Cincinnati Children's™
Research Foundation

2020 RESEARCH DISCOVERIES

Contents

ABOUT THE COVER
Called "the universal solvent," water dissolves more substances than any other liquid. Wherever water goes, either through the ground or our bodies, it takes along valuable chemicals, minerals, and nutrients. In the search for life, follow the water.

Illustration by Reed DeWinter

Our Top Five Achievements of 2020

2020

Division Summaries
Scientific Achievements

Indicates Top Breakthrough in 2020

Dear Colleagues,

It is a great privilege that one of my early tasks as Director of the Cincinnati Children's Research Foundation is to introduce the 2020 Research Annual Report. This collection of discoveries and innovations from our exceptionally talented faculty, lab teams, and research collaborators around the world demonstrates what an honor it has been to join this institution.

The work featured in this year's report elegantly reflects the wide breadth of expertise built up by Dr. Margaret Hostetter and her predecessors who have served as the B.K. Rachford Professor of Pediatrics at Cincinnati Children's. History shows that excellence in research has been intertwined with outstanding clinical care for children ever since William Cooper Procter hired Dr. Albert Graeme Mitchell to serve as our second B.K. Rachford Professor. Dr. Mitchell's passion helped persuade Mr. Procter to make the generous gift that launched the Cincinnati Children's Research Foundation in 1931.

In 2020 we marked the 100th anniversary of the founding of the Department of Pediatrics, and in 2021 we will celebrate the 90th anniversary of the CCRF. This long-term commitment to advancing child health outcomes through excellence in research remains a central pillar of Cincinnati Children's mission and is one that I am proud and honored to continue in the years ahead.

This year's report reflects selected work from the powerful flow of more than 2,500 peer-reviewed publications authored or co-authored by a growing faculty whose work has been fueled by external grants exceeding $240 million for the second straight year. Investigators here have published more than a dozen works in the world's top medical journals, including *Nature*, *The New England Journal of Medicine,* and *JAMA*. But more importantly, this work is helping connect more children and families from communities in need to the excellence and expertise that Cincinnati Children's provides.

Investigators here have worked from home to home across our region to help new mothers coping with traumatic personal histories. They have discovered a link between poor air quality and spikes in psychiatric emergency visits. They have crossed continents to advance sickle cell treatment in sub-Saharan Africa. They have led breakthroughs in treatments for rare diseases that few centers have the resources to study.

I have been fortunate to begin with a strong start in this role thanks to Dr. Hector Wong's excellent work as Interim Director and a dedicated team of leaders who have helped manage our transition. Please join me in congratulating all of the scientists who contributed to the studies featured in this report. I look forward to working with you to report even more life-enhancing discoveries in the years ahead.

Tina L. Cheng
BK Rachford Professor
Chair, Department of Pediatrics
Director, Cincinnati Children's Research Foundation
Chief Medical Officer

NEARLY ONE-THIRD OF THE MORE THAN 16,000 EMPLOYEES OF CINCINNATI CHILDREN'S DEVOTE COUNTLESS HOURS TO RESEARCH STUDIES THAT ARE IMPROVING THE OUTCOMES OF CHILDREN IN NEED—HERE AT HOME AND AROUND THE WORLD.

They include physicians, PhD scientists, research nurses, pharmacologists, informatics experts and more. Together, they have helped build Cincinnati Children's into a powerhouse of discovery and innovation.

Our success springs from decades of investment in programs, infrastructure, research cores, and talent–as well as a culture of collaboration, which thrives within more than 50 research divisions at Cincinnati Children's.

Highlights of our team's work from Fiscal Year 2020 are featured in the following pages. These premier scientific discoveries, selected by a committee of senior research leaders, represent the most innovative and impactful achievements.

In addition to our federal funding and commercial partners, we're grateful to the donors who help make these discoveries possible. Philanthropic gifts for research grew to $26.3 million in Fiscal Year 2020, compared with $19.5 million the prior year. And, special thanks to the Jack Rubinstein Foundation for Developmental Disorders for its generous $8.8 million gift this year.

Looking ahead, we are inspired by the passion of so many researchers who have shifted their focus to defeating the novel coronavirus. Already, scientists here have authored or co-authored more than 130 manuscripts related to COVID-19. We expect more to come on that front.

Meanwhile, Cincinnati Children's is leading the way in evaluating vaccines to combat the pandemic, with clinical trials that include adolescents ages 12-17.

We are especially grateful to the children, young adults, and families who place their trust in our compassionate scientists and clinicians. Many of the advancements featured in this report could not have occurred without their participation in our clinical research. By volunteering, they have contributed not only to the betterment of science but also humanity.

Congratulations and thank you. With your partnership, we are pursuing our potential together so all kids can pursue theirs

