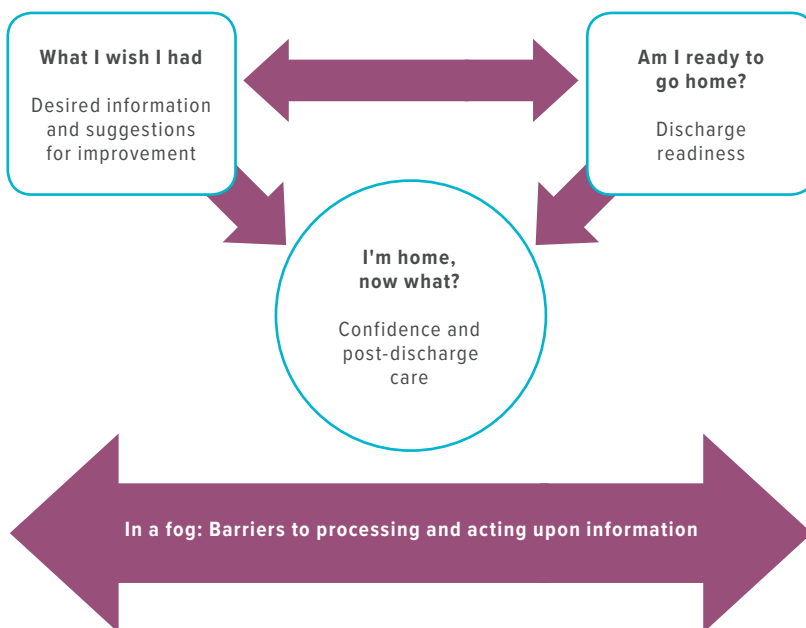
The study identified a four-category conceptual model to describe the “family voice” caregivers often use to relate their experiences after discharge:

- “In a fog” (barriers to processing and acting on information)
- “What I wish I had” (desired information and suggestions for improvement)
- “Am I ready to go home?” (discharge readiness)
- And “I’m home, now what?” (confidence and discharge care.)

“One surprise was the all-encompassing nature of ‘fog’ experienced by caregivers,” says Samir Shah, MD, MSCE, Director, Division of Hospital Medicine. “We know that in the hospital, parents are dealing with a variety of issues, such as stress, sleep deprivation, and balancing other responsibilities. But they described this ‘fog’ as being a factor not only during hospitalization but also after arriving home, making it difficult for them to remember important care instructions.”

Shah and Jeffrey Simmons, MD, MSc, co-led the H2O study. A grant from the Patient-Centered Outcomes Research Institute funded the work.

Using insights from the study, the Division of Hospital Medicine and the Department of Patient Services are working together to develop more innovative interventions to improve patient and family transitions.



A conceptual model based on focus groups and interviews with parents and caregivers identified key elements of the family's experience with the hospital-to-home transition. Within 30 days of a child's discharge from the hospital, family members identified a range of transitional challenges, including mental exhaustion, information overload, and lack of emotional readiness or confidence to care for a sick child.

Fate of Neural Cells in Developing Mammalian Forebrain Could Hinge on Cholesterol Biosynthesis Enzyme



Ashley Driver, PhD



Rolf Stottmann, PhD

RESEARCH & TRAINING DETAILS

Faculty	28
Joint Appointment Faculty	5
Research Fellows & Post Docs	5
Research Graduate Students	5
Total Annual Grant Awards	\$4.5M
Total Annual Industry Awards	\$430,694
Total Publications	103

Driver AM, Kratz LE, Kelley RI, Stottmann RW. Altered cholesterol biosynthesis causes precocious neurogenesis in the developing mouse forebrain. *Neurobiol Dis.* 2016;91:69-82.

PUBLISHED ONLINE FEB. 24, 2016
Neurobiology of Disease

Research into the developing forebrain of mice shows for the first time that loss of proper cholesterol biosynthetic enzyme function can alter the very fate of the neural cell.

The study follows up on previous research in which the team reported that a mutation in *hydroxysteroid (17-beta) dehydrogenase 7 (Hsd17b7)* resulted in “striking” embryonic forebrain congenital malformations.

This study adds several new observations. Evidence suggests mutant cells undergo abnormal interkinetic nuclear migration. Intermediate progenitors increase at the expense of apical progenitors. Also, an *in vitro* primary neuron culture supports the team’s model of accelerated cortical differentiation in the mutant.

The findings show how much neural cells rely on proper enzyme function to keep brain development on course.

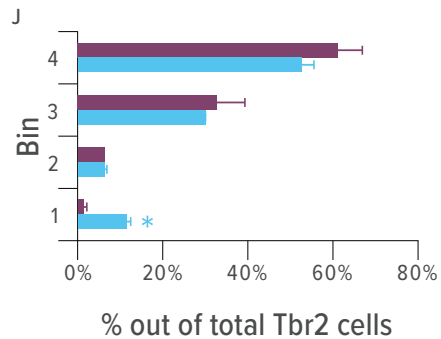
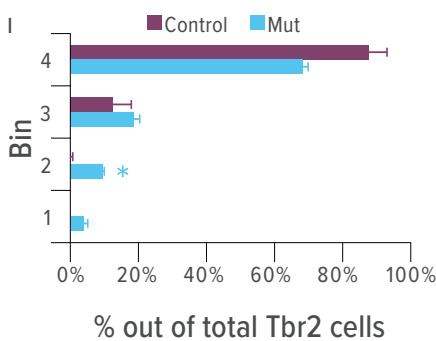
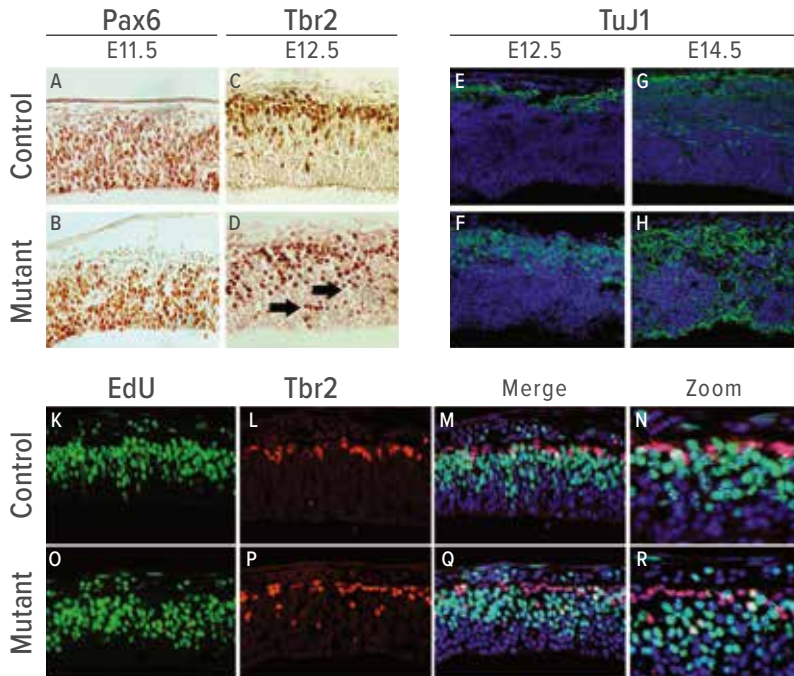
“Specifically, neural stem cells in the brain of mutant embryos are differentiating into mature neurons at a rate significantly faster than in normal developing brains,” says senior author Rolf Stottmann, PhD.

As a result, the embryos were unable to maintain critical stem cell populations and exhibited dramatic reductions in brain cell formation.

The team, led by first author Ashley Driver, PhD, also reported early steps toward a potential treatment. *In utero* administration of statins and dietary cholesterol produced partial rescue of brain development.

“This is a nice demonstration,” Stottmann says, “of the power of forward genetics in the mouse to identify new genes and go on to uncover fundamental mechanisms of mammalian development and disease.”

Next, the team plans to study how enzyme synthesis malfunctions might affect other congenital malformations.



Because the brain is particularly sensitive to changes in cholesterol metabolism, researchers focused on understanding the mechanisms behind enzyme deficiencies.

These images show how neural progenitor and differentiated neuron populations are altered in the *Hsd17b7*^{rudolph} mutant mouse brain cortex. Images (A) and (B) show Pax6 apical progenitors at E11.5, and (C) and (D) show Tbr2 intermediate progenitors at E12.5. Post-mitotic populations are shown in the control and mutant at both E12.5 (E and F) and E14.5 (G and H). Scientists used double-immunostaining for EdU (K and O) and Tbr2 (L and P) at E11.5 to show increased double-positive cells in the mutant (Q and R) compared to the control (M and N). This indicates a premature differentiation program in the mutant brain.

The bar charts I and J show the distribution and number of Tbr2 cells at E11.5 (I) and E12.5 (J)

Microchimeric Maternal Cells Promote Reproductive Fitness Across Generations



Sing Sing Way, MD, PhD

RESEARCH & TRAINING DETAILS

Faculty	16
Joint Appointment Faculty	7
Research Fellows & Post Docs	2
Research Graduate Students	4
Total Annual Grant Awards	\$10.3M
Total Annual Industry Awards	\$1.8M
Total Publications	63

Kinder JM, Jiang TT, Ertelt JM, Xin L, Strong BS, Shaaban AF, Way SS. Cross-Generational Reproductive Fitness Enforced by Microchimeric Maternal Cells. *Cell*. 2015;162(3):505-515.

PUBLISHED ONLINE JULY 23, 2015
Cell

The long-standing scientific mystery of how the developing fetus avoids rejection by their mother’s immune cells remains unresolved. However, new clues are emerging.

A research team led by Sing Sing Way, MD, PhD, Division of Infectious Diseases, reports the bidirectional exchange and persistence of maternal cells in offspring, and offspring cells in mothers during pregnancy, may help unlock the mystery of how pregnancy naturally works.

Genetically foreign maternal cells promote in offspring a systemic accumulation of immune-suppressive regulatory T cells. These cells are specific to non-inherited maternal antigens (NIMA), the team reports.

Exposure to NIMA enhances the odds of successful pregnancy when a woman encounters a partner with similar genetic traits as her own mother. This process, common to all placental mammals, helps protect against pregnancy complications often triggered by prenatal infection.

“Our research proves one aspect of nature’s intent in this intricately orchestrated transfer of cells during fetal development,” Way says.

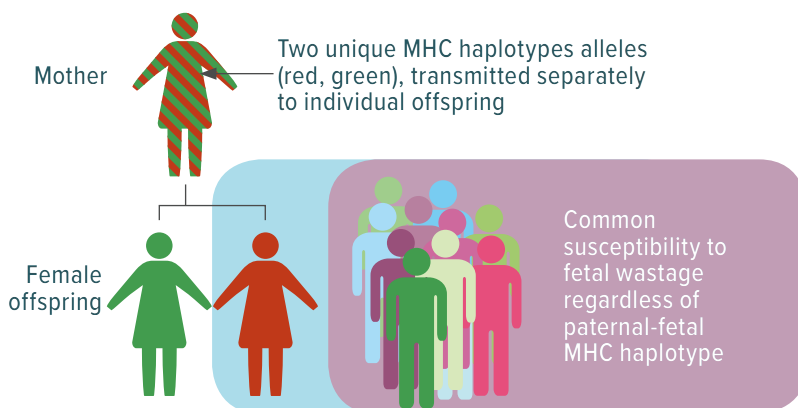
These microchimeric cells are very rare, ranging from one in 100,000 to one in one million offspring cells. Humans are comprised of more than 30 trillion cells. That means each may contain up to 300 million of our mother’s cells.

“It was just miraculous to us that these cells could persist despite being genetically and immunological foreign,” says first author Jeremy Kinder, a graduate student in Way’s lab. “When we looked at them quantitatively, we saw that they’re able to mediate reproductive benefits.”

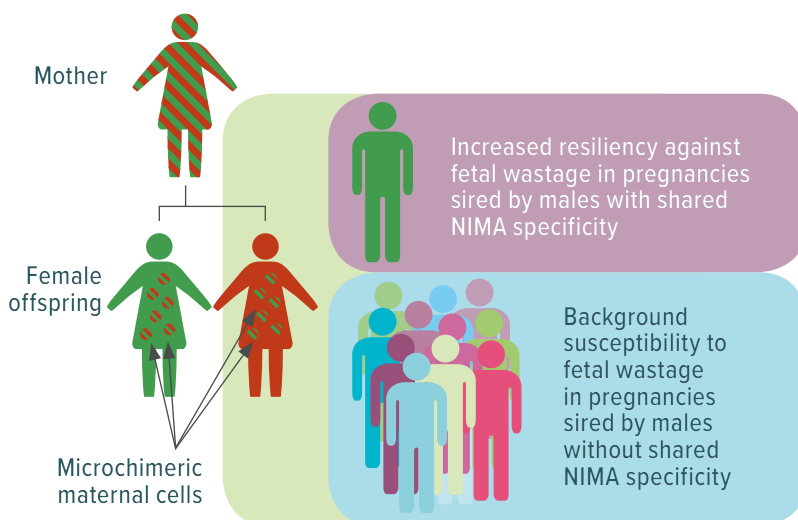
Understanding how these cells work could help prevent preterm births, treat certain autoimmune disorders, or help avoid transplant tissue rejection.

“We’re letting these cells teach us fundamental immunology,” Way says, “because they have learned some tricks that we didn’t appreciate before. But clearly nature has figured it out.”

Traditional Mendelian genetics



Cross-generational reproductive fitness (enforced by tolerance to non-inherited maternal antigen)



In traditional Mendelian genetics (top image), pregnancies among female offspring are equally susceptible to fetal wastage or other complications. This stems from disruptions in fetal tolerance regardless of paternal major histocompatibility complex haplotype specificity.

Comparatively, persistent postnatal maintenance of tolerogenic microchimeric maternal cells in female offspring promotes cross-generational reproductive fitness (bottom image). It does this by selectively protecting against fetal wastage during next-generation pregnancies sired by males with shared overlapping non-inherited maternal antigens specificity.

Learning Networks Play Crucial Role in Reducing Mortality Rate for Newborns With Heart Syndrome



Carole Lannon, MD, MPH



Jeffrey Anderson, MD, MPH

RESEARCH & TRAINING DETAILS

Faculty	10
Joint Appointment Faculty	25
Research Fellows & Post Docs	1
Total Annual Grant Awards	\$14.1M
Total Publications	33

Anderson JB, Beekman RH, 3rd, Kugler JD, Rosenthal GL, Jenkins KJ, Klitzner TS, Martin GR, Neish SR, Brown DW, Mangeot C, King E, Peterson LE, Provost L, Lannon C, National Pediatric Cardiology Quality Improvement C. Improvement in Interstage Survival in a National Pediatric Cardiology Learning Network. *Circ Cardiovasc Qual Outcomes*. 2015;8(4):428-436.

PUBLISHED JUNE 9, 2015

Circulation: Cardiovascular Quality and Outcomes

Newborns with hypoplastic left heart syndrome (HLHS) need open-heart surgery shortly after birth, then a second several months later, and a third several years later. Yet after the initial operation, 10 to 15 percent of babies never make it to the second surgery.

That high-risk interstage timeframe became the focus of a multi-institutional learning network supported by the Anderson Center. The network brings together parents, clinicians, and researchers to improve outcomes by sharing research and quality improvement data.

This network involves 60 U.S. pediatric cardiology centers that participate in the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC).

The study, published June 9, 2015, was led by Jeffrey Anderson, MD, MPH, Chief Quality Officer at the Heart Institute; and senior author Carole Lannon, MD, MPH, Director of Learning Networks at the Anderson Center.

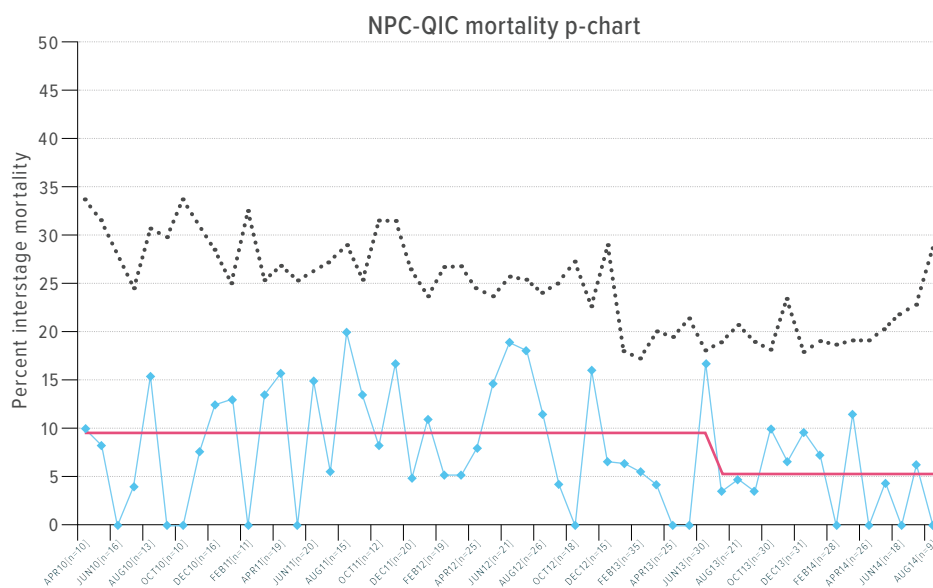
“Networks are the best way to improve outcomes for populations of patients at scale,” says Lannon, “especially for those with a rare disease.”

Researchers analyzed data on 1,163 infants from 52 surgical centers. This included 1,050 who completed the interstage with second-surgery palliation, 18 who underwent transplantation during interstage, and 95 who died during interstage.

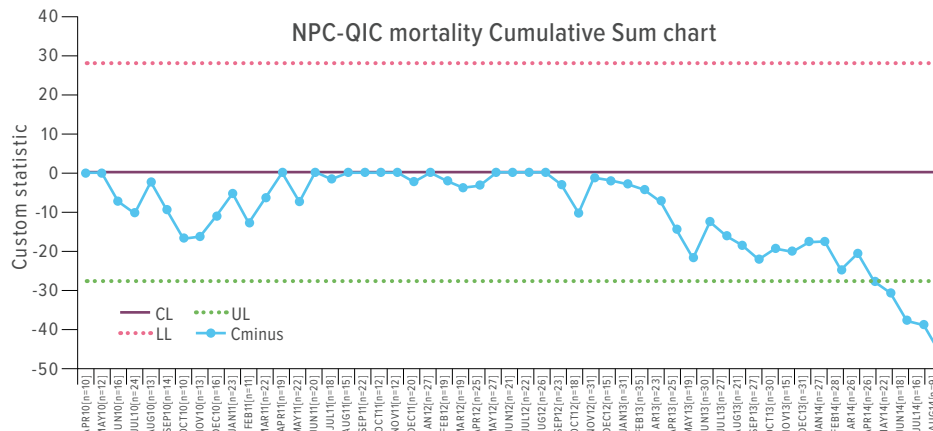
The team found improvements in survival rates over time, despite no clear changes in medications or therapy strategies. The key: clinical care centers learning from each other and families, testing strategies, and developing reliable care processes.

“While the improvement in mortality, with no new surgical or cardiac interventions, is important to our field,” Anderson says, “just as important is the proof that cardiac centers can come together, collaborate, and improve outcomes by sharing practices.”

A



B



In chart A, each point indicates the monthly interstage mortality rate within the network. The solid red line is the median monthly mortality percentage. The dotted black line is the upper control limit.

In chart B, each point indicates the cumulative deviation from a historic mortality level. The green line demonstrates cumulative deviation from a target of 9.5% mortality, the cumulative mortality from 2008 to May 2013.

A significant change was first noted in April 2014 with continued reduction in mortality thereafter. The chart starts in 2010 when the metric within the collaboration was stable. CL indicates center line (median); LL, lower control limit; and UL, upper control limit.

CARE Program Vital to Understanding, Treating and Preventing Child Abuse



Erica Messer, PsyD

RESEARCH & TRAINING DETAILS

Faculty	2
Joint Appointment Faculty	10
Research Fellows & Post Docs	0
Research Graduate Students	0
Total Annual Grant Awards	\$614,766
Total Publications	5

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Gurwitch RH, Messer EP, Masse J, Olafson E, Boat BW, Putnam FW. Child-Adult Relationship Enhancement (CARE): An evidence-informed program for children with a history of trauma and other behavioral challenges. *Child Abuse Negl.* 2016;53:138-145.

PUBLISHED ONLINE NOV. 22, 2015

Child Abuse & Neglect

When it comes to the role the Mayerson Center plays in treating abused and maltreated children, two important numbers emerge: 2 million and 2,000.

The former reflects documented abuse cases occurring annually in the U.S. The latter shows how many children our Child Abuse Team treats each year.

The center's experience at helping abused children has made it a leader in training others. Now a study in *Child Abuse & Neglect* demonstrates the effectiveness of that training.

The center launched the Child-Adult Relationship Enhancement (CARE) program in 2006 to enhance trauma-informed skills of mental health providers. It has expanded to involve caregivers, child-welfare workers, educators, and others.

The program trains adults how to support and engage children considered at risk for abuse, such as foster kids. These children often struggle with mental and physical health, and with forming positive social relationships.

A survey of more than 100 CARE trainees reports that 99.2 percent said the training changed their practices. Also, 98 percent said they would recommend the program.

Now, the center is studying CARE training for foster parents.

The study's authors included Erica Messer, PsyD, Behavioral Medicine and Clinical Psychology; and Erna Olafson, PhD, PsyD, and Barbara Boat, PhD, of the Childhood Trust.

Messer says CARE training can help caregivers provide the stable relationships that so many abused children need.

"Children depend on stable relationships to thrive academically, emotionally, medically and socially," says Messer. "Most in foster-care are victims of maltreatment, including abuse, neglect or abandonment that has brought them to the attention of Child Protective Services."