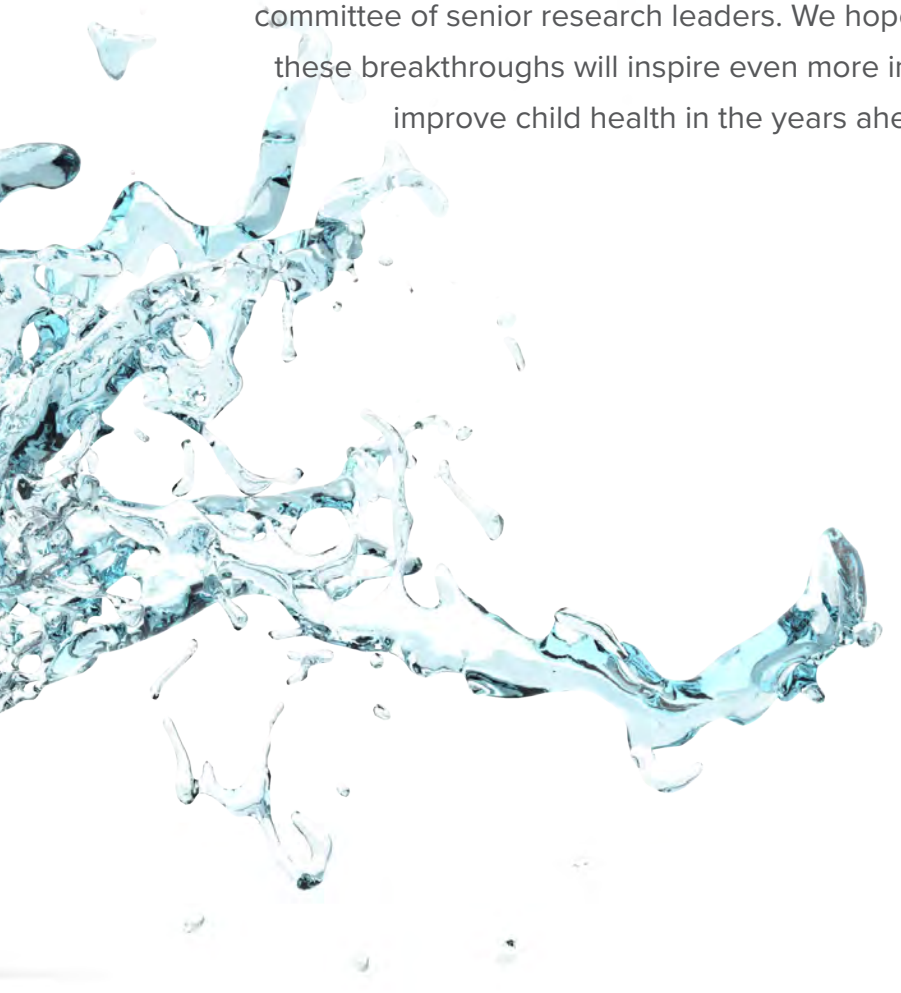
Mark Jahnke
Chair, Board of Trustees

Nancy Krieger Eddy, PhD
Research Chair

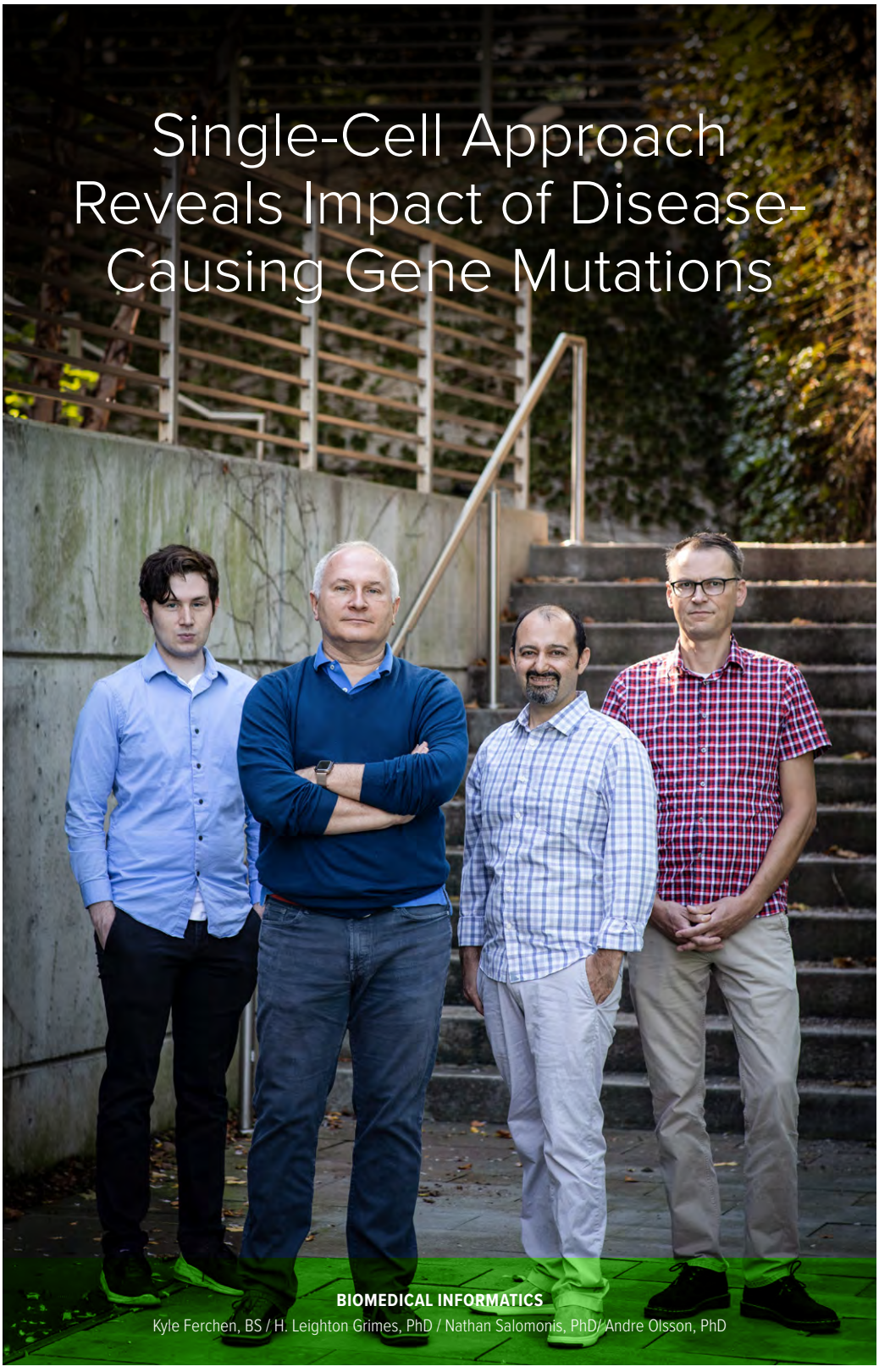
Michael Fisher
President and CEO

Our Top 5 Breakthroughs of 2020

In the past fiscal year, the outstanding faculty of the Cincinnati Children's Research Foundation have delivered on an impressive body of work. The following stories summarize our most significant findings of the year, as selected by a committee of senior research leaders. We hope that sharing these breakthroughs will inspire even more innovation to improve child health in the years ahead.



Single-Cell Approach Reveals Impact of Disease-Causing Gene Mutations



BIOMEDICAL INFORMATICS

Kyle Ferchen, BS / H. Leighton Grimes, PhD / Nathan Salomonis, PhD/ Andre Olsson, PhD

Changes in DNA can have very different consequences—some cause disease, while others have no effect. So how can we determine which mutations are important and which aren't?

Single-cell methods hold the key to finding answers, according to a breakthrough study in the journal *Nature* led by H. Leighton Grimes, PhD, of the Division of Immunobiology, and Nathan Salomonis, PhD, of the Division of Biomedical Informatics.

The study introduces a new workflow to tackle the challenge of linking gene mutations with disease-causing processes. Researchers and clinicians can use this platform to study the single-cell genomics of a variety of diseases—potentially improving the precision and effectiveness of genetic-based diagnoses in the clinic.

FINDING MISSING LINKS

Advances in genetics and sequencing technologies have revealed many gene alterations that are associated with disease. Despite these insights, determining causality between genetics and disease can be tedious and difficult.

"We can already sequence a child's genome and link a DNA sequence difference to the disease," says Grimes. "However, determining which of these DNA changes is a real disease-causing mutation is difficult, but critical to understanding the molecular mechanisms of a disease, and driving toward a cure."

Why are these connections so tricky to identify? The more we learn about gene and protein expression in each cell at a given moment, the more complex the task becomes. Single-cell analyses are vastly increasing the number of cellular populations to be studied, and each can be affected by mutations in unique ways.