A



B



A: Psychologists Robin Gurwitch, in front in light green shirt, and Erica Messer, in front row (center), are joined by a group of CARE trainees in 2015. B: In 2008, Messer traveled to Tokyo, Japan, where she taught the principles of CARE to a group of mental health professionals, shown here. The group continues to use CARE and CARE research in Japan is currently under way.

Even After Bariatric Surgery, Severely Obese Teens Should Be Monitored for Kidney Injury



Mark Mitsnefes, MD, MS

PUBLISHED JUNE 2015

Obesity

Even after undergoing bariatric surgery to control severe obesity, adolescents continue to show underlying, subclinical biomarkers of kidney disease.

A research team led by Mark Mitsnefes, MD, MS, Director of the Clinical and Translational Research Center, studied 28 patients under age 20 who had undergone bariatric surgery for severe obesity. Their findings were published in June 2015 in *Obesity*.

The team measured baseline urine levels of neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), and interleukin-18 (IL-18), three biomarkers previously linked to early structural and inflammatory kidney injury. Levels were measured at baseline, and 6 and 12 months after surgery, and compared against 44 age and sex-matched control subjects.

The team expected to find a decline in signs of kidney disease that corresponded a decline in weight. However, despite weight losses as high as 30 percent, biomarkers remained high enough to indicate continuous kidney injury.

These findings raise questions for clinicians working to prevent childhood obesity from leading to chronic kidney disease in adulthood, Mitsnefes says. Are these biomarkers reversible? How much kidney injury risk do children who undergo bariatric surgery still face as adults?

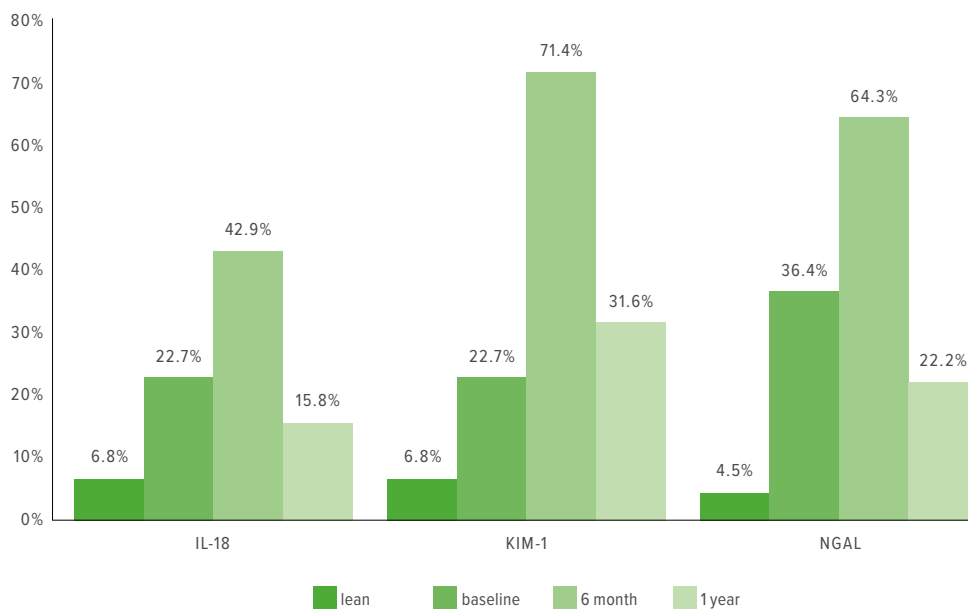
“We can’t answer these questions unless we follow these patients for many more years,” Mitsnefes says. “However, our initial findings of persistently elevated biomarkers of kidney injury, despite weight loss, warrant long-term follow-up of kidney status in these adolescents.”

RESEARCH & TRAINING DETAILS

Faculty	12
Total Annual Grant Awards	\$3.3M
Total Annual Industry Awards	\$557,355
Total Publications	64

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Xiao N, Devarajan P, Inge TH, Jenkins TM, Bennett M, Mitsnefes MM. Subclinical kidney injury before and 1 year after bariatric surgery among adolescents with severe obesity. *Obesity (Silver Spring)*. 2015;23(6):1234-1238.

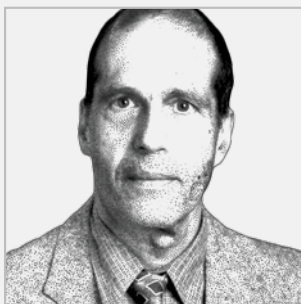


This chart shows the percentage of subjects with biomarker levels above the 95th percentile of normal values. Urine NGAL, IL-18, and KIM-1 were significantly elevated in subjects with obesity compared to lean controls at baseline. The obese cohort had a further significant increase in NGAL and KIM-1 at 6 months, followed by a decline at 1 year.

High Initial Costs of Epilepsy Surgery Can Be Offset by Longer-Term Savings



Shannon Standridge, DO, MPH



Paul Horn, PhD

RESEARCH & TRAINING DETAILS

Faculty	42
Joint Appointment Faculty	3
Research Fellows & Post Docs	4
Research Graduate Students	5
Total Annual Grant Awards	\$2.9M
Total Annual Industry Awards	\$3M
Total Publications	124

Oldham MS, Horn PS, Tsevat J, Standridge S. Costs and Clinical Outcomes of Epilepsy Surgery in Children With Drug-Resistant Epilepsy. *Pediatr Neurol.* 2015;53(3):216-220.

PUBLISHED SEPTEMBER 2015

Pediatric Neurology

Epilepsy can be a costly, long-term disease, especially for the estimated 20 percent of children who do not respond to commonly prescribed anti-seizure drugs.

In Canada, studies have shown that epilepsy surgery can reduce long-term medical costs and seizure frequency for such children. However, similar data has not been available in the United States.

Now, a retrospective study in the September 2015 issue of *Pediatric Neurology* confirms the long-term financial benefits of surgery for children in the U.S. The study, led by Shannon Standridge, DO, MPH, Co-Director of the Rett Syndrome Clinic, followed 94 U.S. patients.

The study included 78 patients who underwent procedures between 2008-2011, including hemispherectomy, corpus callostomy or placement of a vagus nerve stimulator. Another 16 patients were treated medically by managing seizures with anti-epilepsy drugs or diet.

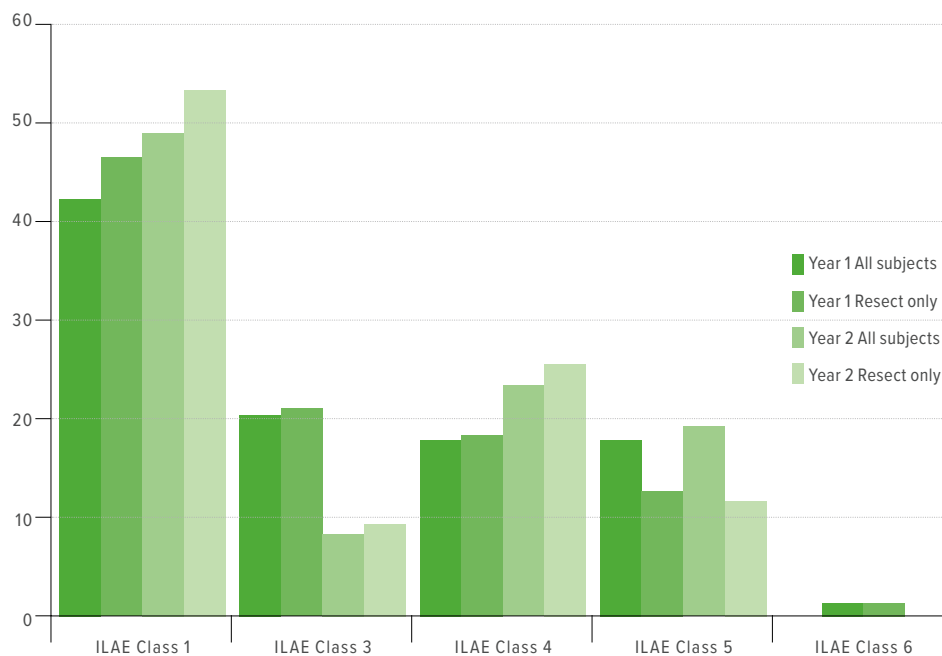
Median cost of surgery was \$118,400. Total median annual follow-up costs (not including the cost of surgical hospitalization) were not significantly different between the two groups at one- and two-year intervals.

However, surgical patients who achieved complete remission from seizures had lower medical costs: \$8,000 for the surgery group vs. \$16,000 for the medical group at one year; and \$5,200 for the surgery group vs. \$7,600 for the medical group after two years. Those receiving surgery also had fewer seizures than the medical group after one year.

“Although epilepsy surgery is expensive and the overall costs of surgical and medical management are similar in the first two years, patients who achieved seizure freedom after surgery had lower costs compared with those treated medically,” according to Standridge.

These findings suggest possible cost containment ideas for epilepsy surgery and may help clinicians improve as “appropriate stewards of (healthcare) resources.”

ILAE classification by year post-operative, all surgical subjects and subcategory of only resective subjects.



ILAE class 1 = completely seizure free, no auras; ILAE class 2 = only auras; ILAE class 3 = 1-3 seizure days/year; ILAE=4 seizure days/year to 50% reduction of baseline seizure days; ILAE5 = less than 50% reduction to 100% increase of baseline seizure days; ILAE 6 = more than 100% increase of baseline seizure days.
There were no subjects with ILAE class 2.

Diffusion Tensor Imaging Shows Value for Investigating White Matter Abnormalities



Francesco Mangano, DO

PUBLISHED ONLINE MAY 20, 2016

Journal of Neurosurgery: Pediatrics

The tiny microstructures of white matter in the brain can hold important clues to post-surgery development of children with hydrocephalus.

Diffusion tensor imaging (DTI)—a more detailed form of MRI—plays an increasingly important role in capturing these clues. The technique also might help predict future outcomes, according to authors of revealing research into the landscape of the brain.

The prospective study included Cincinnati Children's researchers from the divisions of Neurosurgery, Biostatistics and Epidemiology, Neurology, Radiology and Developmental and Behavioral Pediatrics. It was led by Weihong Yuan, PhD, Radiology, and Francesco Mangano, DO, Chief of Neurosurgery.

"The study is significant in that it further establishes DTI as a non-invasive objective biomarker with predictive prognostic value in the study of congenital hydrocephalus," Mangano says.

"The authors," he adds, "plan to build on this knowledge to translate research into an everyday clinical tool that may be used by many different pediatric subspecialists caring for complex neurologic conditions."

The team analyzed data from 54 patients with congenital hydrocephalus, caused when cerebrospinal fluid abnormally accumulates in the brain. The condition occurs in three of 1,000 live births.

It can raise intracranial pressure at birth, resulting in severe brain damage. It can be fatal if left untreated, but often is not diagnosed until signs emerge, such as swelling of the head.

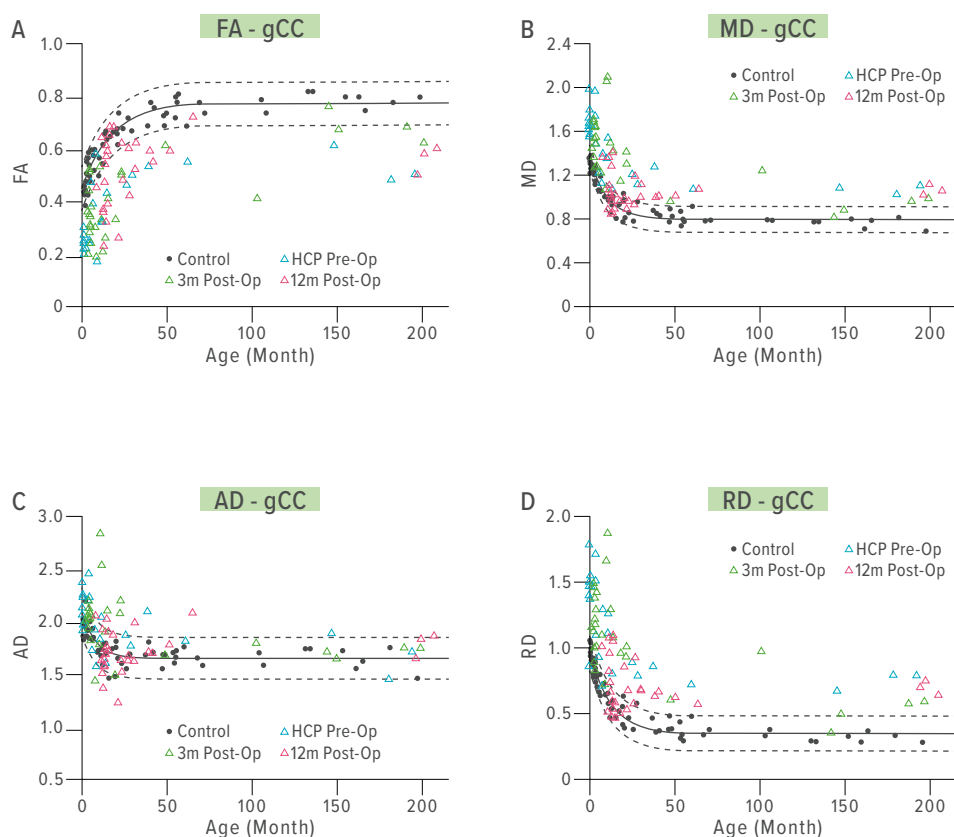
Researchers looked at data at three intervals: prior to surgery, and at three and 12 months after surgery.

DTI showed significant white matter abnormality in two major areas. But in the posterior limb of the internal capsule, these abnormalities did not persist at the 12-month mark indicating a prognostic predictive value of DTI.

RESEARCH & TRAINING DETAILS

Faculty	7
Joint Appointment Faculty	4
Research Fellows & Post Docs	3
Research Graduate Students	2
Total Annual Grant Awards	\$203,000
Total Publications	31

Mangano FT, Altaye M, McKinstry RC, Shimony JS, Powell SK, Phillips JM, Barnard H, Limbrick DD, Jr., Holland SK, Jones BV, Dodd J, Simpson S, Mercer D, Rajagopal A, Bidwell S, Yuan W. Diffusion tensor imaging study of pediatric patients with congenital hydrocephalus: 1-year postsurgical outcomes. *J. Neurosurg. Pediatr.* 2016;1-14.



These scatter plots show four types of diffusion tensor imaging (DTI) measures conducted after patients received surgery for congenital hydrocephalus: (A) fractional anisotropy, (B) mean diffusivity, (C) axial diffusivity and (D) radial diffusivity. Each symbol represents the DTI value extracted from a single participant. The solid black line and two dashed lines show results of regression analysis based on the control group. The study suggests that DTI can serve as a sensitive imaging biomarker for underlying neuroanatomical changes and post-surgical developmental outcome, and even as a predictor for future outcomes.

Retina’s Biological Clock Shows Independence From the Brain



Richard Lang, PhD



Shruti Vemaraju, PhD

RESEARCH & TRAINING DETAILS

Faculty	2
Research Fellows & Post Docs	9
Total Annual Grant Awards	\$1.2M
Total Annual Industry Awards	\$37,387
Total Publications	14

Buhr ED, Yue WW, Ren X, Jiang Z, Liao HW, Mei X, Vemaraju S, Nguyen MT, Reed RR, Lang RA, Yau KW, Van Gelder RN. Neuropsin (OPN5)-mediated photoentrainment of local circadian oscillators in mammalian retina and cornea. *Proc Natl Acad Sci U. S. A.* 2015;112(42):13093-13098.

PUBLISHED ONLINE SEPT. 15, 2015
Proceedings of the National Academy of Sciences

The retina, the light-sensitive inner layer of the eye, always knows what time is it. The enduring question has been: How?

That question led to a light-bulb moment for researchers, who determined that the retina’s own biological clock functions independently from the one in the brain.

They also found that the retinal clock uses daylight as a time-setting signal, a process called photoentrainment.

“In other words,” says Richard Lang, PhD, “as long as the retina continues to receive daily light stimulation, it will maintain time.”

In the multi-institutional study, published in *Proceedings of the National Academy of Sciences*, researchers made a second significant finding. They revealed that this light-dependent time-setting mechanism uses a new opsin molecule called neuropsin as a light detector.

Lang directs the Visual Systems Group and the Center for Chronobiology at Cincinnati Children’s. Other investigators included Shruti Vemaraju, PhD, and Minh-Thanh Nguyen, PhD.

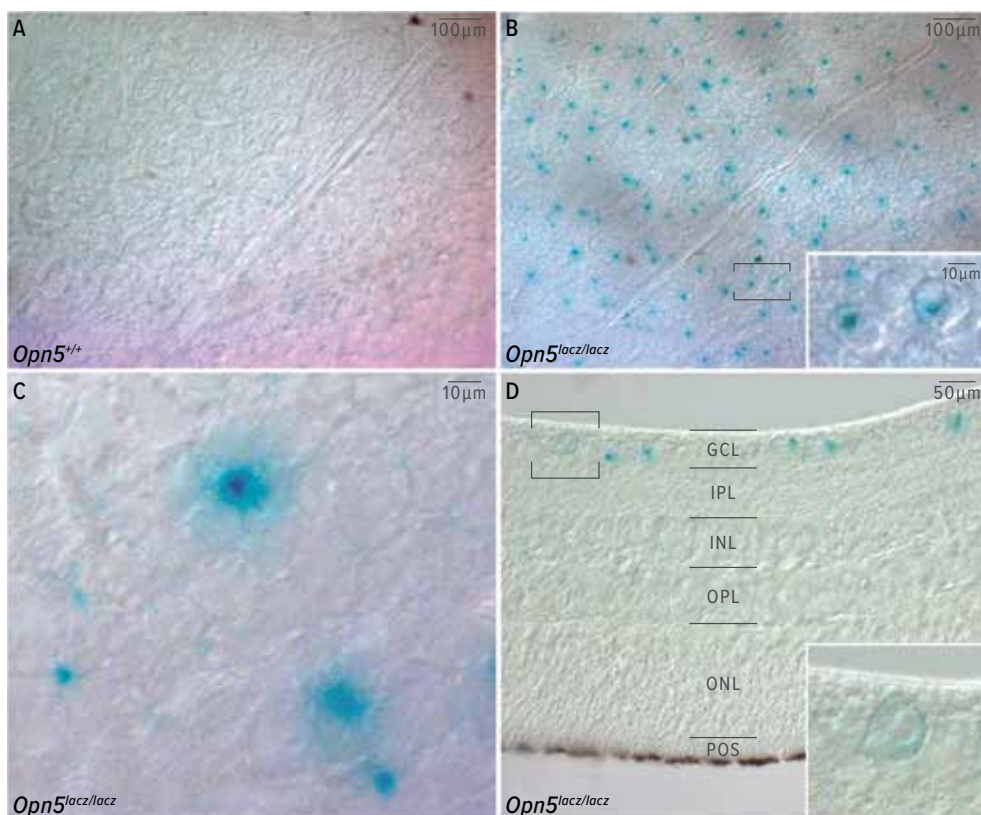
In mammals, behavioral circadian rhythms are synchronized to light and dark cycles through rods, cones, and photosensitive cells in the retina.

These molecular circadian rhythms in the retina are themselves synchronized to light and dark signals, but the study was the first to show how this photoentrainment, in an *ex vivo* setting, requires neuropsin.

“Remarkably,” researchers wrote, “the circadian clocks in the cornea are also photoentrained *ex vivo* in an OPN5-dependent manner.”

Many tissues in the body have their own biological clocks. But this study suggests that these tissues may function independently of the brain’s biological clock, located in the suprachiasmatic nucleus.

“We are investigating this possibility,” Lang says.



Neuropsin expression in ganglion cells of the mouse retina: In these images, the expression of the Neuropsin gene (Opn5) is indicated by the blue labeling. Panel A is a control retina that does not contain the Opn5lacZ reporter gene and so no blue labeling is apparent. Panels B and C show retina, labeled for Opn5lacZ expression and showing the retinal ganglion cells that express Neuropsin. Panel D shows, in a section through the labeled retina, that Neuropsin expressing cells reside in the innermost layer of the retina.

Rereduction Proves Effective, Reduces Cost of Treating Both-Bone Forearm Fractures in Children



Shital Parikh, MD



Viral Jain, MD

PUBLISHED JUNE 2016

Journal of Pediatric Orthopaedics

Forearm fractures of both the radius and ulna can be treated with a less invasive, more conservative approach called rereduction—a procedure that is as effective as surgery but delivers up to 50 percent cost savings.

The approach involves a second re-setting of fractured bones that have lost alignment several days after being initially manipulated into position and placed in a cast. In about 25 percent of cases, fractured bones misalign as they heal, which typically prompts surgical treatment using nails or plates to stabilize them.

Shital Parikh, MD, Co-Director of the Orthopaedic Sports Center, and Viral Jain, MD, analyzed the outcomes of 31 children treated between 2008-2013 with the rereduction approach. Their findings appear in the June 2016 *Journal of Pediatric Orthopaedics*.

Re-aligning the bones and applying a second cast produced satisfactory radiographic outcomes in 87 percent of cases. The average cost of treatment was \$2,056, compared to \$4,589 for surgery.

“The second reduction was able to hold the fracture in place in a very good, very stable position,” Parikh says. “Previously, the conventional wisdom was that if initial reduction in the emergency department failed, it would not hold if we reduced it again. We proved that the bone does hold.”

The cost savings resulted from avoiding an operation to implant stabilization devices, and a second procedure six months later to remove the hardware.

RESEARCH & TRAINING DETAILS

Faculty	14
Joint Appointment Faculty	1
Research Fellows & Post Docs	2
Research Graduate Students	6
Total Annual Grant Awards	\$116,149
Total Annual Industry Awards	\$54,283
Total Publications	39

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Eismann EA, Parikh SN, Jain VV.
Rereduction for Redisplacement of Both-
Bone Forearm Shaft Fractures in Children. *J*
Pediatr Orthop. 2016;36(4):405-409.



Despite conventional wisdom, these images demonstrate that rereduction of both-bone forearm fractures produces satisfactory outcomes, with apex angulations less than 5 degrees. Rereduction also costs less than surgery.

Aerospace Engineering Provides Rocket Boost to Virtual Sleep Apnea Surgery



Sally Shott, MD

PUBLISHED ONLINE NOV. 5, 2015

Otolaryngology-Head and Neck Surgery

In a feasibility study that could transform surgical strategies for children with persistent obstructive sleep apnea (OSA), researchers at Cincinnati Children's found insight from an unlikely corner.

The team sought to improve surgical outcomes involving the soft tissues of the upper airway. They got a hard-data assist from decidedly non-medical scientists in the University of Cincinnati's Department of Aerospace Engineering and Engineering Mechanics.

The challenge: Airway tissue above the larynx is much more elastic than tissue below it. The soft tissue reacts differently to changes in air pressure and behaves differently after surgery, which can lead to multiple procedures.

The solution: engineers and physicians applied principles of airflow, turbulence, resistance and fluid dynamics to create a 3D "virtual surgery" system that predicts soft tissue behavior after a procedure.

Results from digitally replicated surgeries appeared Nov. 15, 2015, in *Otolaryngology-Head and Neck Surgery*. The testing led to adjustments that would have achieved desired results in eight of the 10 cases, compared to just six successes achieved in the actual surgeries.

The research team included senior author Sally Shott, MD; Raouf Amin, MD, Director of Pulmonary Medicine; and Stacey Ishman, MD, MPH, Surgical Director of the Upper Airway Center.

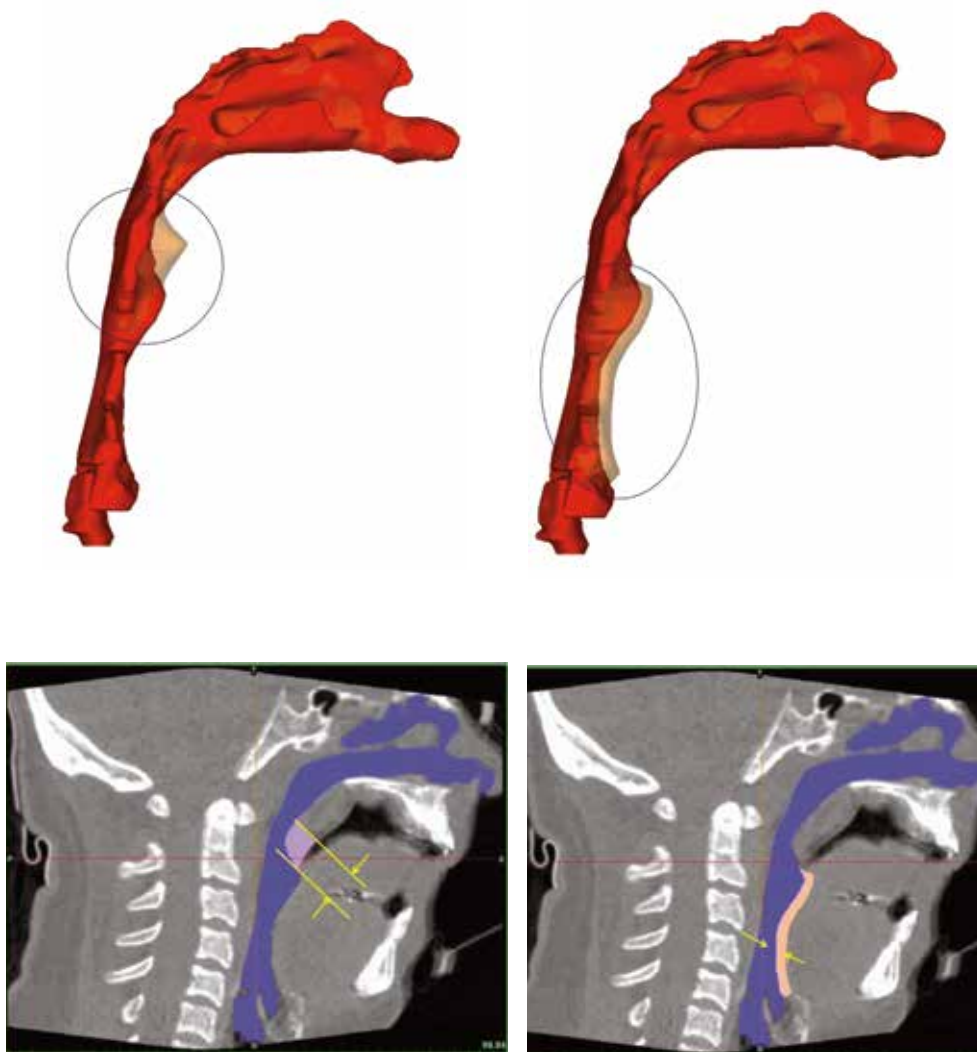
"Aerospace engineers design the outside of the airplane such that it can move through the air with the least resistance," Shott says. "We applied similar principles. In obstructive sleep apnea, each patient's airway collapses in different degrees and at different locations. This study shows the potential for tailoring specific surgeries for each individual patient."

Ishman adds, "For those who truly need surgery, we can use the ideal approach."

RESEARCH & TRAINING DETAILS

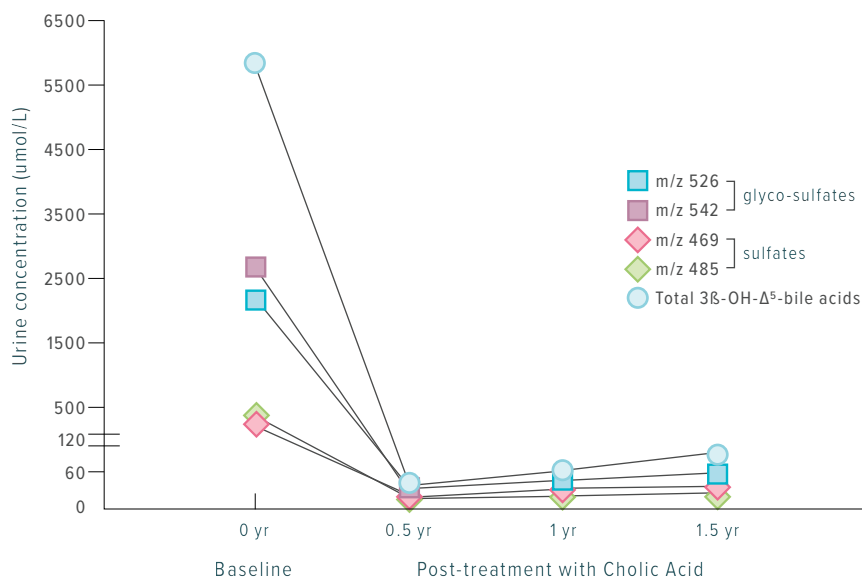
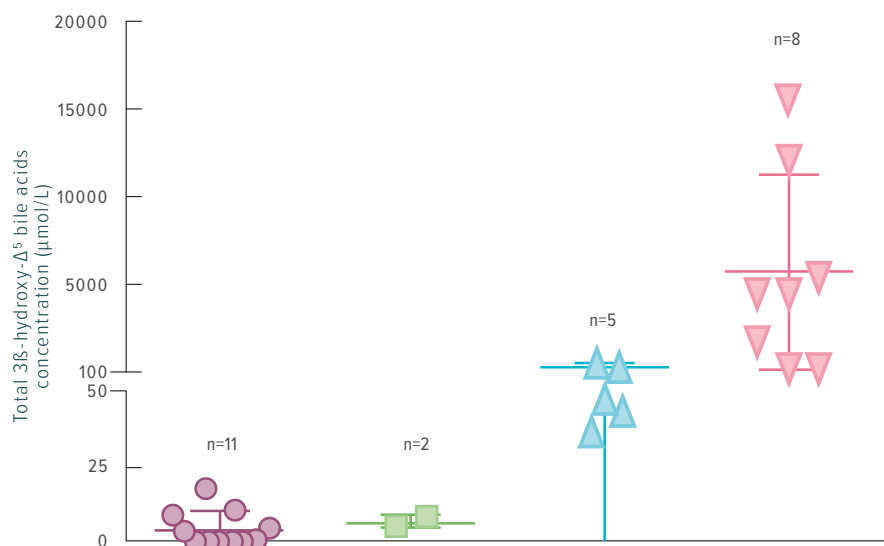
Faculty	11
Joint Appointment Faculty	3
Research Fellows & Post Docs	1
Research Graduate Students	2
Total Annual Grant Awards	\$60,513
Total Publications	49

Mylavarapu G, Subramaniam D, Jonnagiri R, Gutmark EJ, Fleck RJ, Amin RS, Mahmoud M, Ishman SL, Shott SR. Computational Modeling of Airway Obstruction in Sleep Apnea in Down Syndrome: A Feasibility Study. *Otolaryngol Head Neck Surg*. 2016;155(1):184-187.



These 3D airway models were reconstructed from respiratory-gated computed tomography and magnetic resonance imaging. These virtual surgeries reflect palate and tongue procedures that demonstrate how surgical changes can affect airflow resistance.





Correlation between urinary concentrations of total 3β-sulfooxy-Δ⁵-chole-24-oic acids measured by LC-ESIMS/MS with the concentrations determined by a scoring after FAB-MS analysis for a selection of urine samples from 10 patients with HSD3B7 deficiency before and during bile acid therapy with cholic acid (n=10) and noncholestatic controls (n=5).

Adult Survivors of Childhood Cancers Require Long-Term Monitoring, Screening, Prevention and Therapeutic Care



Gylynthia Trotman, MD, MPH



Susan Rose, MD

PUBLISHED JUNE 2016

Nature Reviews Endocrinology

With cure rates for some pediatric cancers reaching 80 percent, health-care providers face a growing challenge: how to provide appropriate monitoring and care of long-term cancer survivors.

Some cancer survivors develop endocrine disorders as adults, caused by the cancer itself or the therapies used to treat it. An extensive review by Gylynthia Trotman, MD, MPH, and Susan Rose, MD, urges providers to help survivors into a “purposeful and planned transition” to a multi-disciplinary adult care team that can provide long-term screening, prevention and other interventions.

The study examined pediatric cancers including leukemia and lymphoma, brain tumors and bone tumors. Endocrine problems linked to cancer treatment can include growth hormone deficiency, hypothyroidism, adrenocorticotropin deficiency, hyperprolactinemia, precocious puberty, hypogonadism, altered fertility and/or sexual dysfunction, low bone mineral density, metabolic syndrome and hypothalamic obesity.

While some disorders emerge during treatment, others may not appear until years later. Overall, 90 percent of cancer survivors will develop a chronic health condition by age 45, and many struggle with altered sexual and fertility issues.

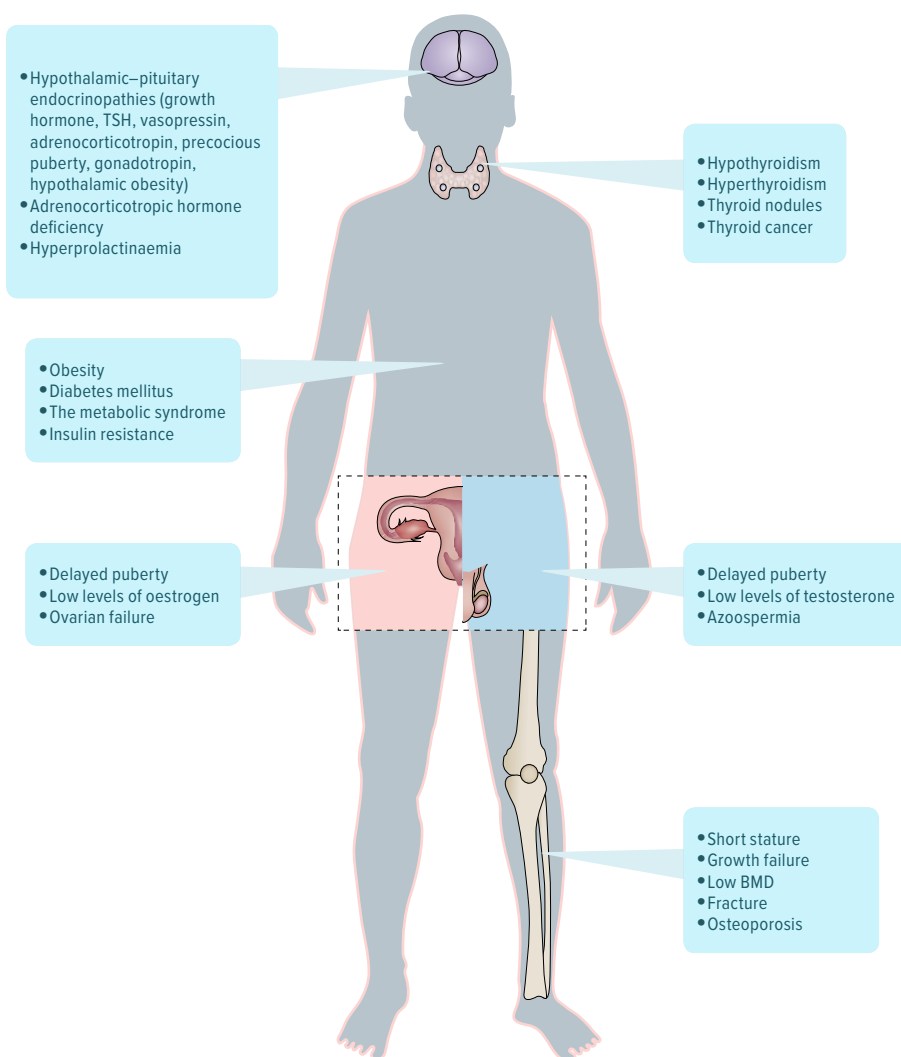
Some problems trace back to chemotherapy, alkylating agents, radiation, corticosteroids and other common cancer treatments. New protocols, such as proton beam therapy and reduced intensity transplantation, likely will reduce post-cancer endocrinopathies. However, discussing fertility impacts and options with families will likely remain important.

“The ability to have biological children is often an important quality-of-life issue for both survivors and parents,” Trotman says. “Parents want information about fertility preservation for children; adult survivors wish they had been informed of fertility risks. Receiving specialized counseling and pursuing fertility preservation leads to less regret and improved quality of life.”

RESEARCH & TRAINING DETAILS

Faculty	3
Research Graduate Students	6
Total Publications	6

Rose SR, Horne VE, Howell J, Lawson SA, Rutter MM, Trotman GE, Corathers SD. Late endocrine effects of childhood cancer. *Nat Rev Endocrinol.* 2016;12(6):319-336.



This illustration indicates the wide variety of disorders that pediatric cancer survivors can face as they reach adulthood. Some emerge during treatment, others may take years to appear. Overall, 90 percent of cancer survivors will develop some form of chronic health condition by age 45.

Drug Reverses Lung Damage in Mice



Tanya Kalin, MD, PhD

The Perinatal Institute includes the Divisions of Neonatology, Perinatal and Pulmonary Biology, Developmental Biology, Reproductive Sciences, the Center for Prevention of Preterm Birth, and the Cincinnati Fetal Center.

INSTITUTE RESEARCH & TRAINING DETAILS

Faculty	56
Joint Appointment Faculty	1
Research Fellows & Post Docs	13
Research Graduate Students	31
Direct Annual Grant Support	\$12.6M
Direct Annual Industry Support	\$575,404
Publications	143

Cai Y, Bolte C, Le T, Goda C, Xu Y, Kalin TV, Kalinichenko VV. FOXF1 maintains endothelial barrier function and prevents edema after lung injury. *Sci Signal.* 2016;9(424):ra40.

PUBLISHED APRIL 19, 2016

Science Signaling

Researchers here have developed a compound that appears to reverse often-fatal lung damage.

The findings, published April 19, 2016, in *Science Signaling*, eventually could improve treatments for pneumonia caused by various types of infection, or in premature infants with underdeveloped lungs, and people undergoing certain cancer treatments.

The study's leading co-authors were Vladimir Kalinichenko, MD, PhD, of the Divisions of Pulmonary Biology and Developmental Biology, and Tanya Kalin, MD, PhD, of the Perinatal Institute.

Their team analyzed mice bred with lungs lacking the transcription factor FOXF1. This resulted in abnormal endothelial cells lining the lungs' blood vessels, which in turn made the lungs prone to deadly levels of inflammation and fluid build-up.

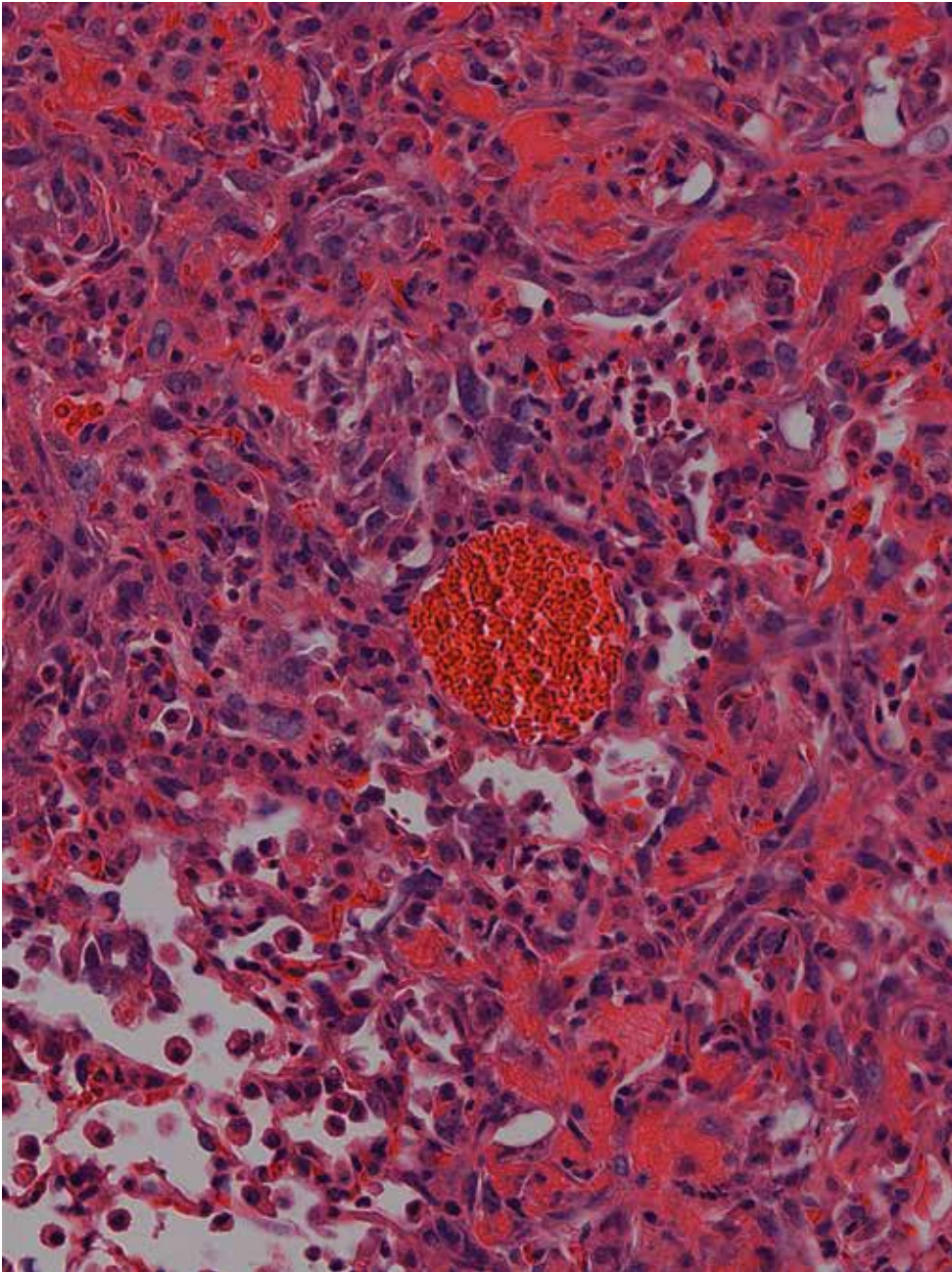
However, a compound that simulates FOXF1 promotes recovery from lung injury, according to the new study.

"The small molecule compound we developed stabilizes the FOXF1 protein in cell cultures and mouse lungs, and shows promise in inhibiting lung inflammation and injury," says Kalinichenko.

The new findings are important because acute respiratory distress syndrome—a complication of lung injury—carries a 35 percent mortality rate. It accounts for about 75,000 deaths and 3.5 million hospital days each year in the United States.

"Given the lack of major improvements in the clinical management of acute lung injury and respiratory distress, there is a compelling need for innovative molecular approaches that complement existing therapies," Kalin says.

Researchers will need to conduct much more work to prepare the compound for human clinical trials. If proven safe and effective, the compound may be useful in treating lung damage from a wide range of conditions.

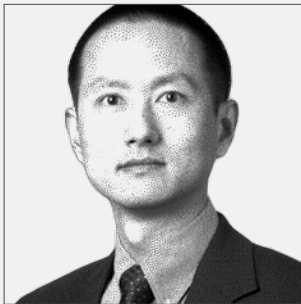


This microscope image shows adult mouse lung tissue in which the FOXF1 gene has been deleted from endothelial cells. The lungs' air sacs show thickening, congestion and severe inflammation that can lead to death. In laboratory tests, an experimental compound stabilizes FOXF1 and allows the lungs to recover.