To get a complete picture of how cells work, accurate models of genetic disease are essential. By analyzing these models at a single-cell level, researchers can evaluate how mutations and medications impact different cell states.

> "Our aim is to create a general workflow that can be applied to many diseases. To achieve this, we leverage new genomics approaches and computational strategies to find out which mutations, cell-types, developmental periods, and molecular pathways are likely driving the disease."
>
> — Nathan Salomonis, PhD

MAPPING GENETIC CHANGES

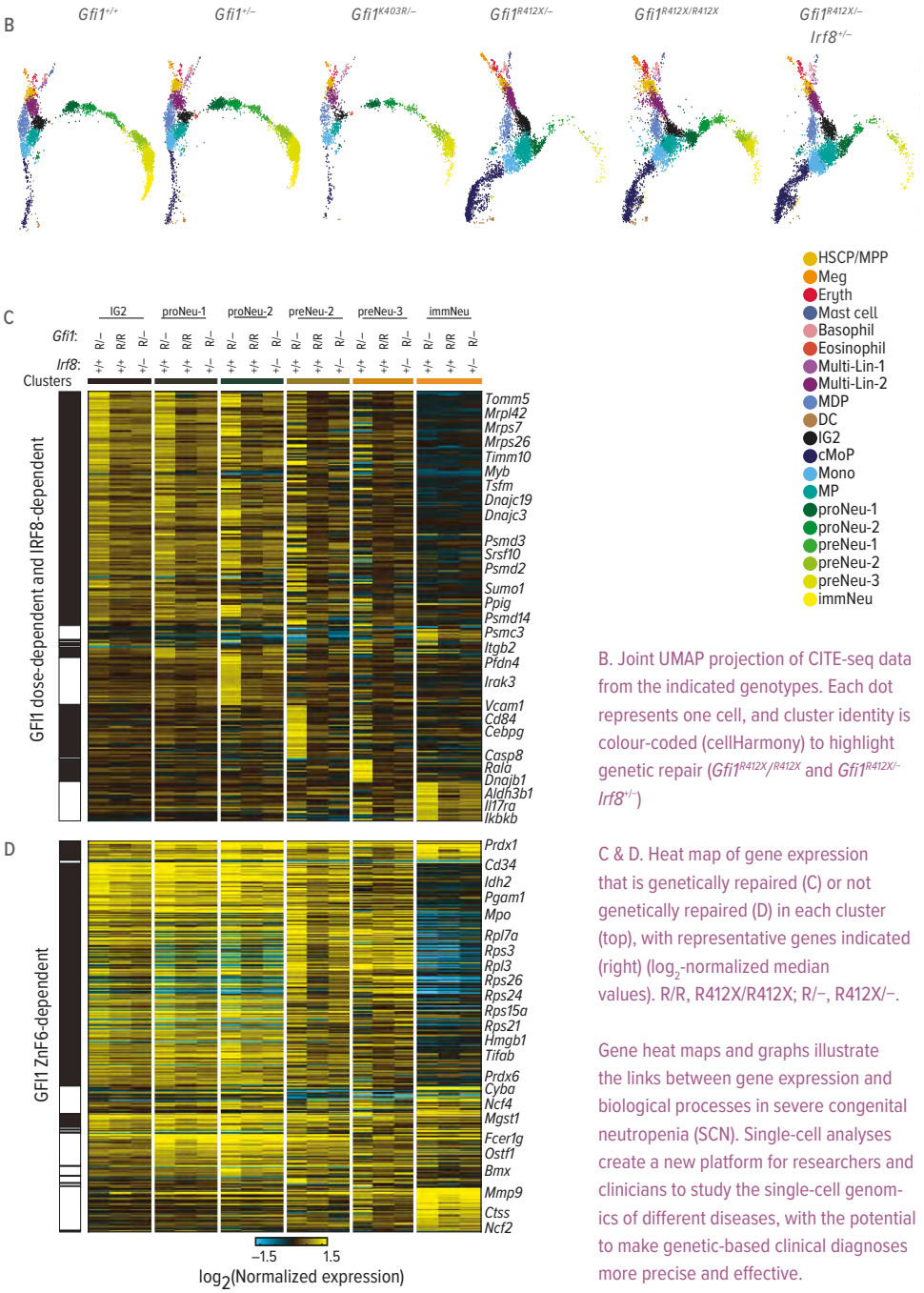
The research team focused on identifying a gene mutation that causes severe congenital neutropenia (SCN) in children. SCN is a blood disorder characterized by a deficiency of neutrophils, a type of white blood cell, which leads to recurrent infections and high risk of disease.

First, researchers sequenced the genomes of cells from 225 children with SCN. They identified DNA sequence alterations in the Growth Factor Independent-1 (*GFI1*) gene—some known to cause neutropenia, and others of unknown clinical significance.

Next, the team created genetic models of SCN using human cells and mice to explore whether any of the new DNA changes cause neutropenia. By genetically introducing the SCN patients' *GFI1* mutations into the mouse genome, or to human induced pluripotent stem cells that generate neutrophils, they were able to study the effects in real time.

As the neutrophils developed, researchers captured the expressed genes, proteomes, and other molecular components at each stage. Using the computational tool cellHarmony, they compared downstream target genes and molecular activities

Linking Single-Cell Gene Expression and Biological Processes



B. Joint UMAP projection of CITE-seq data from the indicated genotypes. Each dot represents one cell, and cluster identity is colour-coded (cellHarmony) to highlight genetic repair (*Gfi1*$^{R412X/R412X}$ and *Gfi1*$^{R412X/–}$ *Irf8*$^{+/–}$)

C & D. Heat map of gene expression that is genetically repaired (C) or not genetically repaired (D) in each cluster (top), with representative genes indicated (right) (log_2-normalized median values). R/R, R412X/R412X; R/–, R412X/–.

Gene heat maps and graphs illustrate the links between gene expression and biological processes in severe congenital neutropenia (SCN). Single-cell analyses create a new platform for researchers and clinicians to study the single-cell genomics of different diseases, with the potential to make genetic-based clinical diagnoses more precise and effective.

of normal and mutant cells throughout neutrophil development.

The results confirmed the disease-causing effect of *GFI1* mutations. In human cells and mice, these alterations triggered molecular dysfunction that blocked the development of neutrophils.

Researchers discovered that the major problem involved chromatin in the mutant cells' nuclei that remained open long beyond normal. This helped the team identify which cell states are most affected by the mutant gene.

"Our aim is to create a general workflow that can be applied to many diseases," says Salomonis. "To achieve this, we leverage new genomics approaches and computational strategies to find out which mutations, cell-types, developmental periods, and molecular pathways are likely driving the disease."

EXPLORING NEW TREATMENTS

With a better understanding of the *GFI1* mutation's impact at each stage of cell development, researchers were able to successfully treat and partially rescue neutrophils in the SCN models.

Genetic manipulations rescued the impact of the *GFI1* mutations on neutrophil specification, an initial step of differentiation. But the resulting cells were still defective in commitment, a later stage of differentiation where effector functions are programmed, leaving them unable to do their job properly in the immune system.

These findings emphasize the importance of evaluating the impact of mutations and therapies within each relevant cell state. Using the study's new molecular workflow system, therapeutic interventions can be strategically targeted.

WHAT'S NEXT?

Future work will focus on understanding the steps of neutrophil commitment—specifically, how these cells program chromatin and gene expression to fight bacterial and fungal infections.

Could the new single-cell and computational methods unlock insights for other diseases? With several projects in the works, researchers aim to find out.

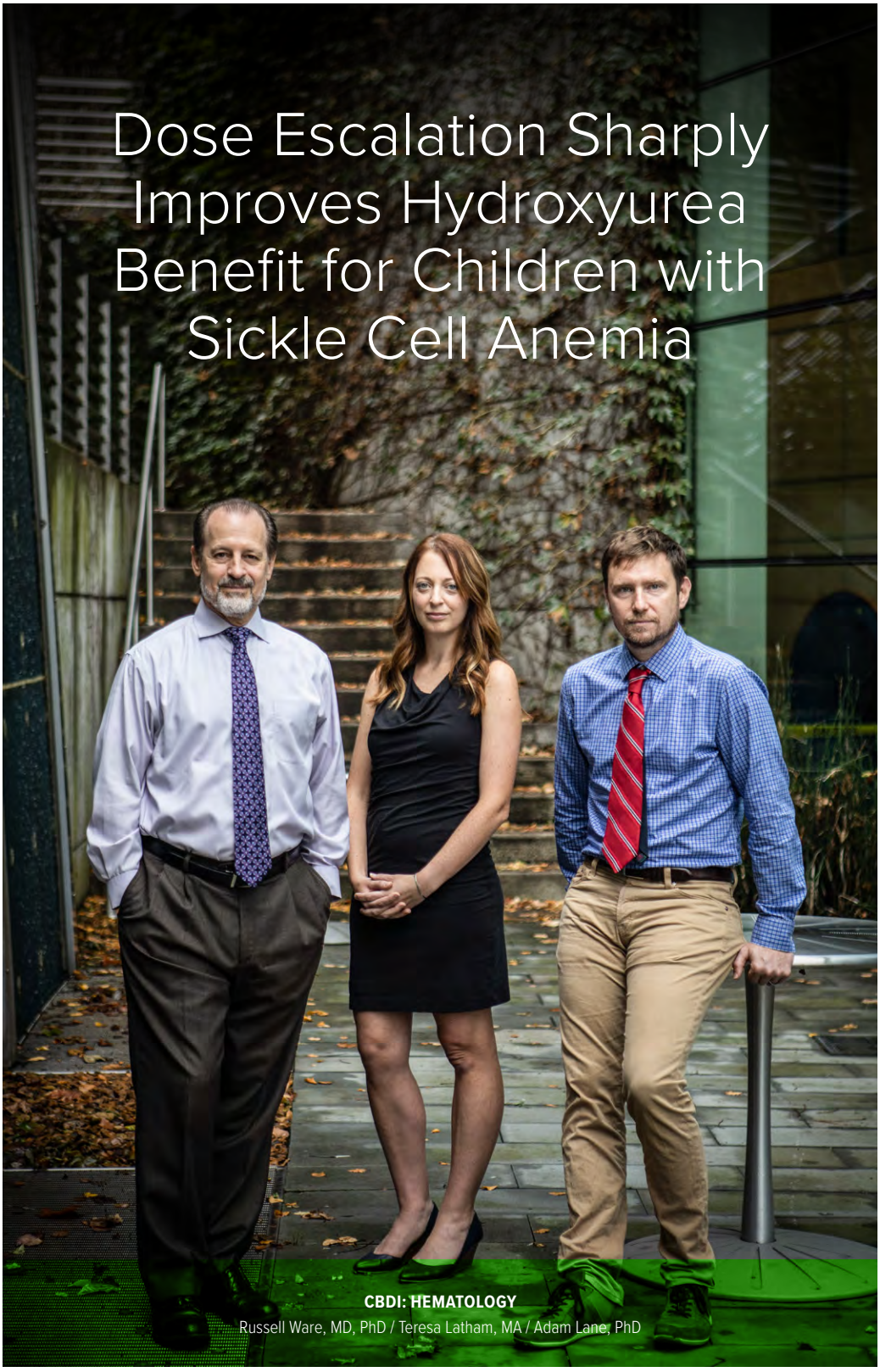
"We are currently working on extending these bioinformatics approaches to the direct analysis of large patient cohorts," says Salomonis. "These include funded studies of adult and pediatric hematological malignancies, neurofibroma, prenatal inflammation, ulcerative colitis, kidney transplant rejection, lung, and autoinflammatory disease."

Biomedical Informatics

RESEARCH & TRAINING DETAILS	
Faculty	15
Joint Appointment Faculty	14
Research Fellows & Post Docs	5
Research Graduate Students	25
Total Annual Grant Awards	$5.5M
Total Annual Industry Awards	$80,000

Muench DE, Olsson A, Ferchen K, Pham G, Serafin RA, Chutipongtanate S, Dwivedi P, Song B, Hay S, Chetal K, Trump-Durbin LR, Mookerjee-Basu J, Zhang K, Yu JC, Lutzko C, Myers KC, Nazor KL, Greis KD, Kappes DJ, Way SS, Salomonis N, Grimes HL. Mouse models of neutropenia reveal progenitor-stage-specific defects. Nature. 2020;582(7810):109-114.

Dose Escalation Sharply Improves Hydroxyurea Benefit for Children with Sickle Cell Anemia



CBDI: HEMATOLOGY

Russell Ware, MD, PhD / Teresa Latham, MA / Adam Lane, PhD

The clinical trial results in Uganda were so clear the study was stopped early.

Rather than using a single, common dosage of the drug hydroxyurea, escalating the dose to a maximum tolerated level significantly lowered the complications from sickle cell anemia.

Gradually increasing dosages to about 50% higher than previously used levels reduced hospitalizations by 79%, transfusions by 70%, the risk of acute chest syndrome or pneumonia by 73%, and the risk of a vaso-occlusive pain crisis by 57%, according to data from the NOHARM MTD study. (Novel use Of Hydroxyurea in an African Region with Malaria – Maximum Tolerated Dose).

The clinical trial results were the latest step forward for a years-long effort led by Russell Ware, MD, PhD, at Cincinnati Children's and collaborators to demonstrate that hydroxyurea offers an effective, low-cost treatment for sickle cell anemia without increasing malaria risks.