SNP Analysis Explains Why Shorter Mothers Have Shorter Pregnancies and Smaller Babies



Louis Muglia, MD, PhD



Ge Zhang, MD, PhD

INSTITUTE RESEARCH & TRAINING DETAILS

Faculty	56
Joint Appointment Faculty	1
Direct Annual Grant Support	\$12.6M
Direct Annual Industry Support	\$575,404
Publications	143

Zhang G, Bacelis J, Lengyel C, Teramo K, Hallman M, Helgeland O, Johansson S, Myhre R, Sengpiel V, Njolstad PR, Jacobsson B, Muglia L. Assessing the Causal Relationship of Maternal Height on Birth Size and Gestational Age at Birth: A Mendelian Randomization Analysis. *PLoS Med.* 2015;12(8):e1001865.

PUBLISHED ONLINE AUG. 18, 2015
PLoS Medicine

Shorter women face a higher risk of preterm birth, independent of the genes they pass on to their infants. This surprising finding, based on pregnancy data from more than 3,400 Nordic women, was published online Aug. 18, 2015, in *PLoS Medicine*.

Cincinnati Children’s scientists Louis Muglia, MD, PhD, and Ge Zhang, MD, PhD, led the project. Based on a Mendelian randomization analysis, the team found a key link between birth length, weight and height-related single nucleotide polymorphisms (SNPs) transmitted from the mother.

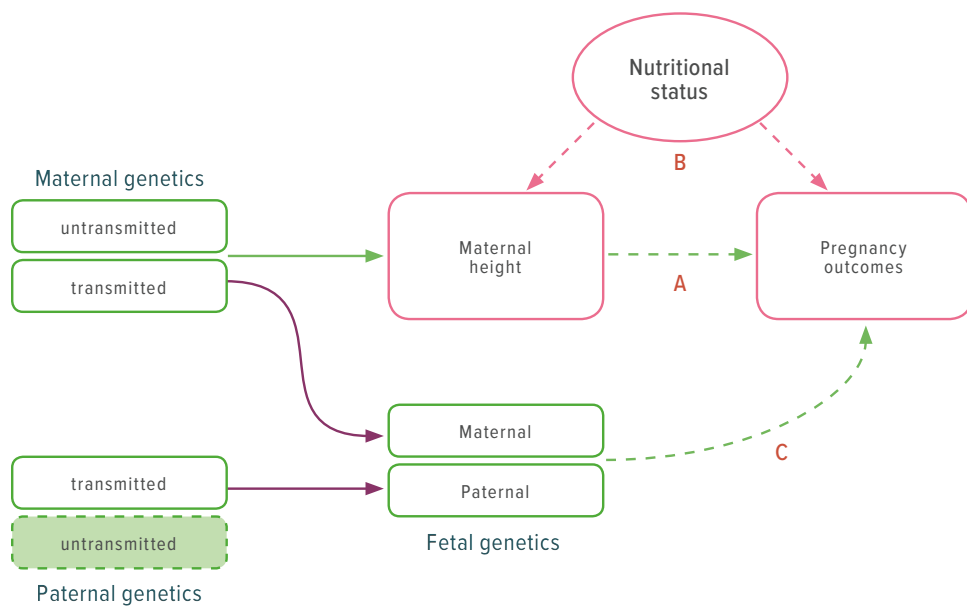
“The explanation for how this happens is unclear,” Muglia says. “It could be related to height affecting the size of the uterus and pelvis, or it could be related to the mother’s metabolic rate and the amount of nutrition she can supply to the growing baby.”

Associations with non-transmitted SNPs were far less significant for birth length and birth weight. However, gestational age was associated with the maternal non-transmitted SNPs.

The findings are important because preterm birth is the leading killer of newborns in the U.S.

“Knowing that a mother’s height can be a factor suggests that optimizing a woman’s growth in childhood or adolescence should decrease the risk for preterm birth later,” Muglia says.

The March of Dimes Prematurity Research Center’s Ohio Collaborative sponsored this study. Researchers plan further studies to determine if the findings apply to low- and middle-income countries, where nutrition-related factors also can restrict growth.



Conceptual model depicting key elements of the family's experience with the hospital-to-home transition.

SINCERA: A Breakthrough Tool for Single-Cell RNA Profiling



Jeffrey Whitsett, MD



Yan Xu, PhD

INSTITUTE RESEARCH & TRAINING DETAILS

Faculty	56
Joint Appointment Faculty	1
Direct Annual Grant Support	\$12.6M
Direct Annual Industry Support	\$575,404
Publications	143

Guo M, Wang H, Potter SS, Whitsett JA, Xu Y. SINCERA: A Pipeline for Single-Cell RNA-Seq Profiling Analysis. *PLoS Comput Biol.* 2015;11(11):e1004575.

PUBLISHED NOV. 24, 2015
PLoS Computational Biology

A new open-source analytic tool called SINCERA is helping scientists gain new insight into how organs form in a developing embryo.

A paper describing the tool appeared Nov. 24, 2015, in *PLoS Computational Biology*. A team led by Yan Xu, PhD, Pulmonary Biology and Biomedical Informatics, and Jeffrey Whitsett, MD, Co-Director, Perinatal Institute, developed the tool.

Single-cell transcriptomics is a powerful way to profile cell-to-cell variability on a genomic scale. Its use will advance decades of research, led in large part at Cincinnati Children’s, to produce the world’s most-detailed map of lung development.

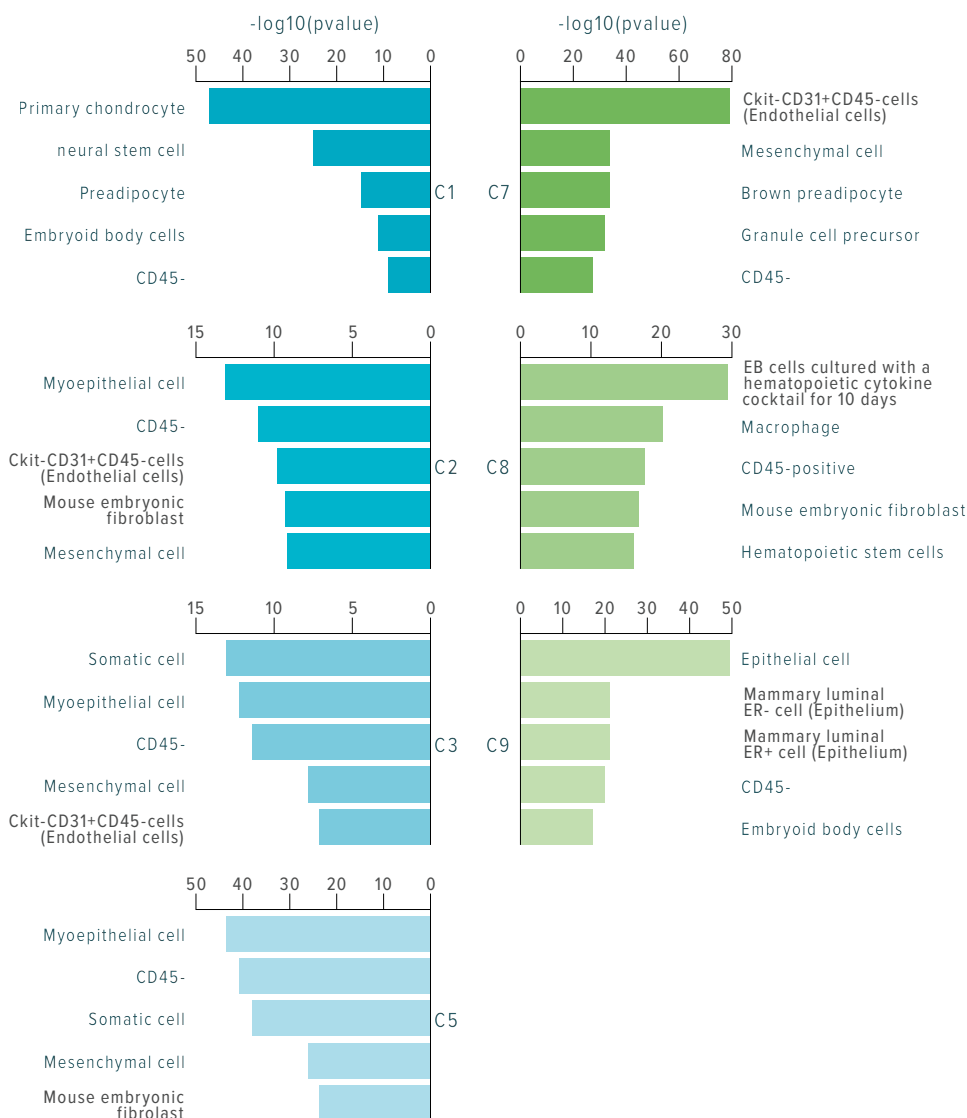
“A thorough understanding of the cells and gene expression driving normal lung maturation will promote the understanding of lung diseases in both infants and children,” Xu says. “However, the paucity of analytic tools for processing extensive single-cell genomic data has been a major challenge.”

SINCERA is an acronym drawn from “a computational pipeline for single-cell RNA-seq profiling analysis.” The tool allows investigators to use standard desktop and laptop computers for data filtering, clustering, cell type identification, gene signature prediction and more.

The tool makes it easier to identify major cell types, the gene signatures specific to cell types, and the driving forces of given cell types. Among its early uses: producing multiple single-cell datasets reflecting different time points in organ development.

The NIH-funded Lung-MAP consortium has supported this project as part of its mission to develop a comprehensive atlas of lung development. SINCERA and LungGENS, a related tool, are both freely available to the research community.

Cell Type Enrichment Analysis



Cell type enrichment analysis is just one of several ways the new SINCERA tool can help accelerate the study of organ development.

Parenting Styles, Home Resources Play Key Roles in Recovery



Shari Wade, PhD

PUBLISHED APRIL 2016
JAMA Pediatrics

Improving parenting skills and home environments could help more children overcome the longer-term effects of traumatic brain injury (TBI).

That’s the conclusion of a study comparing long-term outcomes of 58 children who suffered TBIs with 72 children who sustained orthopaedic injuries (OI). Shari Wade, PhD, Director of Research, Division of Physical Medicine and Rehabilitation, led the project.

The study found that children with moderate and severe TBIs had more impairments in multiple domains nearly seven years after their injury than the OI group. Children with complicated mild TBIs also had more school and thinking impairments than the OI group.

The study builds on Wade’s previous research about how a child’s social environment can affect recovery from TBI. It explores the use of online problem-solving therapy and family intervention programs to improve an injured child’s success.

The latest research encompassed observations performed from January 2010 through April 2015 at schools, homes and at four participating Midwest hospitals. The team used the Child and Adolescent Functional Assessment Scale (CAFAS) to measure outcomes.

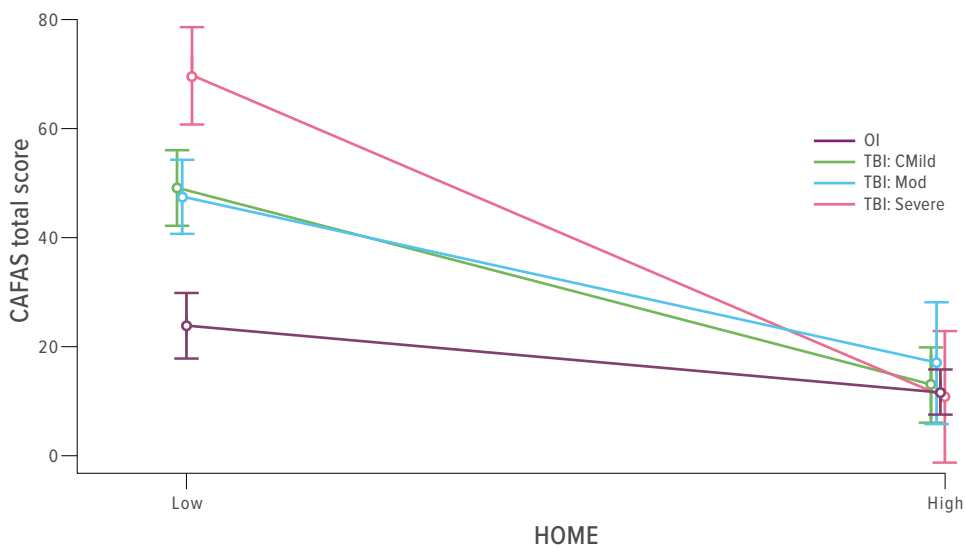
Wade and colleagues found that more-pronounced impairments in behavior and academic performance occurred among children in homes where parenting styles were either highly permissive or authoritative. Impairment levels also were elevated in homes with access to fewer resources.

“Even children with relatively mild early TBI experience long-term functional impairments, particularly in the context of less favorable home environments,” says Wade. “These findings suggest that improving parenting skills and the quality of the home environment may promote functional recovery following early TBI.”

RESEARCH & TRAINING DETAILS

Faculty	8
Research Fellows & Post Docs	2
Research Graduate Students	3
Total Annual Grant Awards	\$2M
Total Publications	23

Wade SL, Zhang N, Yeates KO, Stancin T, Taylor HG. Social Environmental Moderators of Long-term Functional Outcomes of Early Childhood Brain Injury. *JAMA Pediatr.* 2016;170(4):343-349.



Significant group x home environment interaction ($F(3,114) = 3.28$; $p = .024$) revealing significantly poorer long-term functioning outcomes for children with a TBI than children with an OI when the home environment had low enrichment, while high facilitative home environments revealed no significant group differences in functional impairment.

Advancing Technology Fuels Discovery of Novel Mechanism Underlying Cleft Palate



Yu Lan, PhD



Rulang Jiang, PhD

RESEARCH & TRAINING DETAILS

Faculty	10
Joint Appointment Faculty	1
Research Fellows & Post Docs	3
Research Graduate Students	2
Total Annual Grant Awards	\$688,028
Total Publications	15

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Lan Y, Zhang N, Liu H, Xu J, Jiang R. Golgb1 regulates protein glycosylation and is crucial for mammalian palate development. *Development*. 2016;143(13):2344-2355.

PUBLISHED ONLINE MAY 25, 2016

Development

Finding a genetic mutation linked to cleft palate—one of the world’s most common birth defects—was just part of the story for this research project. How the team made the discovery was nearly as important as the discovery itself.

The paper, published online in May 2016, reveals that mutations in the Golgb1 gene can lead to cleft palate. Specifically, Golgb1 mutant mouse embryos exhibit increased cell density, reduced hyaluronan accumulation and impaired protein glycosylation during palate development.

Normally, embryonic palatal shelves initiate and grow vertically from the oral side of the maxilla and then elevate to the horizontal position above the tongue to fuse at the midline to form the roof of the oral cavity. However, in mice with the mutation, the palatal tissue proteins do not glycosylate properly. Palatal shelves remain in the vertical position and unable to bond. This results in cleft palate at birth.

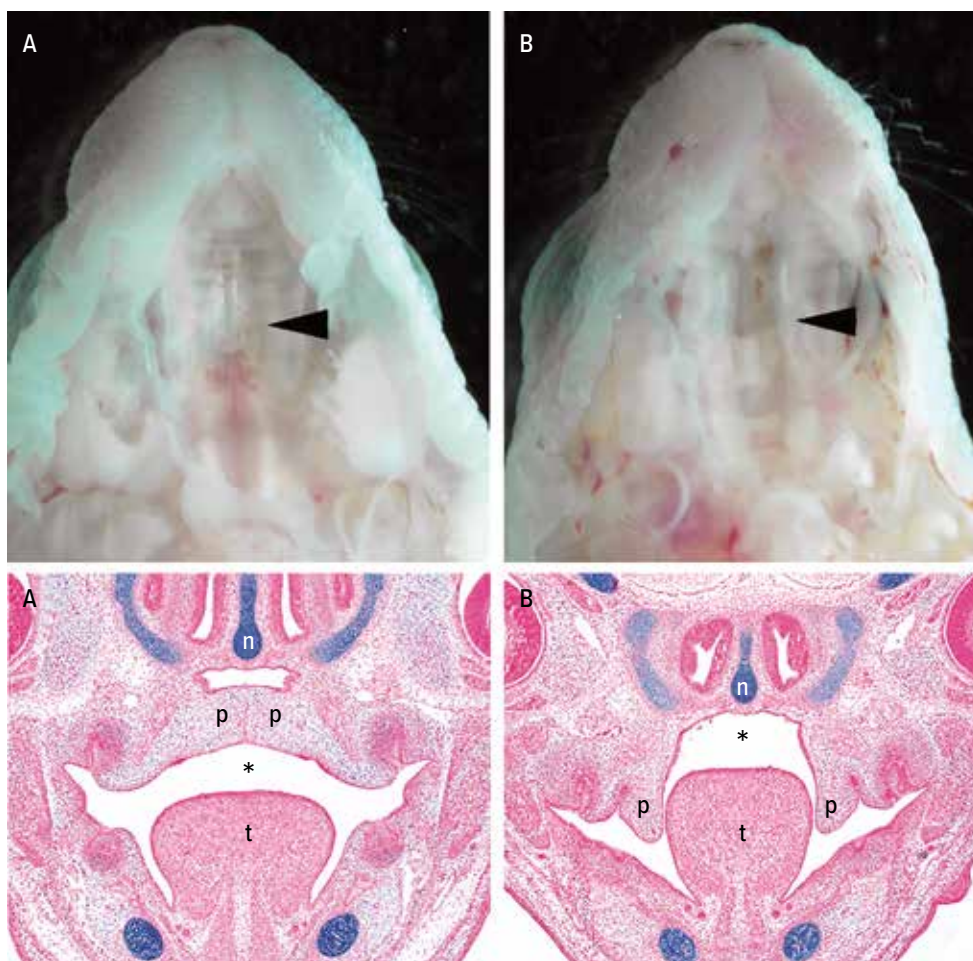
Yu Lan, PhD, Plastic Surgery, and Rulang Jiang, PhD, Developmental Biology, collaborated on the study.

“Identification of the link between the Golgb1 gene and cleft palate was completely unexpected because Golgb1 is expressed in every cell, but the results reveal that Golgb1 has specific functions in protein glycosylation and tissue morphogenesis,” Jiang says.

This study was unusual among palate development studies because Lan’s team used chemical mutagenesis to screen mice pups. They used whole-exome sequencing to identify mutant genes. Finally, they used CRISPR-Cas9 technology to validate the role of Golgb1 in palate development.

CRISPR’s genome-editing capabilities are influencing a wide range of research work at Cincinnati Children’s and around the world.

Jiang says the cleft palate discovery “has wide implication in using the phenotype-based screening to find unexpected biology and disease mechanisms. This was purely discovery-based research that finds a specific cause and validates it.”



The Golgi-associated Golgb1 protein is required for normal palate development. In oral views, arrowheads show a cleft palate in the Golgb1 mutant mouse pup (B) in comparison with the closed palate in the normal littermate (A). Frontal sections of each mouse reveal failure of palatal morphogenesis in the Golgb1 mutant embryo.

Transcranial Magnetic Stimulation Detects Potential Biomarker for Autism-Related Brain Activity



Ernest Pedapati, MD, MS



Craig Erickson, MD

RESEARCH & TRAINING DETAILS

Faculty	20
Joint Appointment Faculty	2
Research Fellows & Post Docs	1
Total Annual Grant Awards	\$1.5M
Total Annual Industry Awards	\$880,600
Total Publications	24

Pedapati EV, Gilbert DL, Erickson CA, Horn PS, Shaffer RC, Wink LK, Laue CS, Wu SW. Abnormal Cortical Plasticity in Youth with Autism Spectrum Disorder: A Transcranial Magnetic Stimulation Case-Control Pilot Study. *J Child Adolesc Psychopharmacol*. 2016

PUBLISHED MARCH 2016

Journal of Child and Adolescent Psychopharmacology

One of the challenges of studying autism spectrum disorder (ASD) is a limited understanding about how the brain reacts internally, regardless of external symptoms of diagnosis.

However, new research suggests that transcranial magnetic stimulation (TMS) can serve as a tool for grouping children with ASD according to differences in their brain activity.

Ernest Pedapati, MD, MS, and colleagues Craig Erickson, MD, and Logan Wink, MD, led a team of scientists from Cincinnati Children's who reported their findings in March 2016 in the *Journal of Child and Adolescent Psychopharmacology*.

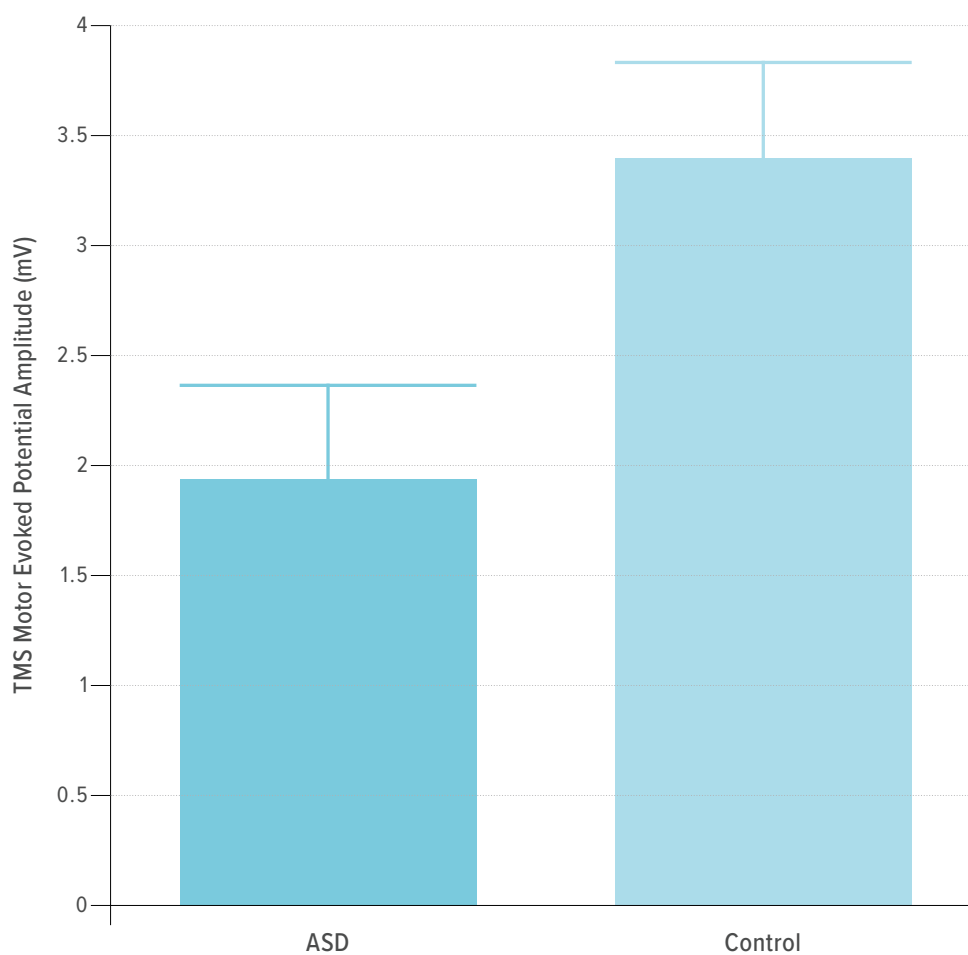
The team delivered intermittent theta burst stimulation (iTBS)—a brief, controlled magnetic pulse that activates brain neurons—to nine children with ASD and nine children without ASD. The ASD group showed a unique and significant decrease in brain excitability after 20 minutes.