Collaborators on the NOHARM-MTD study included experts from Makerere University in Kampala, Uganda, and the Indiana University School of Medicine.

"Our study's data safety and monitoring board noted a highly significant difference between the treatment groups, with the children on escalated dosing having superior clinical results but the same number of side effects, so at their recommendation we halted the trial and moved all of the children to that escalated dosing strategy," said Robert Opoka, MMed, who oversaw the study at Makerere University.

HOW THE STUDY WORKED

About half of the 187 study participants received a fixed dose of 20 mg per kilogram of body weight per day. The other half received an escalating dose, which started at 25 mg per kilogram of body weight then increased up to 35 mg per kilogram of body weight per day, if tolerated.

Doctors evaluated the children every 2-3 months. Dose-limiting toxic effects were similar in the two groups, and there were no cases of severe neutropenia or thrombocytopenia.

The study called for tracking the two groups for two years, but the monitoring board opened the dose escalation arm to all participants at about 18 months into the project.

"The study shows clearly that the optimized dosing strategy for hydroxyurea, though it requires more effort than a fixed-dose treatment regimen, results in far better outcomes for children with sickle cell anemia."

— Russell Ware, MD, PhD

"The study shows clearly that the optimized dosing strategy for hydroxyurea, though it requires more effort than a fixed-dose treatment regimen, results in far better outcomes for children with sickle cell anemia," Ware says.

LOW-COST TREATMENT FOR CHILDREN IN NEED

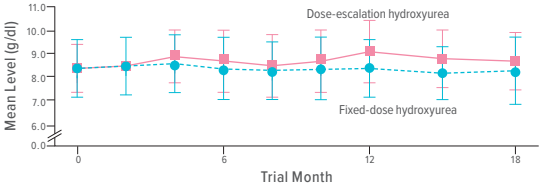
Sickle cell anemia affects about 100,000 people in the United States and millions more worldwide. Globally, an estimated 300,000 children are born with sickle cell each year, with about 80% located in sub-Saharan Africa. In the US, most people with sickle cell live well into adulthood, but in low-resource nations the disease kills many children before they reach age 5.

Hydroxyurea works by boosting fetal hemoglobin, Ware says, which reduces sickling in red blood cells, ameliorates anemia, moderates pain and prevents other sickle-related events.

The dose escalation approach will come with some higher costs for up-front testing, but the researchers say those costs pale in comparison to the reduction in longer term hospital care. Unlike regular blood transfusions, a long-used treatment

Laboratory Results for Participants in the NOHARM-MTD Study

A



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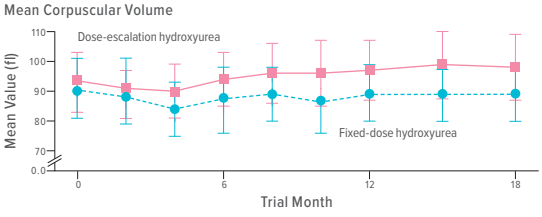

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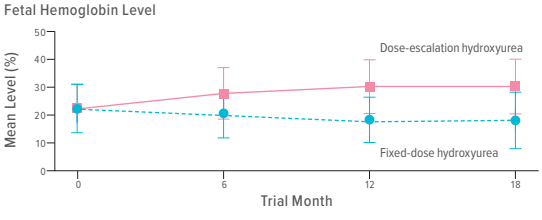

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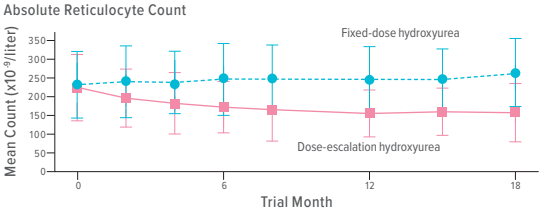

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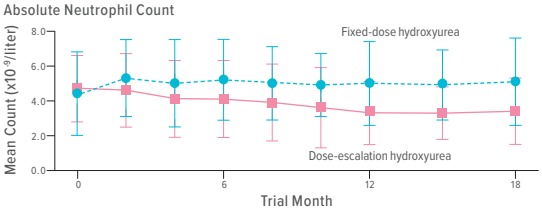

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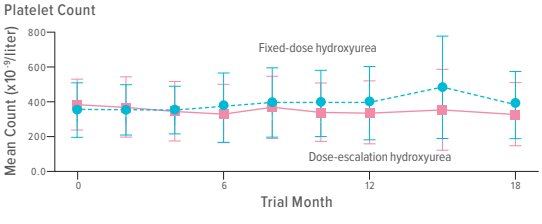


in richer countries, hydroxyurea could become accessible to children in any nation.

A LONG JOURNEY FOR A HOPEFUL THERAPY

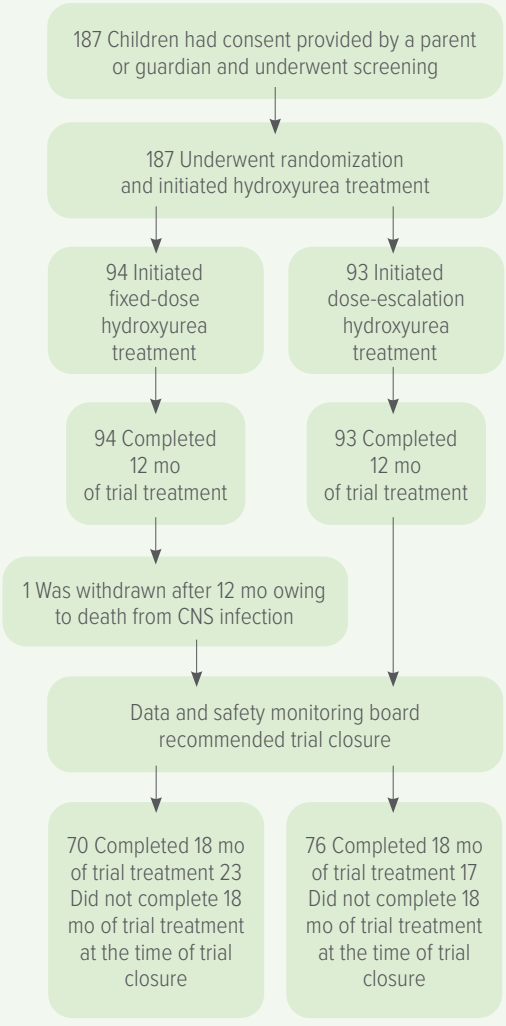
Cincinnati Children's co-authors in this *NEJM* study included Adam Lane, PhD, and Teresa Latham, MA.

For Ware and colleagues, the study caps an effort that includes data from the REACH study, published in the *NEJM* in December 2018; results from the initial NOHARM study, published in *Blood* in December 2017; and the US-based BABY HUG trial, with results published in 2011 in *The Lancet*.

Doctors have used hydroxyurea as an off-label treatment for sickle cell disease since the 1980s. The U.S. Food and Drug Administration (FDA) approved it for treating adults with sickle cell in 1998. It took another 19 years for the FDA to approve hydroxyurea for use in children.

Now, Ware says the next big steps in extending the lifespans of children with sickle cell anemia rest with leaders of health systems in Africa and the global health community who can combine forces to assure that hydroxyurea reaches all the children who need it.

More than 180 children in Uganda participated in the NOHARM-MTD clinical trial, which showed such positive results that the fixed dose arm of the study ended six months early.



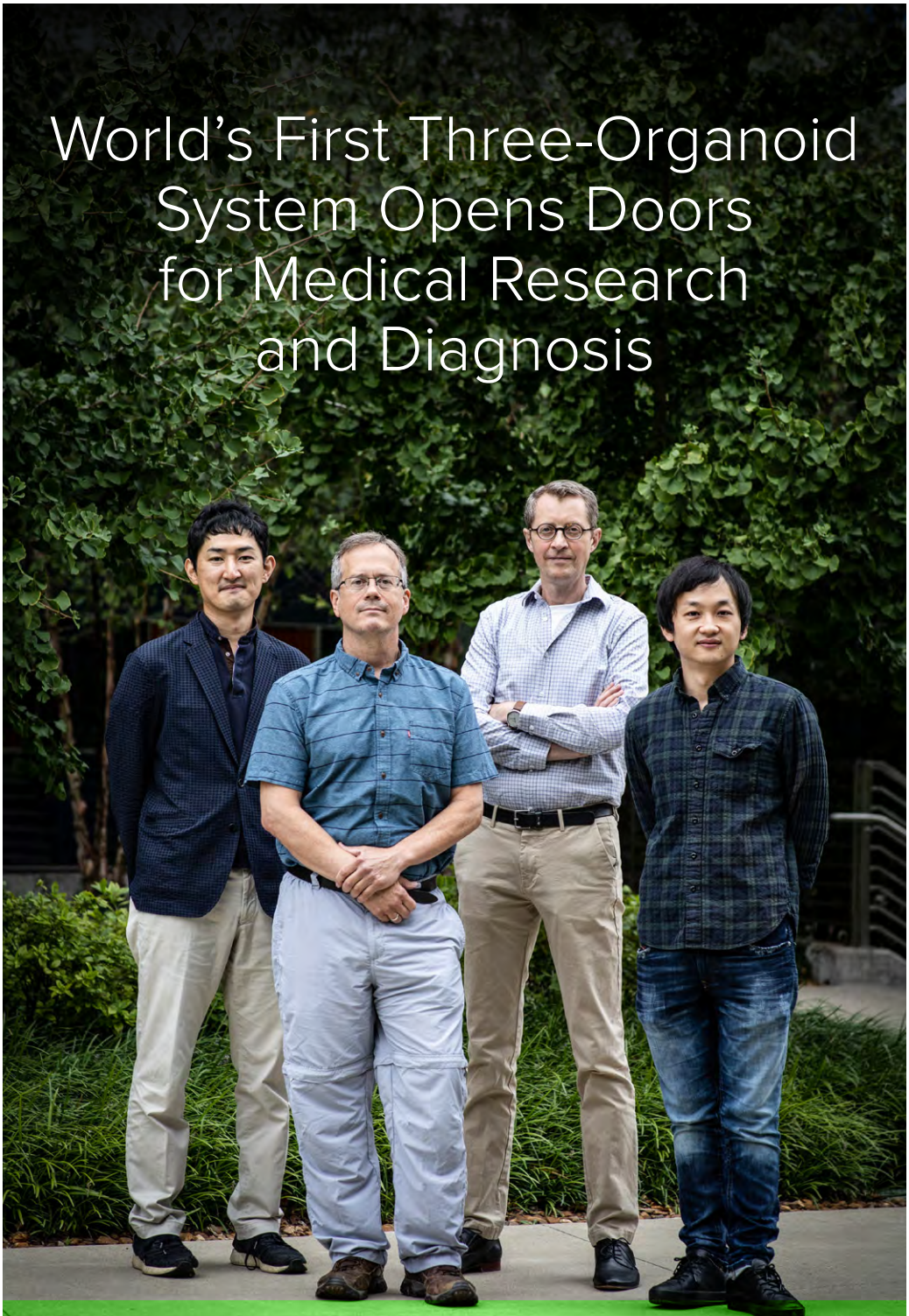
This flowchart details how participants were divided in the NOHARM-MTD study

CBDI: Hematology

RESEARCH & TRAINING DETAILS	
Faculty	12
Joint Appointment Faculty	1
Research Graduate Students	1
Total Annual Grant Awards	$4.1M
Total Annual Industry Awards	$803,775

John CC, Opoka RO, Latham TS, Hume HA, Nabaggala C, Kasirye P, Ndugwa CM, Lane A, Ware RE. Hydroxyurea Dose Escalation for Sickle Cell Anemia in Sub-Saharan Africa. N Engl J Med. 2020;382(26):2524-2533.

World's First Three-Organoid System Opens Doors for Medical Research and Diagnosis



DEVELOPMENTAL BIOLOGY & GASTROENTEROLOGY, HEPATOLOGY AND NUTRITION

Kentaro Iwasawa, MD / Jim Wells, PhD / Aaron Zorn, PhD / Takanori Takebe, MD, PhD

More than five years of painstaking research went into the project, and yet, its success came almost by accident.

Many in the field of regenerative medicine took note when a team of scientists led by first author Hiroyuki Koike, PhD, and senior author Takanori Takebe, MD, PhD, revealed in the journal *Nature* that they successfully produced a connected set of three organoids: the liver, pancreas and biliary ducts.

Organoids, grown from stem cells, are tiny 3D formations of human tissue that contain multiple cell types and can perform the functions of full-sized organs. Organoid experts at Cincinnati Children's led by Jim Wells, PhD, have already grown intestines that feature nutrient-absorbing villi, stomach organoids that produce digestive acids, and others.

By themselves, human organoids already provide a sophisticated tool for research. But this advance allows scientists to study how human tissues work in concert. Eventually, organoid systems could begin reducing the need for animal-based medication studies, sharply accelerate the concept of precision medicine, and someday lead to transplantable tissues grown in labs.

"The connectivity is the most important part of this," Takebe says. "What we have done is design a method for producing pre-organ, formation-stage tissues so that they can develop naturally. We are maximizing our capacity to make multiple organs much like our body does."

"Connecting the organs is a crucial unmet challenge to move organoid therapy into reality."