These results provide “early evidence for a potential physiological biomarker of cortical plasticity in youth,” the team reports.

Long-term, psychiatrists hope to use these types of biomarkers to guide treatment according to differences in ASD brain activity, Pedapati says. As improved neurological signatures of ASD emerge, clinicians could become more accurate at providing the most effective treatment.

Biomarkers also could help guide patients to the most appropriate drug studies when they do not respond well to existing therapy.

“Some children really do get better, but we lose them in the noise,” Pedapati notes. “This approach uses technology to profile brain activities and brain responses so that they don’t get lost in the noise.”



Linear mixed model estimates with standard errors of post-iTBS motor evoked potential amplitudes. Post-hoc comparison indicated a significant difference at 20 minutes (shown), with ASD demonstrating significantly less facilitation than TDC. ASD, autism spectrum disorder group; Control, typically developing control group; iTBS, intermittent theta burst stimulation.

MRI Improves Analysis of Bronchopulmonary Dysplasia



Jason Woods, PhD



Laura Walkup, PhD

RESEARCH & TRAINING DETAILS

Faculty	28
Joint Appointment Faculty	8
Research Fellows & Post Docs	12
Research Graduate Students	2
Total Annual Grant Awards	\$6.5M
Total Annual Industry Awards	\$1.4M
Total Publications	95

Walkup LL, Tkach JA, Higano NS, Thomen RP, Fain SB, Merhar SL, Fleck RJ, Amin RS, Woods JC. Quantitative Magnetic Resonance Imaging of Bronchopulmonary Dysplasia in the Neonatal Intensive Care Unit Environment. *Am J Respir Crit Care Med.* 2015;192(10):1215-1222.

PUBLISHED NOV. 15, 2015
American Journal of Respiratory and Critical Care Medicine

Physicians have long faced challenges in detecting subtle differences in bronchopulmonary dysplasia (BPD), a serious but poorly characterized complication in premature infants.

Most infants with BPD are born more than 10 weeks early, at less than two pounds. However, two leading diagnostic options come with limitations.

Radiation from CT scans can pose a risk to these especially fragile infants. Meanwhile, tracking oxygen dependence at 36 weeks gestational age does not provide objective measures of structural abnormalities across disease severity.

Now a third option—magnetic resonance imaging (MRI)—is emerging, according to research published Nov. 15, 2015, in the *American Journal of Respiratory and Critical Care Medicine*.

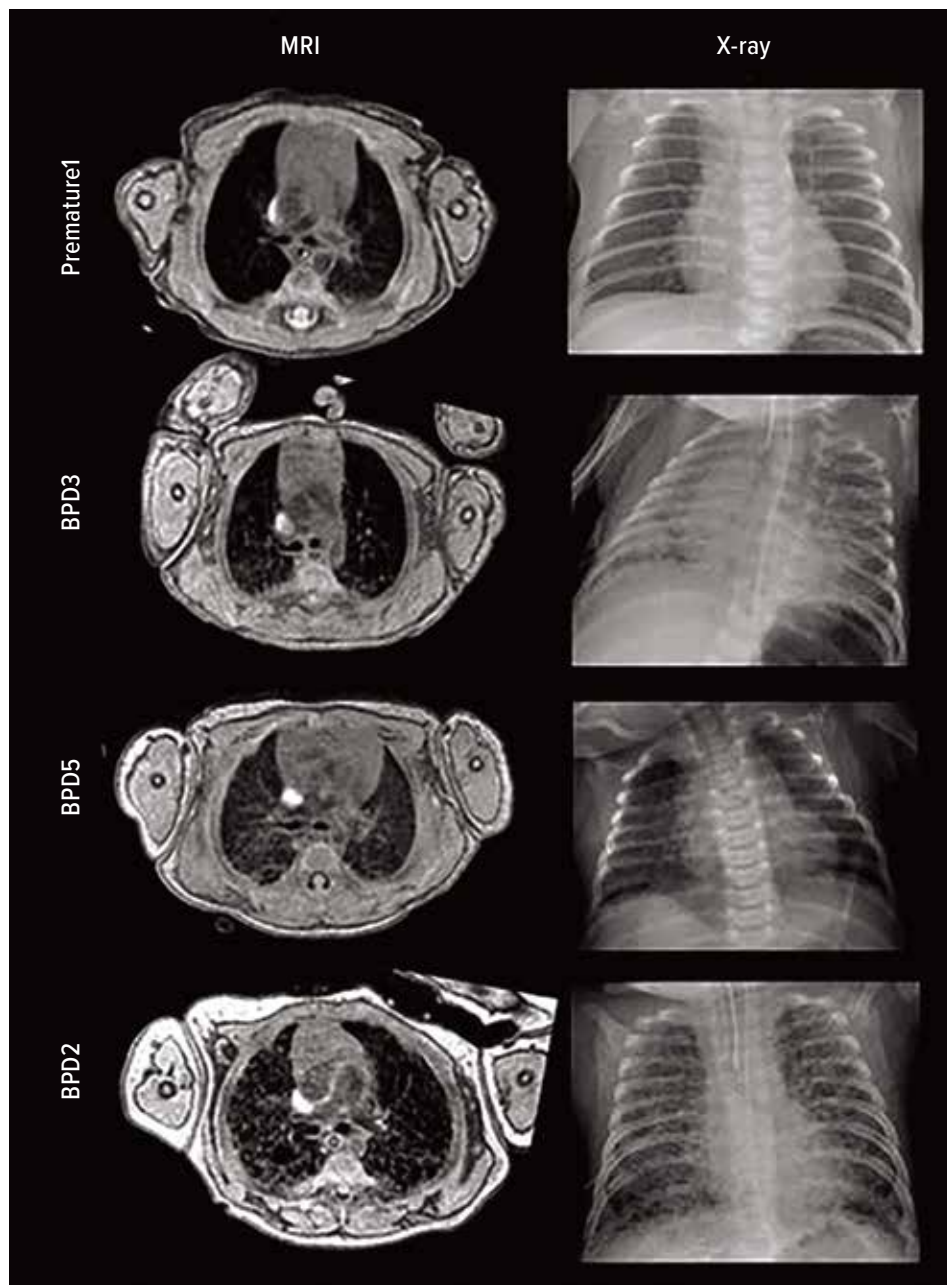
“We demonstrated that we can differentiate subtle differences in mild and more severe disease,” says Jason Woods, PhD, Director, Center for Pulmonary Imaging Research. “We also can perform the scans in the NICU itself.

The research team included center colleague and first author Laura Walkup, PhD, and Raouf Amin, MD, Director, Pulmonary Medicine.

The team used a unique, small-footprint MRI scanner—developed at Cincinnati Children’s—that is located in the NICU. The team scanned six premature infants with BPD, six premature patients without BPD, and six full-term NICU patients.

A radiologist graded the images using a modified Ochiai score. The team also used segmentation and threshold analysis to quantify volumes of high- and low-signal intensity lung parenchyma.

The MRI detected quantifiable, significant differences in lung tissue between the three groups. “These methods,” the authors wrote, “could be implemented to individually phenotype disease, which may impact clinical care and predict future outcomes.”



Researchers used MRI to compare the axial fast gradient echo slice of four premature babies, three with bronchopulmonary dysplasia (BPD) and one without. The MRIs more clearly indicate that Patient BPD5 shows signs of fibrotic opacities. In Patients BPD2 and BPD3, these features and multiple regions of emphysema and hyperexpansion are described in the X-rays.

Ultrasound Proves Effective as Alternate to Biopsy for Measuring Liver Stiffness and Health



Andrew Trout, MD

PUBLISHED ONLINE MAY 26, 2016

Radiology

Ultrasound is an effective tool for measuring liver stiffness, one of the key indicators of disease. It has additional value as a less-invasive alternative to biopsy. But it comes with a catch.

The weight of the children matters significantly. Ultrasound was less effective for patients with a body-mass index (BMI) exceeding 30 kg/m², according to an analysis of ultrasonographic point shear-wave elastography. This ultrasound method has been increasingly used to quantify liver fibrosis.

The study, published online in *Radiology*, included first-author Andrew Trout, MD, Department of Radiology, and Cincinnati Children's colleagues in Radiology and the Division of Gastroenterology, Hepatology and Nutrition.

Researchers evaluated 55 patients with a mean age of 14 years. They looked at the correlation between ultrasound and magnetic resonance (MR) elastography liver shear-wave speed measurements.

Elastography maps a target organ to show how stiff the tissue is. MR elastography is considered the reference standard in the absence of biopsy.

The goal was to see how well ultrasound data matched the MR data. Both methods were effective for the less heavy patients, but in the heavier group, the ultrasound data broke down.

"We believe this relates to technical (hardware and software) limitations and we are working with the equipment manufacturers to address these issues," Trout says.

Despite its limitations in patients with higher BMI, ultrasound has become another effective way to evaluate the liver without the risk of biopsy.

"Ultrasound," Trout adds, "has advantages over MRI in terms of cost, portability and ease of application that make this an attractive technique for measuring liver stiffness in children."

RESEARCH & TRAINING DETAILS

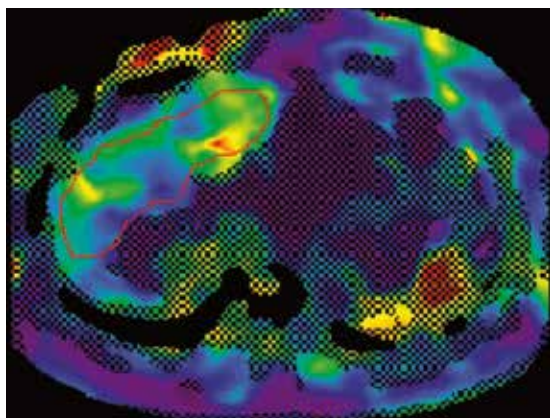
Faculty	45
Joint Appointment Faculty	8
Research Fellows & Post Docs	1
Research Graduate Students	7
Total Annual Grant Awards	\$624,545
Total Annual Industry Awards	\$203,008
Total Publications	179

Trout AT, Dillman JR, Xanthakos S, Kohli R, Sprague G, Serai S, Mahley AD, Podberesky DJ. Prospective Assessment of Correlation between US Acoustic Radiation Force Impulse and MR Elastography in a Pediatric Population: Dispersion of US Shear-Wave Speed Measurement Matters. *Radiology*. 2016;152797.

A

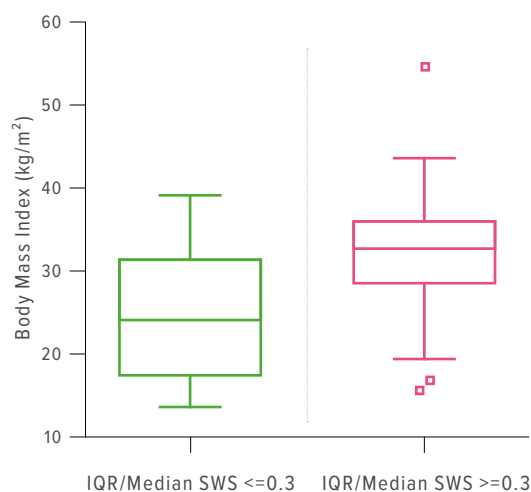


B



These ultrasound (A) and MR elastography (B) images of the liver are from a study patient with a BMI of 35.7 kg/m². The green box in the ultrasound image is where the liver stiffness measurement is being made. The color coding in the MRI image reflects areas of the liver that have different measured stiffness values.

C



C: This chart plots BMI values for patients with good quality ultrasound data (IQR/Median SWS ≤ 0.3) versus BMI values for patients with poor quality data (IQR/Median SWS > 0.3). On average, patients with poor quality data have higher BMI values demonstrating that the ultrasound technique breaks down in larger patients.

Macrophages Play Unexpected Role in Sperm Production



Tony DeFalco, PhD

PUBLISHED AUG 18, 2015
Cell Reports

Macrophages are white blood cells best known for their role in engulfing and digesting harmful microbes, cell debris, and other foreign particles. However, these cellular scavengers also play a surprising role in the cycle of sperm production.

The latest findings from a research team led by Tony DeFalco, PhD, were striking enough to be featured on the Aug. 18, 2015, cover of *Cell Reports*. The journal *Biology of Reproduction* also included the study in its “World of Reproductive Biology” collection of breakthrough findings.

Despite earlier success in simpler fruit flies and roundworms, scientists have spent years hunting for the niche within more complex mammalian testes, where stem cells begin the cycle of sperm production. In a series of experiments with mice, DeFalco and colleagues found an unexpected answer.

Their work describes a macrophage population located at the surface of seminiferous tubules in the adult mouse. These unusual, small-bodied macrophages appear to contribute to a niche that supports sperm stem cell differentiation.

When the team ablated these macrophages, stem cells in the mice testes produced far fewer daughter cells. Macrophage presence appears to be required specifically for Asingle spermatogonia to differentiate into Aaligned spermatogonia.

These findings shed new light on the potential causes of male infertility, and may eventually lead to improved treatments. “Macrophages have largely been overlooked in reproductive contexts,” DeFalco says.

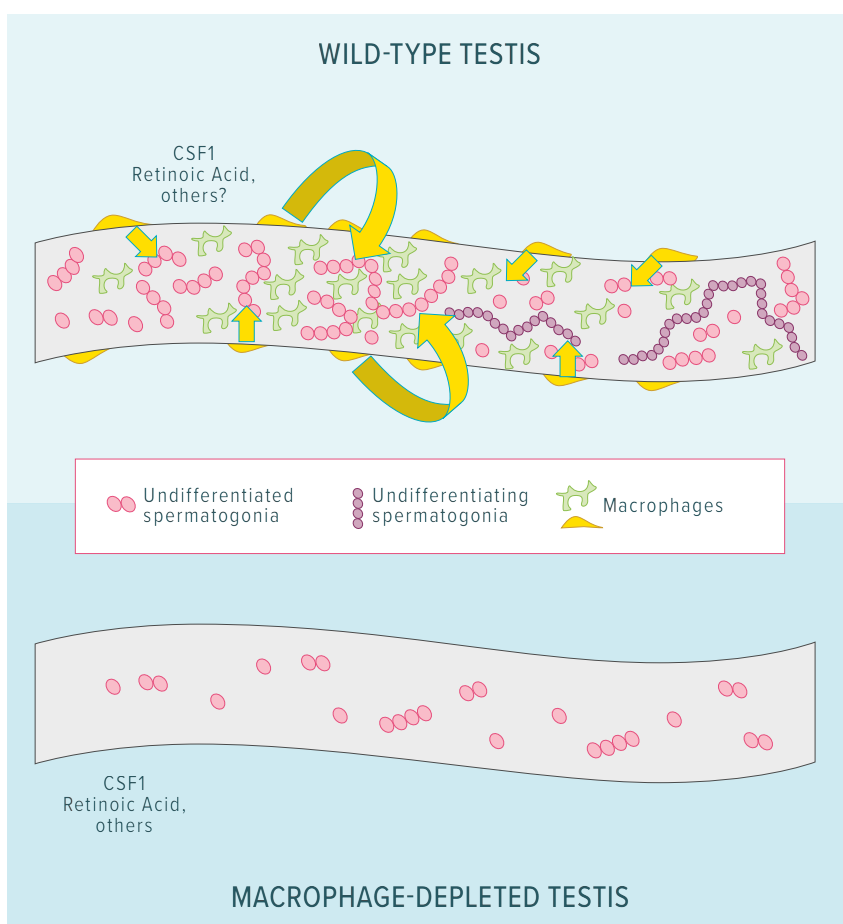
However, the discovery has implications beyond reproduction.

“Immune cells interact with other cell types during organ formation and secrete factors critical for growth, development, and homeostasis,” DeFalco says. “This unexpected role for macrophages in the spermatogonial niche further supports the idea that macrophages may be broadly important in regulating stem cell populations.”

RESEARCH & TRAINING DETAILS

Faculty	8
Joint Appointment Faculty	1
Research Fellows & Post Docs	8
Total Annual Grant Awards	\$1.6M
Total Publications	21

DeFalco T, Potter SJ, Williams AV, Waller B, Kan MJ, Capel B. Macrophages Contribute to the Spermatogonial Niche in the Adult Testis. *Cell Rep.* 2015;12(7):1107-1119.



New research published in *Cell Reports* describes how macrophages influence sperm cell production in mammalian testes. This illustration shows that macrophages are enriched near sperm cell precursors and are required for sperm stem cell differentiation, potentially acting through CSF1 and retinoic acid pathways.

This is a Child’s Brain on Books: How Reading to Children Can Shape the Developing Brain



John S. Hutton, MD

RESEARCH & TRAINING DETAILS

Faculty	8
Joint Appointment Faculty	9
Research Fellows & Post Docs	3
Total Annual Grant Awards	\$892,798
Total Annual Industry Awards	\$132,010
Total Publications	49

Hutton JS, Horowitz-Kraus T, Mendelsohn AL, DeWitt T, Holland SK, Consortium CMA. Home Reading Environment and Brain Activation in Preschool Children Listening to Stories. *Pediatrics*. 2015;136(3):466-478.

PUBLISHED AUGUST 2015
Pediatrics

Educators and pediatricians have long encouraged parents to read early and often to infants and preschoolers. Now research from the Reading and Literacy Discovery Center (RLDC) shows why this good habit can be good for the brain.

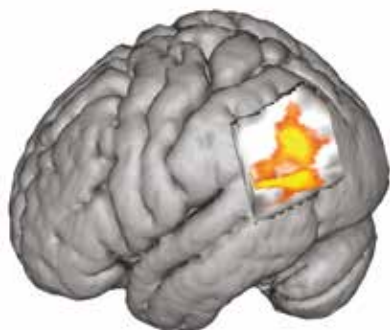
The project included 19 children, ages 3-5, listening to a narrated story through headphones while researchers monitored their brain activity. The team used functional MRI imaging to gather brain data. They also used the StimQ-P home cognitive stimulation scale to evaluate the child’s home reading environment.

Children from robust home reading environments showed greater activity in the left parietal-temporal-occipital (PTO) association cortex, a brain “hub” linked to semantic processing, long-term memory and the integration of visual imagery. This hub is thought to facilitate imagination and language comprehension.

“As providers and pediatricians, we can talk about the importance of reading to parents until we’re blue in the face, but now we can point to an image of a child’s brain ‘on books’ and make a compelling case that reading is a critical health issue,” says the study’s lead author, John S. Hutton, MD.

Hutton is a member of General and Community Pediatrics and Research in Patient Services, which houses the RLDC. He also is the “bookstore pediatrician” who owns Cincinnati’s blue manatee children’s bookstore.

“The amazing thing is that even when the stories had no pictures, we observed strong activity in visual areas of the brain, suggesting a link to imagination and creativity during this formative time,” says Hutton. “This study adds novel, neurobiological evidence to the known benefits of reading together during early childhood. A brain-based model also provides insight into how reading together may shape neural development, and what interventions may be most effective.”



This 3-D image of the posterior left hemisphere—the side typically dominant for language—features a bright area of increased brain activation when children listen to stories read to them. The activated area is the parietal-temporal-occipital multi-modal association cortex, a hub for integrating multi-sensory inputs. This study indicates that children with greater exposure to books and shared reading at home tend to be better at self-generating the visual images associated with imagination and narrative comprehension.



For Some, H1N1 Flu Triggers Fatal Reactive HLH



Grant Schulert, MD, PhD



Alexei Grom, MD

RESEARCH & TRAINING DETAILS

Faculty	10
Joint Appointment Faculty	2
Research Graduate Students	3
Total Annual Grant Awards	\$937,626
Total Annual Industry Awards	\$1M
Total Publications	48

Schulert GS, Zhang M, Fall N, Husami A, Kissell D, Hanosh A, Zhang K, Davis K, Jentzen JM, Napolitano L, Siddiqui J, Smith LB, Harms PW, Grom AA, Cron RQ. Whole-Exome Sequencing Reveals Mutations in Genes Linked to Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome in Fatal Cases of H1N1 Influenza. *J Infect Dis.* 2016;213(7):1180-1188.

PUBLISHED NOV. 23, 2015

Journal of Infectious Diseases

Whole-exome sequencing of samples from 16 fatal cases of H1N1 influenza reveals that some deaths may have occurred because the virus triggers a rare form of immune system disease.

This discovery comes from a team of rheumatology and human genetics experts at Cincinnati Children's who worked with colleagues from the University of Alabama at Birmingham, Children's of Alabama and the University of Michigan.