— Takanori Takebe, MD

A 5-YEAR QUEST ACHIEVES KEY GOAL

Takebe, age 32, joined Cincinnati Children's in 2016 and holds a dual appointment at Tokyo Medical and Dental University (TMDU) in Japan. He graduated from medical school in 2011 with plans to become a liver transplant surgeon. But as he learned about the yawning gap between the supply and demand for donor organs, Takebe shifted gears to focus on organ supply.

In previous research, Takebe has demonstrated a method to produce large supplies of liver "buds," an early-stage form of a liver organoid. He also has grown liver organoids that reflect disease states, including steatohepatitis.

But Takebe says this project goes beyond his previous work.

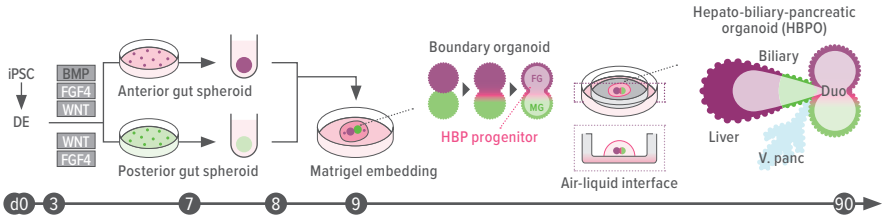
"We noted this point in organ differentiation some time ago. But it took five years to tune up the culture system to allow this development to occur," Takebe says.

HOW THREE PROTO-ORGANS GROW IN CONCERT

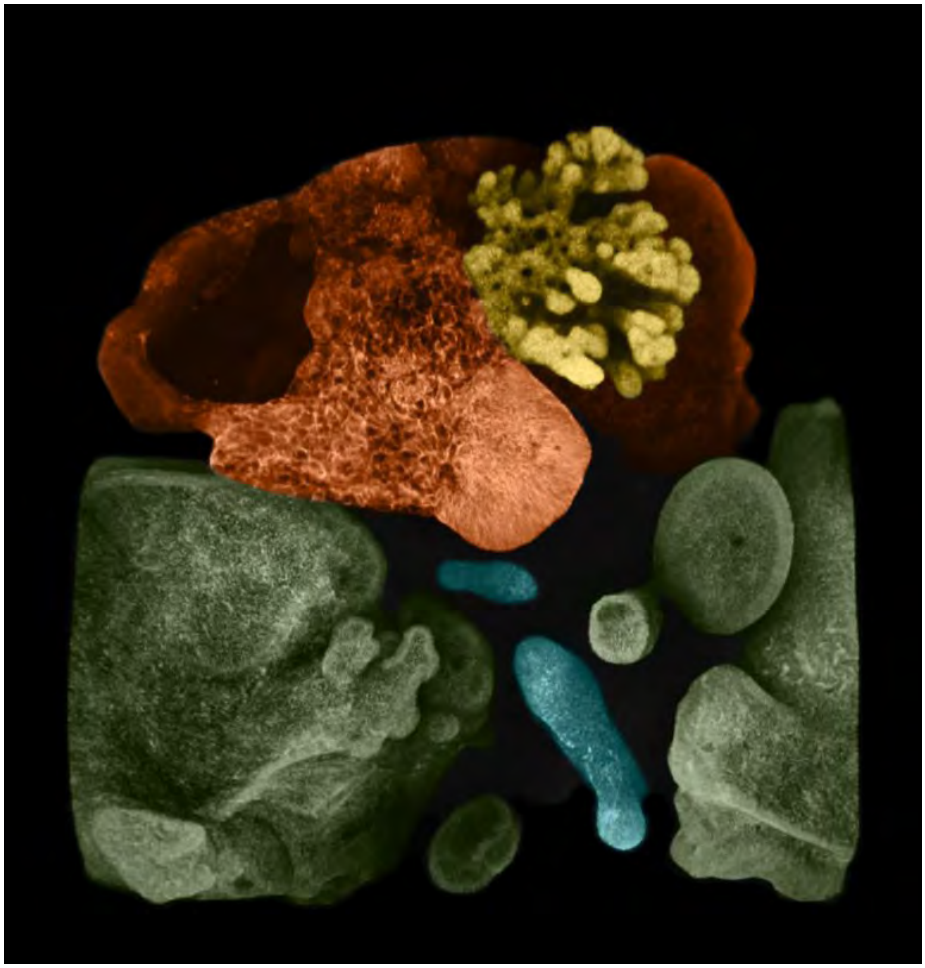
The hardest parts of the process were the earliest steps. Takebe worked for many hours with colleagues at Cincinnati Children's, including first author Hiroyuki Koike, PhD, now at Nippon Medical School in Japan, to perfect the process. They started with human skin cells, converting them back into primitive stem cells, then guiding and prodding those stem cells to form two very early-stage "spheroids" of cells loosely termed the foregut and the midgut.

These balls of cells form very early in embryonic development. In humans, they form late in the first month of gestation. In mice, they form in just 8.5 days. Over time, these spheres merge and morph into the organs that eventually become the digestive tract.

Growing these spheroids in the lab was a complex process that required using the right ingredients at the right time. Once they were mature enough—a timing step that required much work to pinpoint—then came the easier part.



This illustration describes the steps scientists at Cincinnati Children's and colleagues in Japan followed to create the world's first connected set of organoids. Details about the project, led by Takanori Takebe, MD, were posted online Sept. 25, 2019, in the journal *Nature*.



This confocal microscopic image reveals a connected set of human organoids, grown from stem cells. Liver cells appear red, pancreas cells appear yellow, biliary cells appear blue, and other gut cells are green. Image created by Asuka Kodaka and Ken Iwasawa.

The team simply placed the spheroids next to each other in a specially arranged lab dish. The cells were suspended in a gel that's commonly used to support organoid growth, then placed on top of a thin membrane that covered a carefully mixed batch of growth medium.

"From this point, the cells knew what to do," Takebe says. (See video for illustration of this process.)

The lab team watched as cells from each spheroid began to transform upon meeting each other at the boundary between the two. They converted themselves, and each other, into more specialized cells that could be seen changing colors thanks to chemical tags the lab team had attached to the cells.

Soon, the merging, changing spheres sprouted into branches leading to new groups of cells that belonged to specific organs. Over 70 days, these cells multiplied into more refined and distinct cell types. Ultimately, the organoids began processing bile acids as if they were digesting and filtering food.

"This was completely unexpected. We thought we would need to add ingredients or other factors to push this process," Koike says. "Not trying to control this biological process led us to this success."

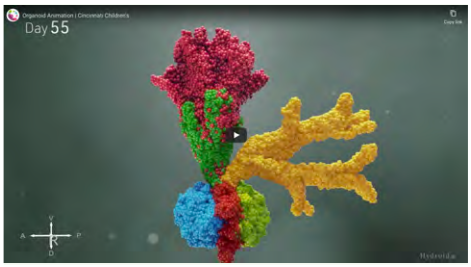
WHAT DOES THIS ADVANCE MEAN?