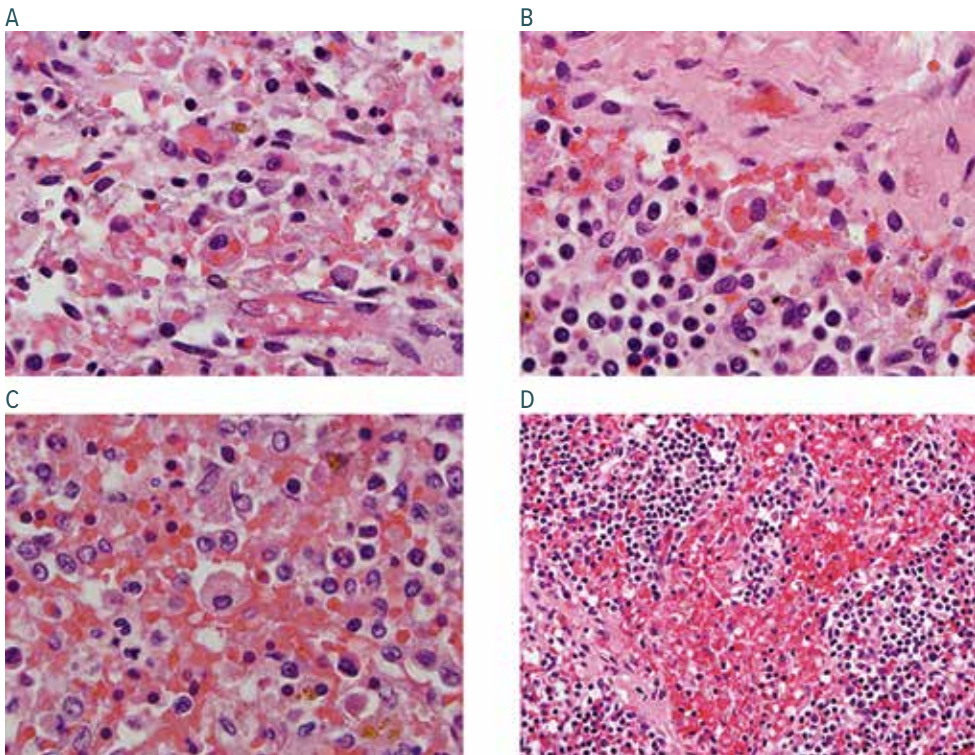
The team, led by Grant Schulert, MD, PhD, and Alexei Grom, MD, reports that those who died carried mutations in several genes linked to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS). In fact, the flu victims studied met 44 percent of the criteria for HLH and 81 percent of the criteria for MAS.

"Our data suggest some people may have a genetic predisposition to develop severe H1N1 influenza, and critically ill H1N1 patients should be carefully evaluated for secondary HLH and MAS," Schulert says. "The question is whether immunosuppressive therapy may benefit some patients with life-threatening influenza infection."

HLH can occur as an independent, directly inherited disease. However, some studies also have detected the devastating cascade of HLH symptoms occurring as a reaction to certain viral and fungal infections as well as rheumatic diseases. This study adds H1N1 influenza to that growing list.

This new understanding suggests that it may be possible to develop a genetic screening test for flu victims that could predict which people are most likely to suffer dangerous HLH reactions. Such a test could help clinicians save lives through earlier, targeted interventions.

This study examined past cases from a single state. Looking ahead, the authors recommend conducting a larger prospective study to determine if genomic testing can predict outcomes during influenza and other types of infections.



These microscope images show examples of hemophagocytosis characterized by macrophages with engulfed red blood cells in lymph node (A, B) and spleen (C, D) in fatal cases of H1N1 influenza.

Compression Collar Protects Athletes From Traumatic Brain Injury



Greg Myer, PhD



Weihong Yuan, PhD

RESEARCH & TRAINING DETAILS

Faculty	9
Joint Appointment Faculty	2
Research Graduate Students	2
Total Annual Grant Awards	\$364,073
Total Annual Industry Awards	\$1M
Total Publications	48

Myer GD, Yuan W, Barber Foss KD, Thomas S, Smith D, Leach J, Kiefer AW, Dicesare C, Adams J, Gubanich PJ, Kitchen K, Schneider DK, Braswell D, Krueger D, Altaye M. Analysis of head impact exposure and brain microstructure response in a season-long application of a jugular vein compression collar: a prospective, neuroimaging investigation in American football. *Br J Sports Med.* 2016

PUBLISHED JUNE 15, 2016
British Journal of Sports Medicine

It may be possible to prevent sports-related brain injuries by augmenting traditional helmets with a device that protects the brain from the inside.

That’s the conclusion of a study that examined how high school football players fared during a season-long test of a novel jugular vein compression collar. A related study involving high school hockey players appeared June 6, 2016, in *Frontiers in Neurology | Neurotrauma*.

While helmets offer important protection for athletes, they do little to prevent “brain slosh,” which occurs when the brain collides against the inside of the skull.

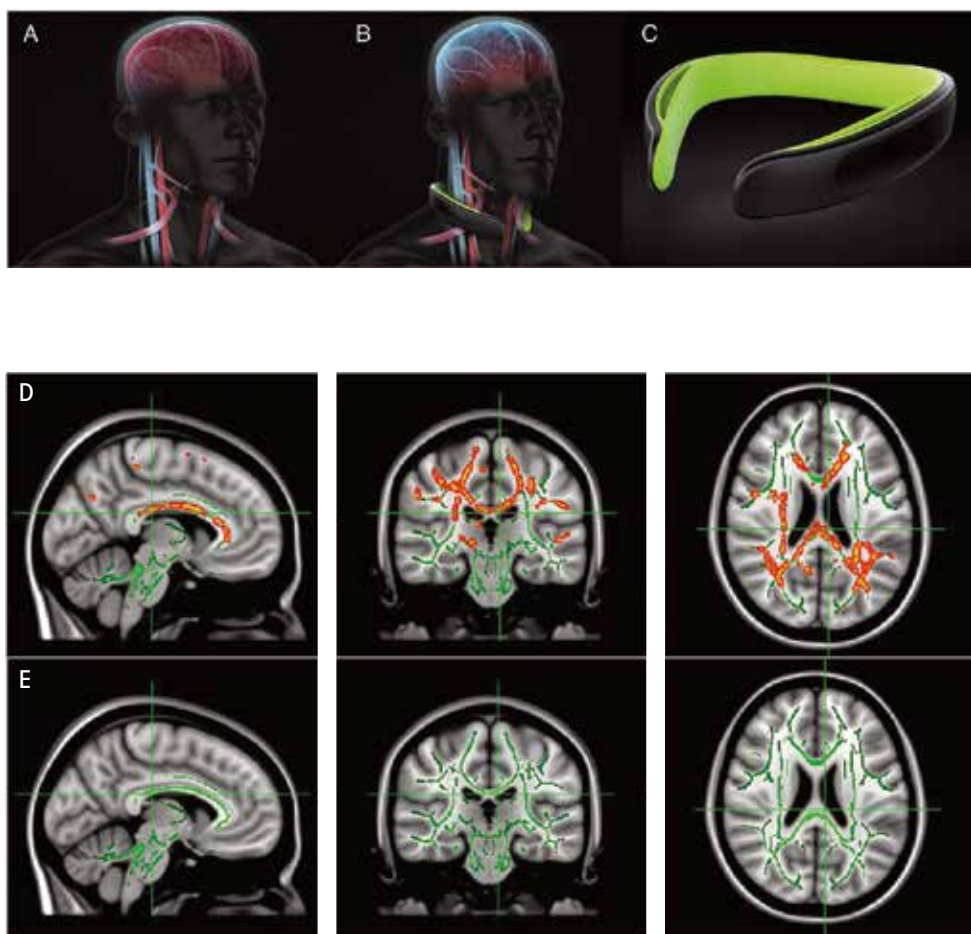
The new device, called a Q-Collar, was inspired by observations of woodpeckers and big horn sheep that avoid brain injury despite frequent head impacts. The collar applies pressure similar to a dress-tie knot that slightly increases blood volume, promoting a tighter fit of the brain inside the cranium.

Greg Myer, PhD, Director of Sports Medicine Research, leads ongoing study of the collar. Weihong Yuan, PhD, and James Leach, MD, experts in neuroradiology, developed an imaging protocol to measure the collar’s effects.

“We still have more data analysis and investigation to do, but this device could be a real game-changer in helping athletes,” Myer says.

The hockey study involved 15 players. In the football study, half of the 42 players wore collars during a season while half, as a control group, did not.

Both groups experienced similar levels of head impact. However, diffusion tensor imaging (DTI) revealed significant preseason to postseason changes in mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) in the white matter of players not wearing the collars compared to those who wore them. Similar findings were observed in the hockey players.



Diffusion tensor imaging shows how sports collisions can affect the brain's white matter. A: Illustrates normal blood flow. B: Illustrates blood volume changes with Q-Collar. C: The Q-Collar. D: Marked areas show increases in mean diffusivity. E: Marked areas in this row show increases in radial diffusivity.

Long-Term Follow-Up Imperative for Minimizing Chronic Kidney Disease in Children with Cloaca



W. Robert DeFoor, MD, MPH

PUBLISHED IN JULY 2015
The Journal of Urology

Early interventions and long-term care strategies are crucial to maintaining renal function in children with chronic kidney disease.

This is particularly challenging among children who undergo complex pelvic reconstruction to repair persistent cloaca.

In this condition, the rectum, urethra and vagina form into one common channel, typically with a single opening at the normal site of the urethra. It is one of the most complex, and potentially fatal, anorectal malformations. It occurs in about one in 20,000 births.

Such children face a variety of long-term risks. However, a study published in *The Journal of Urology*, shows that aggressive bladder management helps prevent progressive renal injury as the child grows.

The team consisted of eight researchers from the Division of Urology and the Colorectal Center at Cincinnati Children's. They tracked 44 girls who had undergone posterior sagittal anorecto-vagino-urethroplasty (PSAVUP) between 2006 and 2013.

PSAVUP is a common repair of cloacal malformations. The median age at the time of the procedure was 7 months; the median age at follow-up was 5 years.

Although one 2-year-old patient with stage IV of the disease ultimately required a kidney transplant, researchers found no patient with initial stage I to III whose condition had worsened with proactive bladder management.

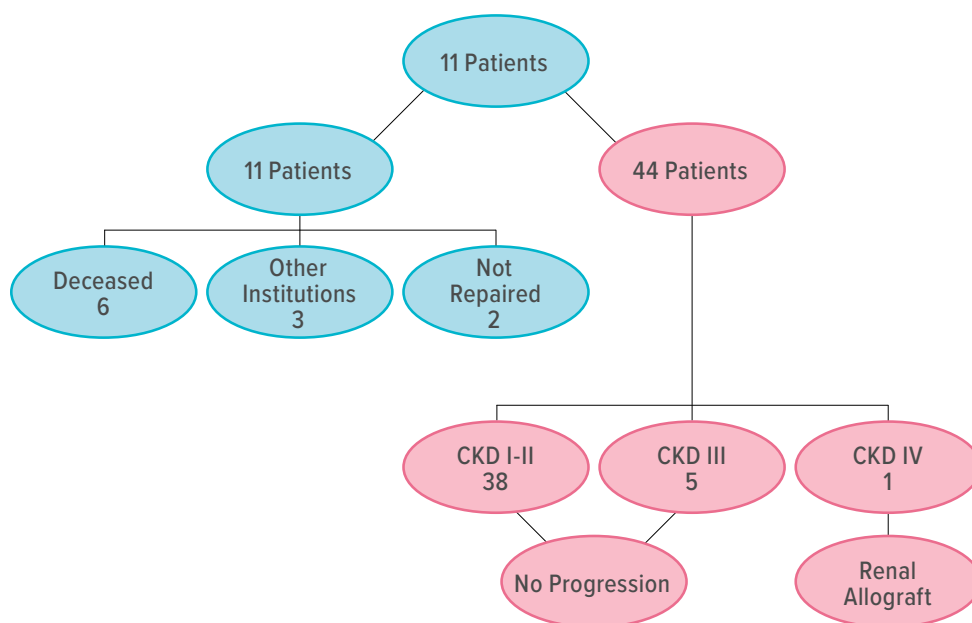
The length of the common channel also mattered. Patients with a length of greater than 3.5 centimeters appeared to have an increased risk of neurogenic bladder.

"We work hard to manage bladder dysfunction and prevent urinary tract infections, which could lead to progressive kidney damage," says W. Robert DeFoor, MD, MPH, Director of Clinical Research in the Division of Urology. "We hope that keeping a close eye on urinary tract function, will help these children keep healthy kidneys for a lifetime."

RESEARCH & TRAINING DETAILS

Faculty	6
Joint Appointment Faculty	2
Research Fellows & Post Docs	1
Total Annual Grant Awards	\$346,800
Total Publications	16

DeFoor WR, Bischoff A, Reddy P, VanderBrink B, Minevich E, Schulte M, Sheldon C, Peña A. Chronic kidney disease stage progression in patients undergoing repair of persistent cloaca. *J Urol*. 2015 Jul;194(1):190-4.



The chart illustrates the importance of early interventions and long-term care strategies in halting the progression of chronic kidney disease in children with cloaca. The 44 patients studied were all treated only at Cincinnati Children's. It also shows the severity of cloaca. Of the 11 children in the initial cohort who were not studied, six died and three were treated at one time at other institutions.



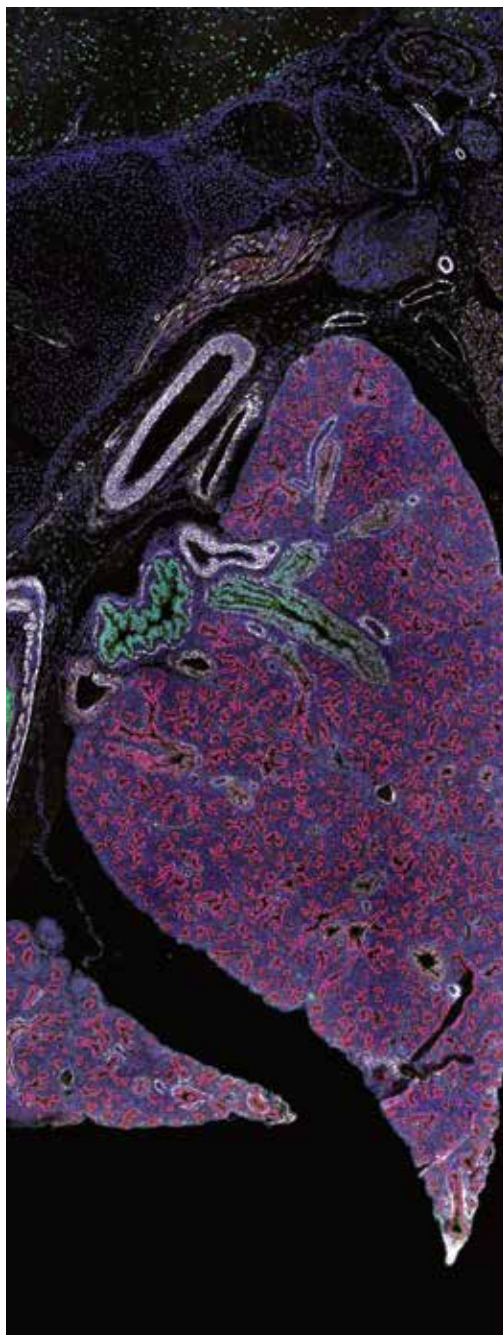
The background of the page is a light blue and white abstract pattern. It features numerous overlapping circles and lines in various colors, including yellow, green, red, and blue, creating a bokeh-like effect. The text is positioned on the right side of the page, with the title 'Shared Facilities' in a large, dark grey font at the top. Below the title is a list of 21 research facilities, each preceded by a small, light blue circular icon. The list is arranged in a single column, with the facilities' names in a smaller, dark grey font. At the bottom of the page, there is a footer with the website address 'CINCINNATICHILDRENS.ORG/RESEARCH' and the page number '133' on the right.

Shared Facilities

- Animal Behavioral Core
- Biostatistical Consulting Unit
- Cardiovascular Imaging Core
- Cell Manipulations Laboratory
- Cell Processing Core
- Cincinnati Biobank
- Comprehensive Mouse and Cancer Core
- Confocal Imaging Core
- Data Management Center
- DNA Sequencing and Genotyping Facility
- Gene Expression Core
- Imaging Research Center
- Mass Spectrometry Facility
- MEG Core
- NMR-Based Metabolomics Core
- Pathology Research Core
- Pluripotent Stem Cell Facility
- Pyrosequencing Core
- Research Flow Cytometry Core
- Transgenic Animal and Genome Editing Core Facility
- Translational Trials Development and Support Laboratory
- Vector Production Facility
- Veterinary Services
- Viral Vector Core

Of Mice and Molecules

Confocal Imaging Core Provides Tools to Capture Images
All the Way Down to the Subcellular Level



A gastroenterology researcher in the Confocal Imaging Core's (CIC) analysis suite pores over a three-dimensional, color-splashed snapshot of organoids on a computer monitor. He rotates and zooms in on the image using a high-end imaging software called IMARIS.

Next door, on a typical day, researchers from Cincinnati Children's or the University of Cincinnati find their seats. Plush black curtains divide the work areas to block stray light. Careful temperature control protects sensitive samples.

Here, deep within the research complex at our Burnet Campus, scientists gather to share access to seven powerful Nikon confocal microscopes. These amazing devices can capture images all the way down to the subcellular level.

But what makes this space so valuable to scientists is not just the high-end microscopes. It is the image analysis tools, the training, and the methodologies used to interpret the images that make this shared facility special.

CENTER OF EXCELLENCE PROVIDES STRONG SUPPORT

"Quantitative analysis of pixel data is important because journals don't just accept a nice picture of a phenotype or cell," says Matthew Kofron, PhD, the CIC's Director. "Proper analysis of data is essential for highly competitive publication and funding. So while a picture is worth a thousand words, a graph with error bars is worth a thousand pictures."

The CIC here is a Nikon Center of Excellence. As such, the company not only provides top-of-the-line tools, but also ongoing training and support. The assistance ranges from initial

training in microscopy to troubleshooting equipment to setting up protocols that allow researchers to get good, reproducible data.

The CIC opened in 2012 and operates 24/7 for badged personnel. Since its grand opening, nearly 400 users from more than 120 labs have used the facility. Their combined work exceeds 1,000 hours per month.

BRINGING COLOR & DIMENSION INTO IMAGING

At one of the microscope stations, CIC manager Michael Muntiferer calls up a slide image. The screen shows a mouse hippocampus represented by 9,000 bright green dots—each dot, a cell.

In some cases, proteins autofluoresce in tissues. In others, researchers use fluorescently labeled antibodies to stain structures of interest.

The confocal microscopes utilize lasers to excite those fluorescent molecules. As the molecules light up, a series of filters separates different wavelengths into color channels that allow differential labeling of cells of interest.

In single-photon confocal microscopy, an advanced method available only at some research centers, a pinhole eliminates out-of-focus light from thick samples. This allows researchers to optically section samples for 3-D reconstruction.

After receiving training from the CIC, Cincinnati Children's researcher Sean McGrath used the microscope for a study published in 2015 in the journal *Diabetes*.

Using images and cell counting data gathered at the CIC, McGrath found that NEUROG3 is essential for endocrine pancreas

development in humans and that as little as 10 percent NEUROG3 is enough to form pancreatic endocrine cells.

FROM A SINGLE DOT, KNOWLEDGE GROWS

Next, Muntiferer brings up a single, living cell on the monitor. "This technology allows us to see exactly where individual molecules are."

He points to one dot on the screen that seems to blink off and on.

That tiny blink demonstrates a quantum mechanics phenomenon called triplet state excitation. This is the backbone of a method for subcellular resolution called stochastic optical reconstruction microscopy. The blinking dot serves as a field marker that allows researchers to locate that molecule across multiple frames of the same cell.

One dot, fluttering in an ocean of data points. That's how deeply the CIC can help scientists dive into their work.

It's not just the high-end microscopes. It's the image analysis tools, the training, and the methodologies used.

Of Isotopes and 'Omics

Our NMR-Based Metabolomics Facility Helps
Science Sleuths 'Dust' for Chemical Fingerprints



Meet “Leonard.” That’s the nickname for our fully automated Bruker IVDr 600MHz nuclear magnetic resonance (NMR) spectroscopy platform.

In 2015, Cincinnati Children’s became the first hospital in the region to install this latest iteration of high-throughput NMR screening technology. “Leonard” is packed with auto-samplers, screening software and other tech needed to produce extremely detailed portraits of the chemical activity happening within a biological sample.

The tool is helping scientists here advance the emerging field of metabolomics, which tracks metabolite levels in cells, organs, tissues or organisms. Observed together, these measurements offer a detailed portrait of a person’s underlying molecular network and could soon become a precious tool in treating and preventing illness.

“The idea of studying metabolism by use of NMR has been around for almost 50 years,” says Lindsey Romick-Rosendale, PhD, Director of the NMR-Based Metabolomics Core since its founding in March 2014. “It has improved recently because only within the last 10 years have our databases of reference spectra become sophisticated enough to really identify significant numbers of metabolites.”

BEYOND A SNAPSHOT

For example, stable isotope labeling experiments have emerged as a new method for understanding the broad implications of metabolites.

Previously, analyzing a blood, urine or fecal sample might provide a snapshot of a

patient's metabolic state. Such snapshots can depict impressive collections of amino acids, antibiotics, pigments, carbohydrates and fatty acids. But that data would not show what complex compounds were converted to make those metabolites, nor where they originated.

Here, investigators run isotope tracer experiments that go beyond static snapshots. NMR can follow stable isotopes as they travel within cells in a dish, within mouse models, even in a cancer patient just before a tumor resection. By following how metabolites break down and flux along multiple pathways, investigators can learn how nutrients are used by healthy cells compared to unhealthy ones.

"You can see what gets ramped up, what pathways get turned off," says Romick-Rosendale. "Eventually, this information could lead to tests to diagnose health risks. Or it could translate in other ways, such as developing ways to supplement patients with certain metabolic deficiencies."

NMR is a non-destructive technology, so if a researcher or clinician only has a few samples from a rare disease population or samples that cannot be acquired again, the facility can run the sample and then return it. The NMR team also tailors study designs, experiments and sample collections to individual studies and investigators.

MULTITUDE OF APPLICATIONS

Among the many ways the NMR-based Metabolomics Core supports scientific exploration:

- Analyzing pregnant women's urine in longitudinal studies—when no other medical risk factors are present—to identify metabolic

biomarkers related to spontaneous preterm delivery.

- A study in the *Journal of Experimental Biology* published by Andrew Rosendale, a fellow at the University of Cincinnati, investigating how ticks survive dehydration while awaiting hosts. New understanding could lead to ways to prevent tick-borne diseases.
- Helping animals at the Cincinnati Zoo. In a recent study, published in *PLOS ONE*, the NMR facility helped analyze an iron-loading disorder in rhinoceroses. The team also works with the zoo to hunt for renal cancer biomarkers in fishing cats and identify pseudo-pregnancies in polar bears.

The facility also offers another useful advantage. "NMR studies are unbelievably reproducible," Romick-Rosendale says.

Some technologies are more sensitive than NMR for identifying metabolites. However, those approaches often come with problems, such as batch-to-batch variability in samples. When data consistency matters, the reliability of NMR makes it useful for verifying results obtained from other technologies, especially for longitudinal studies.

NMR tools can shed light on how healthy and unhealthy cells use nutrients.





Support Services

The productivity of our research faculty is enhanced by a wide variety of research support programs funded by Cincinnati Children's and the University of Cincinnati. We employ teams of experts who consult with investigators on grant writing, project planning, study design, regulatory compliance, intellectual property protection, and much more. This year, we feature three of these special programs.

Building Better Researchers

CCTST Integration Committee Helps Build Bridges
Between Theory and Practice

The Integration Committee of the Center for Clinical and Translational Science and Training (CCTST) was established as a pilot project with three, interconnected goals: help researchers formulate strategies for improvement, overcome environmental challenges and build collaborations.

That was three years ago. Since then, more than 68 faculty at all levels have benefitted from Integration meetings and support, including 22 faculty in fiscal year 2016.

As a testament to its success, demand has grown sufficiently that it is important for investigators to schedule in advance.

The CCTST, directed by James Heubi, MD, serves the University of Cincinnati, its Academic Health Center partners and the community from its location in the “S” building at Cincinnati Children’s.

The core of the Innovation Committee is comprised of senior research faculty from across the Academic Health Center, who share a broad range of expertise.

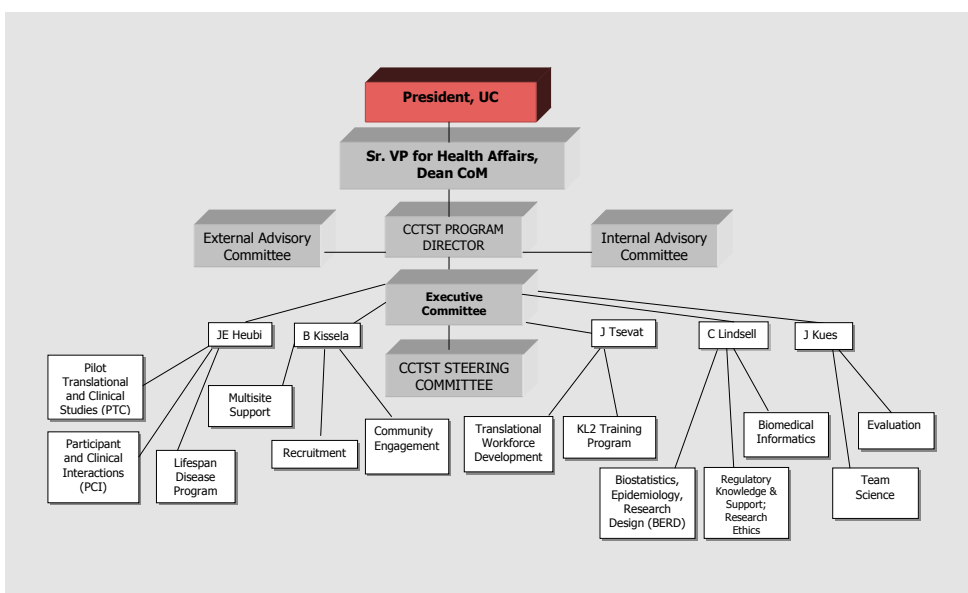
A typical meeting scenario: a researcher or team of researchers is invited to briefly present their work and any challenges they face. Supporting documents are provided in advance. The group

brainstorms ideas for accelerating the research, be it through key collaborators, helping the researcher navigate mentor-mentee relationships, or exploring available support services.

Service does not end when the meetings do. A Committee member is assigned to support the guest(s) longitudinally, following up and tracking progress. Formal evaluation of the program in general and of each individual case is ongoing through the CCTST Evaluation Core.

Follow-up surveys have shown that investigators feel that the help of the Committee has been greatly beneficial to their research and career development.

“Just knowing that this amazingly accomplished group of researchers cared enough to sit down with me and were available down the road was invaluable,” says one participant in an anonymous survey.



CTC Paves the Road Connecting Innovative Ideas and Commercial Markets

Big, innovative ideas with the potential to improve clinical care for children get their business wings at the Center for Technology Commercialization (CTC).

The center collaborates with researchers and physicians, facilitating the translation of their discoveries through a host of services, including patent protection.

The CTC develops technologies through research partnerships, delivers products to the market through licensing, creates start-up companies and provides crucial funding opportunities for emerging projects.

This year, the center received more than 160 new innovation disclosures, and exceeded its goals in licenses and revenue, with more than \$4.1 million in sponsored research agreements.

Its growth is a testament to not only its service to improving health outcomes for kids, but also the breadth of work occurring throughout Cincinnati Children's.

The CTC also launched a new partnership with Adare Pharmaceuticals to develop and commercialize drug reformulation opportunities.

It continued its key partnerships with Alexion and Shire, and has forged a reputation as a national leader in developing new therapies for

rare diseases. One example: lysosomal acid lipase deficiency (LAL-D), a genetic disease caused by massive lysosomal accumulation of cholesteryl esters and triglycerides. It leads to progressive, life-threatening organ damage.

A therapy developed at Cincinnati Children's for LAL-D patients received FDA approval last year and is now approved in the United States, European Union and Japan. The drug, Kanuma, is being marketed by Alexion and stands to have a significant impact on children and adults with the disease.

It also held its first Applied Innovation Advisory Committee meeting, which is comprised of innovators from throughout Cincinnati Children's.

"Cincinnati Children's researchers discover dozens of health innovations every year. Whether they are prospective molecular targets for treating or diagnosing disease or concepts for new medical devices, many discoveries require additional support to get them to the market," says Margaret Hostetter, MD, Director of Cincinnati Children's Research Foundation. "This is where our Center for Technology Commercialization comes in."



The CTC plays a key role in facilitating the translation of discoveries into improved clinical care for children. The CTC protects our innovations through patents, assists in further developing technologies through research partnerships, and delivers products to the market through licensing and the creation of start-up companies.

Guides to Support the Regulatory Journey

The OCTR Provides a One-Stop Shop to Assist Clinicians and Scientists with Every Stage of Clinical Research

The Office for Clinical and Translational Research (OCTR) provides a crucial support system for clinical research investigators and industry sponsors.

OCTR facilitates pediatric and adult clinical research at each step, from identifying and developing research opportunities through the final phases of clinical trials.

Cincinnati Children's is one of the few pediatric institutions in the U.S. with the infrastructure necessary to support such projects.

The 45-plus members of the OCTR's multidisciplinary team function as an in-house agency and "one-stop" clinical research support center for investigators.

The OCTR team works alongside the basic scientists and clinicians. It includes regulatory specialists with strong scientific backgrounds, and partners with experts from the federal Food and Drug Administration and the Institutional Review Board.

Typically, the OCTR assists researchers to improve existing treatments or explore new options. Sometimes, it scrutinizes in-use medications. One recent example is a study analyzing the efficacy of two drugs used to treat migraine headaches.

OCTR Director Scott Powers, PhD, Division of Behavioral Medicine and Clinical Psychology, was a key recipient of research assistance this past year.

In a clinical trial that was halted early, Powers and colleagues found that the commonly prescribed drugs amitriptyline and topiramate were no more effective than a placebo in reducing the severity and frequency of migraines. Both drugs have side effects.

"The OCTR was tremendous," says Powers, who also is co-director of the Headache Center at Cincinnati Children's.

"I used every piece of that office," he says, "from protocol to IND (investigational new drug application) to research nurses to a medical writer."



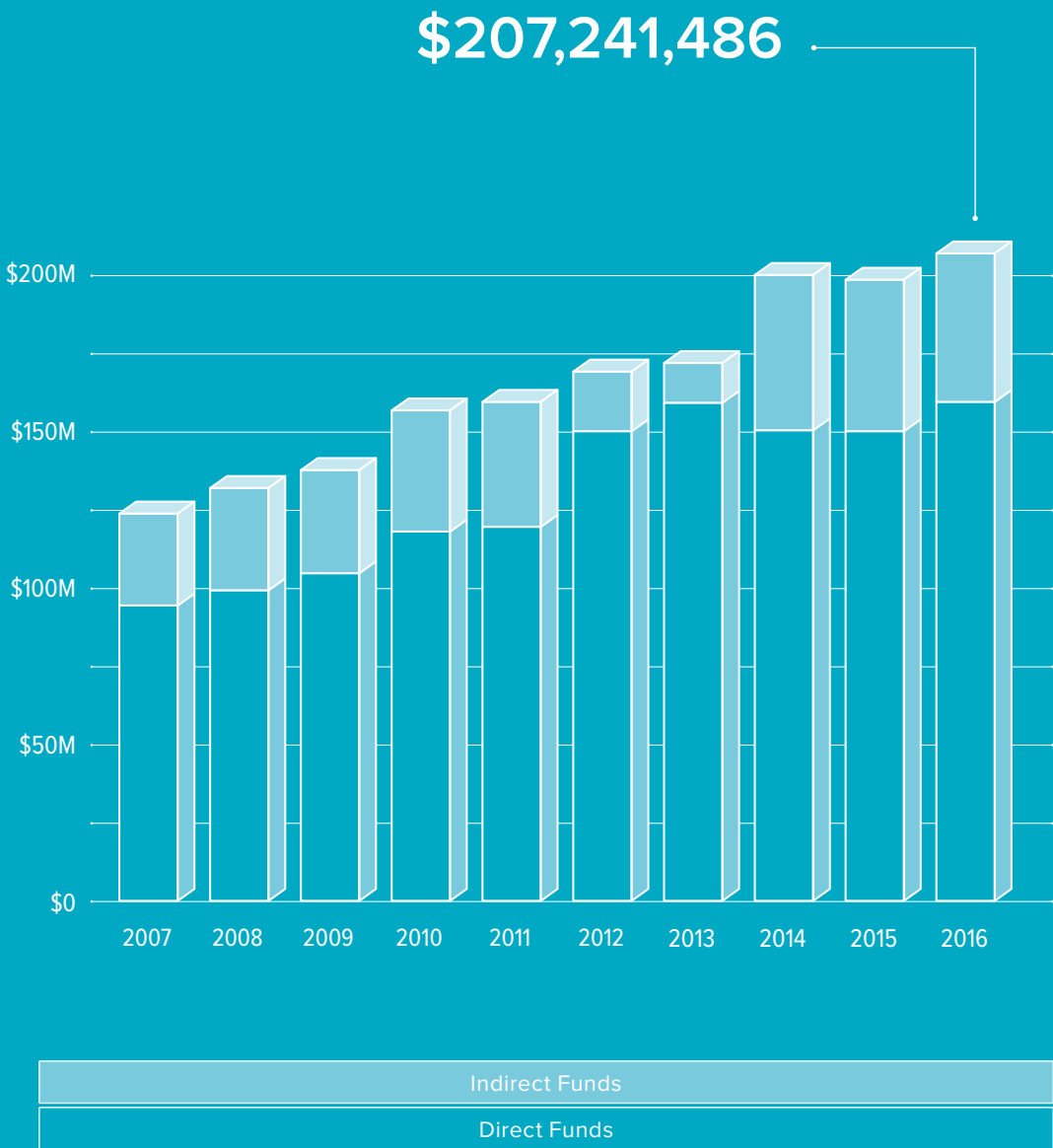
OCTR Support Services & Resources

- Identification & Development of Research Opportunities
- Research Study Management
- Contract and Budgets
- Regulatory Affairs
- Participant Identification & Recruitment
- Data Management & Reports
- Project Management
- Integration with Institutional Research Partners
- Publication Support



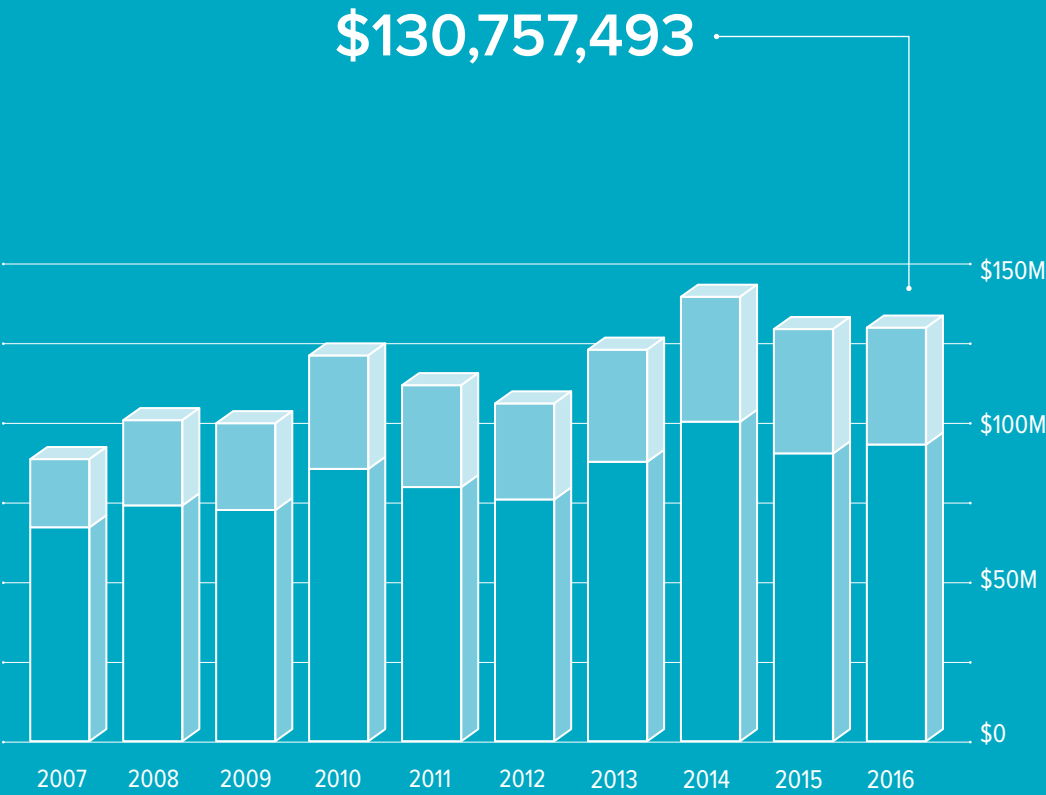
By the Numbers

Sponsored Program Awards



SPONSORED PROGRAM AWARD FIGURES INCLUDE FUNDING AWARDED FOR DIRECT AND INDIRECT COSTS, BUT EXCLUDE FEE-FOR-SERVICE CONTRACTS

National Institutes of Health Awards



Indirect Funds
Direct Funds

APPROXIMATELY \$6.8 MILLION OF ARRA AWARDS RECEIVED IN FY10 WERE AWARDED FOR A TWO-YEAR PERIOD. ALL ARE SHOWN IN FY10. APPROXIMATELY \$13.7 MILLION OF ARRA AWARDS RECEIVED IN FY11 WERE AWARDED FOR A THREE-YEAR PERIOD. ALL ARE SHOWN IN FY11.

Sources of External Funding FY2016



Sources of Federal Funding FY2016

National Institutes of Health (NIH)	\$130,757,493
Health Resources & Services Administration (HRSA)	\$4,215,550
Center for Disease Control and Prevention	\$2,698,029
Center for Medicare/Medicaid Services	\$2,478,677
Agency for Healthcare Research and Quality (AHRQ)	\$2,299,228
Department of Defense	\$3,059,243
Department of Health and Human Services	\$1,210,851
Food & Drug Administration (FDA)	\$649,357
Administration on Intellectual and Developmental Disabilities	\$535,880
U.S. Department of Agriculture	\$349,071
Department of Justice	\$315,626
Department of Veteran Affairs	\$213,485
Substance Abuse & Mental Health Services Administration	\$121,687
National Aeronautics and Space Administration	\$94,889
Maternal & Child Health Bureau	\$86,150
U.S. Department of Housing & Urban Development	\$31,570
Environmental Protection Agency	\$23,689
National Institute of Occupational Safety & Health	\$22,461
TOTAL FUNDING FROM FEDERAL SOURCES	\$149,162,937

State & Other Funding Sources 2016

Patient-Centered Outcome Research Institute
\$5,051,490

March of Dimes
\$2,533,402

Bill & Melinda Gates Foundation
\$2,255,180

Cystic Fibrosis Foundation Therapeutics, Inc.
\$1,863,505

American Heart Association
\$1,436,443

Ohio Department of Medicaid
\$1,342,963

Ohio Department of Health
\$1,188,641

Miscellaneous Other (112)
\$14,863,827

TOTAL STATE AND OTHER FUNDING SOURCES

\$ 30,535,450

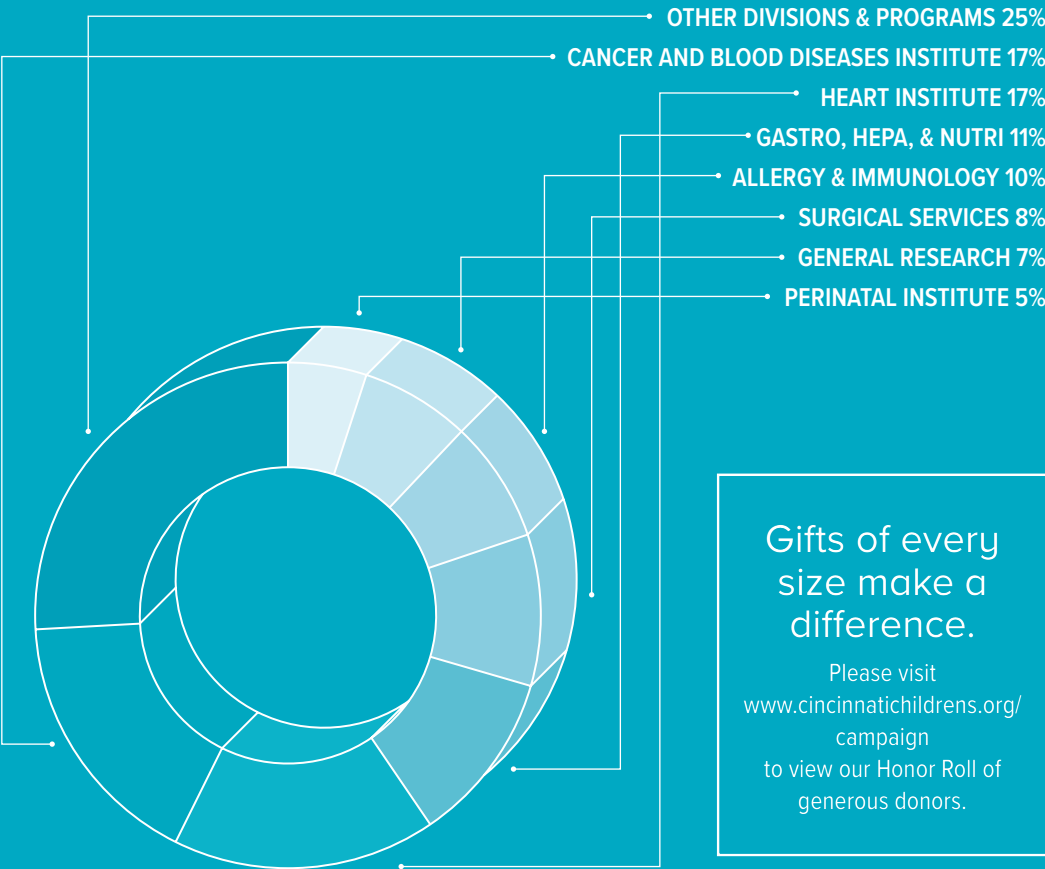
Philanthropic Gifts for Research

Our commitment to improving care for children through the application of research discovery is the backbone of Cincinnati Children's. And as a nonprofit hospital and research center, private donors play an important role in this work.

OF THE \$42 MILLION RAISED THROUGH PHILANTHROPY IN 2016,
34 PERCENT SUPPORTED THE WORK OF OUR RESEARCHERS.

We are profoundly grateful to those who have chosen to partner with Cincinnati Children's to advance scientific innovation and build better futures for kids. Together, we will never stop moving forward to make a difference for children — here in our community and beyond.

\$14.5 million
DONATED TO RESEARCH IN 2016



T-32 Fellowships

The NIH provides these institutional grants to support research training opportunities at the undergraduate, graduate, and postdoctoral levels. Cincinnati Children's received funding for these T32 programs in FY2016

Adherence Psychology

Kevin Hommel, PhD

Behavioral Medicine &

Clinical Psychology

Scott Powers, PhD

Clinical Pharmacology

Alexander Vinks, PharmD, PhD

Critical Care

Hector Wong, MD (Co-P.I.)

Gastroenterology

Lee Denson, MD

General Pediatrics

Kristen Copeland, MD

Immunology

David Bernstein, MD, MA, &

Marc Rothenberg, MD, PhD

Molecular Cardiovascular

Biology

Jeffery Molkentin, PhD

Neonatology &

Pulmonary Biology

Jeffrey Whitsett, MD

Nephrology

Prasad Devarajan, MD

Neurology

Charles Vorhees, PhD

Rheumatology

Alexei Grom, MD

Place Outcomes Research Awards

This program, administered by the James M. Anderson Center for Health Systems Excellence, provides \$60,000 grants to stimulate the development of health services and quality improvement research at Cincinnati Children's and to ensure optimal implementation of clinical and operational innovations in the care delivery system. Awardees receiving funding in FY2016 are:

Kristen Copeland, MD

General and Community Pediatrics

Natoshia Cunningham, PhD

Developmental & Behavioral Pediatrics

Chris Dandoy, MD, MSc

Bone Marrow Transplantation and
Immune Deficiency

Mark Paterno, PT, PhD, MBA, SCS

Occupational Therapy, Physical Therapy
and Sports Medicine

Thomas Sitzman, MD

Plastic Surgery

Kathleen Walsh, MD, MSc, and

Lori Crosby, PsyD

James M. Anderson Center/Behavioral
Medicine and Psychology

Trustee Awards

This program provides research funds ranging from \$30,000 to \$75,000 for junior faculty to support rapid achievement of independent, sustained extramural funding for their research. This year's awardees are:

Theresa Alenghat, VMD, PhD
Immunobiology

Lilliam Ambroggio, PhD
Hospital Medicine

Artem Barski, PhD
Allergy and Immunology

Sarah Beal, PhD
Behavioral Medicine and Clinical Psychology

Stephen Becker, PhD
Behavioral Medicine and Clinical Psychology

Katherine Bowers, PhD, MPH
Biostatistics and Epidemiology

Iouri Chepelev, PhD
Center for Autoimmune Genomics and Etiology

Zackary Cleveland, PhD
Pulmonary Medicine

Steven Crone, PhD
Neurosurgery

Andrew Dauber, MD
Endocrinology

Patricia Fulkerson, MD, PhD
Allergy and Immunology

June Goto, PhD
Neurosurgery

Christina Gross, PhD
Neurology

Tzipi Horowitz-Kraus, PhD
General and Community Pediatrics

Darren Kadis, PhD
Neurology

Yu Lan, PhD
Plastic Surgery

Satish Madala, PhD
Pulmonary Medicine

Catherine Quatman-Yates, PT, DPT, PhD
Sports Medicine

Michael Rosen, MD, MSCI
Gastroenterology, Hepatology and Nutrition

Takuji Suzuki, PhD
Pulmonary Biology

Matthew Weirauch, PhD
Center for Autoimmune Genomics and Etiology

Mei Xin, PhD
Experimental Hematology and Cancer Biology

Chunyue Yin, PhD
Gastroenterology, Hepatology and Nutrition

Fifth Third Bank / Charlotte R. Schmidlapp Women Scholars

This program provides \$50,000 grants to support the academic career development of women faculty who have demonstrated academic potential and leadership skills as they progress toward the ranks of associate and full professor. This year's awardees are:

Fumika Hamada, PhD
Visual Systems Group/Pediatric Ophthalmology

Patricia Fulkerson, MD, PhD
Allergy and Immunology

Ellen Lipstein, MD, MPH
Adolescent Medicine

CCTST Program Awards

Cincinnati Children's partners with the University of Cincinnati and other institutions to support programs funded through the Center for Clinical and Translational Science and Training (CCTST). This list shows faculty who received grants ranging from \$10,000 to \$100,000 to support translational research, build core capabilities, develop innovative research methods, or collaborate with community partners.

Jean Tkach, PhD

Imaging Research Center

Christina Gross, PhD

Neurology

David Hildeman, PhD

Immunobiology

Eddie Merino, PhD

UC Dept. of Chemistry

Jose Cancelas Perez, MD, PhD

Hoxworth Blood Center

Pooja Khandelwal, MD

Cancer and Blood Diseases Institute

Jason Woods, PhD

Pulmonary Medicine

Artem Barski, PhD

Allergy and Immunology and
Human Genetics

Theresa Guilbert, MD, MS

Pulmonary Medicine

Kenneth Kaufman, PhD

Center for Autoimmune Genomics
and Etiology

Richard Ittenbach, PhD

Biostatistics and Epidemiology

Melinda Butsch Kovacic, MPH, PhD

Asthma Research

Alonzo Folger, PhD

Biostatistics and Epidemiology

John Pestian, PhD, MBA

Biomedical Informatics

Kelly Kamimura-Nishimura, MD

Developmental and Behavioral Pediatrics

Erica Messer, PsyD

Behavioral Medicine & Clinical Psychology

Julie Ware, MD, MPH

General and Community Pediatrics

Diversity & Health Disparities Research Award

This award provides \$75,000 in research funding for up to 2 years to faculty members who are from underrepresented minorities and/or have a strong commitment to health disparities research. The recipient of the 2016 award is:

Carley Riley, MD, MPP, MHS

Critical Care Medicine, for
"Eliminating Health Disparities Block
by Block"

Cincinnati Children's Innovation Fund

The Cincinnati Children's Innovation Fund is designed to accelerate the commercialization of discoveries, innovations, projects or products. Recipients this year are:

Hector Wong, MD

Critical Care Medicine

Yizhao Ni, PhD

Biomedical Informatics

Bruce Trapnell, MD, MS

Pulmonary Medicine

Stuart Goldstein, MD, FAAP, FNKF

Nephrology and Hypertension

Doug Millay, PhD

Molecular and Cardiovascular Biology

Abby Hess, DNP, APRN, FNP-BC

Anesthesia

Alexion Rare Disease Innovation Fund

Alexion Pharmaceuticals and Cincinnati Children's have established a collaboration to fund the advancement of research in rare disease. Following completion of the funded research programs, Alexion will have an exclusive option to enter into a licensing agreement for these programs. This year's recipients are:

Pranavkumar Shivakumar, PhD

Gastroenterology, Hepatology and Nutrition

Adare Drug Repurposing And Optimization Innovation Fund

This new fund focuses on research to help medications initially developed for adults better meet the needs of children.

Gurjit Khurana Hershey, MD, PhD

Asthma Research

Procter Scholars

The Procter Scholar Program supports faculty members from the Departments of Pediatrics, Surgery, Radiology, Patient Services, and Anesthesia who are committed to pursuing academic research careers.

3RD YEAR SCHOLARS

Andrew Lindsley, MD, PhD

Allergy and Immunology

Jeffrey Tenney, MD, PhD

Neurology

Jennifer Davis, DO

Oncology

Patrick McGann, MD, MS

Hematology

Brian Varisco, MD

Critical Care Medicine

2ND YEAR SCHOLARS

Ernest Pedapati, MD

Psychiatry

Hitesh Deshmukh, MD, PhD

Neonatology

Child Health Research Career Development Awards (CHRCDA)

This program provides \$93,000 grants to support training physician-scientists to stimulate pediatric research across a variety of disciplines. This year's awardees are:

Andrew Lindsley, MD, PhD

Allergy and Immunology

Kasiani Myers, MD

BMT and Immune Deficiency

Matthew Alder, MD, PhD

BMT and Immune Deficiency

K. Nicole Weaver, MD

Human Genetics

Academic and Research Committee Awards

These grants support multi-disciplinary programs that can become self-sustaining within one to three years. Awardees this year are:

Hansel Greiner, MD

General Pediatrics

Keith Marsolo, PhD

Biomedical Informatics

Lesley Breech, MD

Pediatric and Adolescent Gynecology

Lee Ann Conard, RPh, DO, MPH

Adolescent and Transition Medicine

Andrew Dauber, MD, MMSc

Endocrinology

Gurjit Khurana Hershey, MD, PhD,

Asthma Research;

Theresa Guilbert, MD, MS,

General Pediatrics; and

Carolyn Kerckmar, MD,

Pulmonary Medicine

Lilliam Ambroggio, PhD

Hospital Medicine

Claire Chougnet, PhD

Molecular Immunology

James Mulloy, PhD

Experimental Hematology &
Cancer Biology

GAP Funding Awards

This program provides one year of support at \$75,000 to bridge gaps in R01-level funding or equivalent.

Rulang Jiang, PhD

Developmental Biology

Kimberly Yolton, PhD, and

Kim Cecil, PhD

General Pediatrics/Radiology

Kenneth Campbell, PhD

Developmental Biology and Neurosurgery

Sanjoy Das, PhD

Reproductive Sciences

Paul Andreassen, PhD

Experimental Hematology and
Cancer Biology

Satoshi Namekawa, PhD

Reproductive Sciences

Yan Xu, PhD, and

James Bridges, PhD

Pulmonary Biology/Neonatology
and Pulmonary Biology

Research, Innovation & Pilot Funding Awards

This program provides \$75,000 grants to support collecting preliminary data for innovative and essential projects considered to be good candidates for future external funding. Awardees receiving funding this year include:

Kakajan Komurov, PhD

Experimental Hematology and Cancer Biology

Michael Jankowski, PhD

Anesthesia

Samantha Brugmann, PhD

Plastic Surgery and Developmental Biology

Edith Janssen, PhD

Immunobiology

Daniel Grosseohme, Chaplain

Pulmonary Medicine

Katherine Holland, MD, PhD

Neurology

Jayant (Nick) Pratap, MB, BChir

Anesthesia

Kenneth Setchell, PhD

Pathology

Shari Wade, PhD

Physical Medicine and Rehabilitation

Mohammad Azam, PhD

Experimental Hematology and Cancer Biology

Biplap DasGupta, PhD, MS

Oncology

Tony De Falco, PhD

Reproductive Sciences

Simon Hogan, PhD

Allergy and Immunology

Jun Ma, PhD

Biomedical Informatics

Satoshi Namekawa, PhD

Reproductive Sciences

Saulius Sumanas, PhD

Developmental Biology

Fumika Hamada, PhD

Ophthalmology

Xinhua Lin, PhD

Developmental Biology

Daniel Starczynowski, PhD

Experimental Hematology and Cancer Biology

Daniel Lovell, MD, MPH, and

Diana Taft

Rheumatology

Assem Ziady, PhD

Pulmonary Medicine

Center for Pediatric Genomics Pilot Studies

The Center for Pediatric Genomics (CpG) has established a fund to distribute \$1 million annually among projects that accelerate innovative research, development, and implementation of genomic science. Awardees this year are:

Vidya Chidambaran, MD

Anesthesia

Andrew Dauber, MD

Endocrinology

David Haslam, MD

Infectious Diseases

Hong Ji, PhD

Asthma Research

Andrew Lindsley, MD, PhD and

Artem Barski, PhD

Allergy and Immunology

Q. Richard Lu, PhD

Experimental Hematology and Cancer Biology

Melanie Myers, PhD

Human Genetics

Mihaela Pavlicev, PhD

Center for the Prevention of Preterm Birth

Matthew Weirauch, PhD

Center for Autoimmune Genomics and Etiology

Susanne Wells, PhD

Oncology

Strauss Fellows

The Arnold W. Strauss Fellow Award is a one-year \$10,000 funding opportunity instituted in 2014 in honor of Dr. Strauss' tireless championship of higher education at Cincinnati Children's.

Stacey Cranert, PhD

Center for Autoimmune
Genomics and Etiology

Xuelian He, MD, PhD

Experimental Hematology

Sarah Jablonski, PhD

Neurology

Jung-Mi Lee, PhD

Experimental Hematology

Kimberly Leiken, PhD

Neurology

Keri Drake, MD

Nephrology

Holly Hanson, MD

Emergency Medicine

John Hutton, MD

General and Community
Pediatrics

Kiersten Ricci, MD

Hematology and Oncology

Augusto

Schmidt, MD, PhD

Neonatal Perinatal Medicine

Amery Treble-Barna, PhD

Behavioral Medicine and
Clinical Psychology

Our Faculty

PEDIATRICS

733 total [691 full time / 42 part time]

SURGERY

91 total [84 full time / 7 part time]

ANESTHESIA

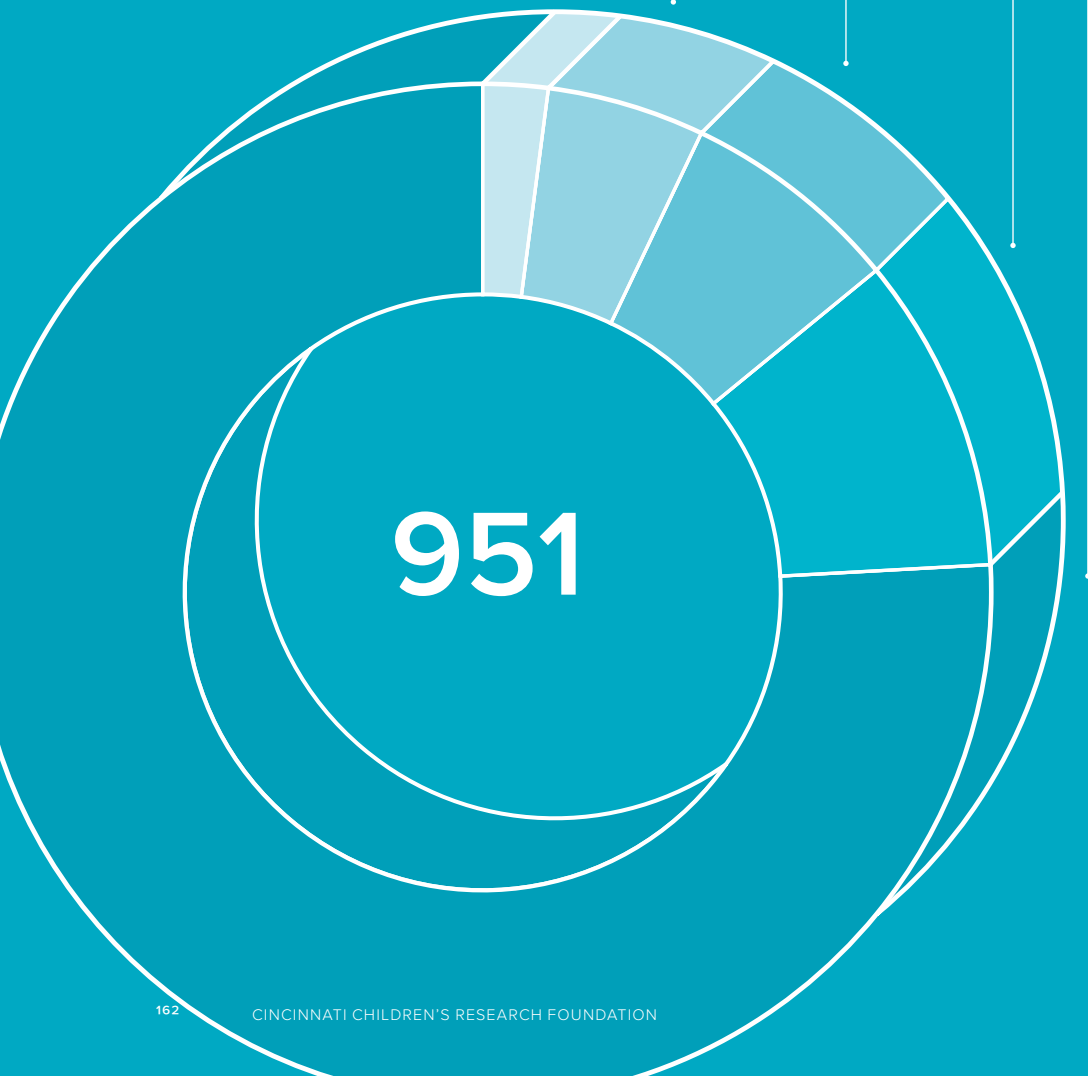
62 total [49 full time / 13 part time]

RADIOLOGY

48 total [40 Full time / 8 part time]

PATIENT SERVICES

17 total [8 Full time / 9 part time]



Postdoctoral Fellows

8	Allergy and Immunology
6	Anesthesia
1	Biomedical Informatics
1	Biostatistics and Epidemiology
1	Bone Marrow Transplantation & Immune Deficiency
4	Center for Autoimmune Genetics & Etiology
3	Center for Prevention of Preterm Birth
3	Clinical Pharmacology
21	Developmental Biology
4	Endocrinology
24	Experimental Hematology
10	Gastroenterology, Hepatology, & Nutrition
2	General & Community Pediatrics
5	Hematology
5	Human Genetics
1	Imaging Research
12	Immunobiology
19	Molecular Cardiovascular Biology
4	Neonatology, Perinatal & Pulmonary Biology
6	Neurology
4	Oncology
3	Pathology & Laboratory Medicine
2	Patient Services
17	Pediatric General & Thoracic Surgery
1	Psychiatry
7	Pulmonary Medicine
7	Reproductive Sciences
181	TOTAL POSTDOCTORAL FELLOWS

Clinical Fellows: 254

Adolescent Medicine	5	Congenital Cardiac Surgery	1
+ Transition Medicine	0	Critical Care	13
Allergy/Immunology	6	Developmental Behavioral Pediatrics	6
Anesthesia	12	Emergency Medicine	12
+ ABA Alternate Pathway	1	Endocrinology	11
+ Adv. Fellowship Quality Improve. & Safety	1	Gastroenterology	12
+ Adv. Ped. Anesthesia Fellowship Education	0	+ Pediatric Transplant Hepatology	1
+ Intraoperative Neurophysiological Monitoring	2	Division of General Pediatrics	0
+ Pediatric & Congenital Cardiac Anesthesia	1	+ Pediatric Master Educator	1
		+ Pediatric Primary Care Research	2
Cardiology	14	Genetics, Medical	1
+ Adult & Adolescent Congenital Heart Disease	1	+ Clinical Biochemical Genetics	0
+ Cardiac Electrophysiology	1	+ Clinical Cytogenics	1
+ Cardiac Imaging	2	+ Clinical Molecular Genetics	2
+ Cardiac Intensive Care	0	Hematology/Oncology	11
+ Fetal Cardiology	0	+ Academic Research in Pediatric Hem/Onc	0
+ Advanced Heart Failure & Transplantation	2	+ Bone Marrow Transplant	0
+ Interventional Cardiac Cath	1	+ Clinical Immunodeficiency	0
+ Preventive Cardiology	1	+ Neuro-Oncology	1
		+ Sickle Cell Disease	0
Child Abuse	2	Hospice & Palliative Medicine	2

Hospital Medicine	7
Infectious Disease	6
Neonatology	15
Nephrology	8
+ Acute Care Nephrology & Dialysis	1
Neurology	0
+ Clinical Neurophysiology	1
+ Pediatric Epilepsy	3
+ Headache	1
+ Neonatal Neuro	1
Neurosurgery	1
Ophthalmology	1
Orthopaedics	3
+ Hand & Upper Extremity Surgery	1
Otolaryngology	6
Pain Medicine	2
Pathology	1
Plastic Surgery	1
Psychiatry	7
Psychology	12
Pulmonary	10

Radiology	8
+ Body MRI	0
+ Interventional Radiology	2
+ Pediatric Neuroradiology	1
Rehabilitation Medicine	4
Rheumatology	6
Sleep Disorder Medicine	2
Sports Medicine	2
Surgery	2
+ Pediatric and Adolescent Gynecology	2
+ Colorectal Surgery	1
+ ECMO	0
+ Fetal Surgery	0
+ Pediatric International Surgical Fellow	1
+ Trauma Surgery	1
+ Vascular Anomalies	1
Urology	2
+ International Pediatric Urology Fellow	2
TOTAL	254

Pediatric Scientist Development Program

This program provides intensive training to prepare entry-level faculty for research careers in academic pediatrics.

2015	2016
6 Recipients	6 Recipients

MEDICAL RESIDENTS: 502

Research Graduate Programs

MDB Graduate Program	MSTP Program	Immunology Program	Biomedical Informatics
58 Students (53 PhD/5 MS)	53 Students	44 Students (31 PhD/13 MS)	13 Students

Summer Research Programs

Medical Students Program	Undergraduate Students	Summer for Sickle Cell Science Program	High School Interns
18 (including 12 in SMURRF program)	131 (including 112 in SURF program)	6	31 (15 High School Senior Summer Interns, 10 BRIMS)

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Papers Appearing in Highest Impact-Factor Journals

<i>New England Journal of Medicine</i>	3
<i>Lancet</i>	3
<i>Nature Biotechnology</i>	2
<i>Nature Reviews Immunology</i>	1
<i>Nature</i>	1
<i>JAMA</i>	6
<i>Science</i>	4
<i>Nature Genetics</i>	3
<i>Nature Medicine</i>	2
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Total	25

Journal Articles	Books (edited or authored)	Chapters of Books	Online Site Contributions
2,236	8	93	23

2,360

TOTAL PUBLICATIONS

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EDITORS:

Tim Bonfield

Project manager for print research annual report

Missy Kataoka and Bri Pennington

Project managers for online research annual report, CMS training and technical support, website writing/editing/design

Kristine Justus, PhD,

Vice President, Research Operations
Editorial Advisor

CONTRIBUTORS:

Kim Ballinger

Grant data collection and review

Clare Douglas

Communication and data coordination

Stephen Gentle

Website development

Allison Kissling and the Edward L. Pratt Research Library

Publication data collection and review

Sue MacDonald

Contributing writer, print research annual report

Tom O'Neill

Contributing writer and editor, print research annual report

Sarah Stankorb

Contributing writer, print research annual report

GRAPHICS AND PHOTOGRAPHY:

Reed DeWinter, Julie Kramer, and Michael Wilson

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The Fairview Agency

PRODUCED BY:

Department of Marketing and Communications
Jane Garvey, Vice President
Cincinnati Children's Hospital Medical Center
3333 Burnet Ave., MLC 9012
Cincinnati, OH 45229-3026
513-636-4420

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