Aaron Zorn, PhD, Director of the Center for Stem Cell and Organoid Medicine (CuSTOM) at Cincinnati Children's, says this advance will be useful in multiple ways.

"The real breakthrough here was to be able to make an integrated organ system," Zorn says. "From a research perspective this is an unprecedented opportunity to study normal human development."

However, Takebe and colleagues were able to grow these organoids only so far. More work is needed to grow tissues large enough to be useful in human transplantation. The organoids also need to be integrated with other cell lines that form blood vessels, connective tissues, and so on.

"Current liver regenerative medicine approaches suffer from the absence of bile duct connectivity," Takebe says. "While much work remains before we can begin human clinical trials, our multi-organoid transplant system is poised to solve this issue."



Computer animation of liver-pancreas-biliary tract organoid growth. Watch online at https://youtu.be/6L6yBLqUhnw

Developmental Biology

RESEARCH & TRAINING DETAILS	
Faculty	23
Joint Appointment Faculty	30
Research Fellows & Post Docs	21
Research Graduate Students	59
Total Annual Grant Awards	$12.4M

Gastroenterology, Hepatology and Nutrition

RESEARCH & TRAINING DETAILS	
Faculty	46
Joint Appointment Faculty	2
Research Fellows & Post Docs	15
Research Graduate Students	1
Total Annual Grant Awards	$11.1M
Total Annual Industry Awards	$858,493

Koike H, Iwasawa K, Ouchi R, Maezawa M, Giesbrecht K, Saiki N, Ferguson A, Kimura M, Thompson WL, Wells JM, Zorn AM, Takebe T. Modelling human hepato-biliary-pancreatic organogenesis from the foregut-midgut boundary. Nature. 2019;574(7776):112-116.

Cardiac Stem Cell Therapy Improves Scar Formation Rather Than Prompting Cardiomyocyte Regeneration

HEART INSTITUTE: MOLECULAR CARDIOVASCULAR BIOLOGY

Ronald Vagnozzi, PhD / Jeffery Molkentin, PhD

Stem cell therapy helps hearts partially recover from a heart attack by triggering an immune response that results in better scar formation and improved performance of surviving tissue—not by helping hearts grow new muscle.

This finding, led by Jeffery Molkentin, PhD, Director of Molecular Cardiovascular Biology at Cincinnati Children's, helps clarify why a number of stem cell therapy trials have produced disappointing, but not entirely negative results.

The work by Molkentin and first author Ronald Vagnozzi, PhD, reveals an unexpected way that the heart responds to cardiac stem cell injections. Instead of the stem cells being integrated into the heart to grow cardiomyocytes as originally hoped, the injections trigger inflammation and an aggressive response from the body's macrophage cells.

"The innate immune response acutely altered cellular activity around the injured area of the heart so that it healed with a more optimized scar and improved contractile properties," Molkentin said. "The implications of our study are very straight forward and present important new evidence about an unsettled debate in the field of cardiovascular medicine."

> "The implications of our study are very straight forward and present important new evidence about an unsettled debate in the field of cardiovascular medicine."
>
> — Jeffery Molkentin, PhD

Molkentin, a Howard Hughes Medical Institute professor, made headlines in 2014 with a study in *Nature* showing that injecting c-kit positive heart stem cells into damaged hearts as a strategy to regenerate cardiomyocytes doesn't work. This study reveals what happens instead.

AN UNEXPECTED DISCOVERY

The study worked with mice using two types of heart stem cells—bone marrow mononuclear cells and cardiac progenitor cells. As the researchers tested their findings under different conditions, they discovered that live stem cells were not necessary for inducing the immune response they had seen. In fact, injecting dead cells produced the same outcome.

Further, they observed that zymosan, an inert chemical designed to induce an innate immune response, also provided a slightly greater and longer-lasting benefit to the heart than injecting stem cells or dead cell debris.

Be it stem cells or zymosan, the injections altered immune cell responses that significantly decreased the formation of extracellular matrix connective tissue in the injury areas, while also improving the mechanical properties of the scar itself. The authors concluded: "Injected hearts produced a significantly greater change in passive force over increasing stretch, a profile that was more like uninjured hearts."

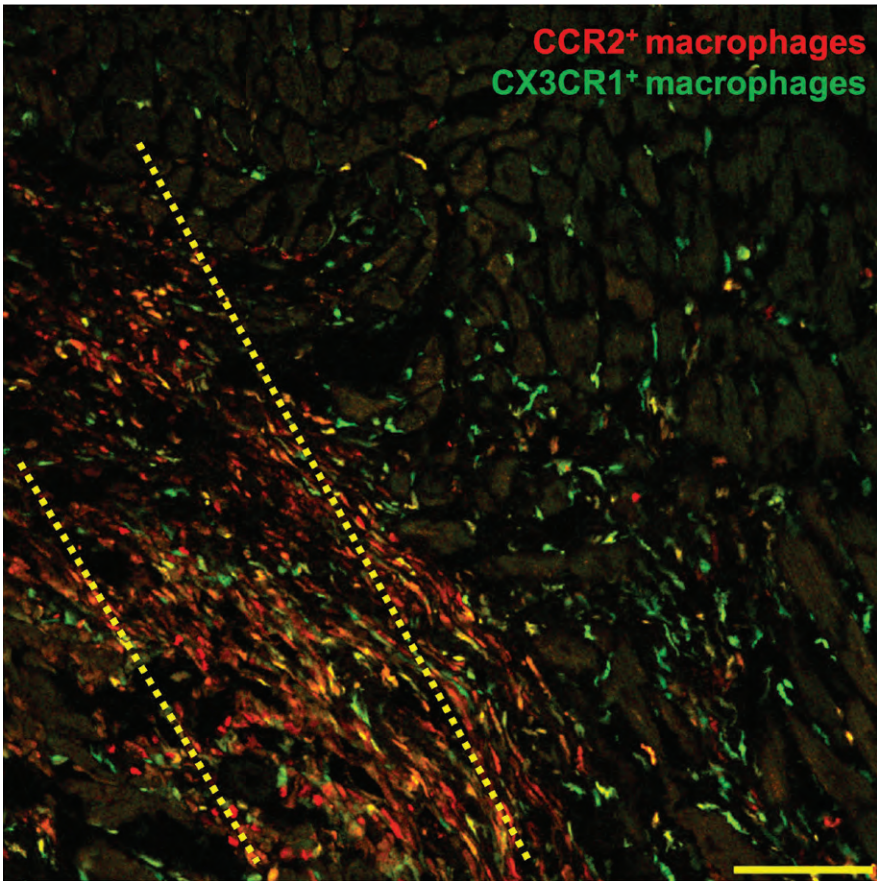
The researchers also found that the response occurs only when the injections occur directly into the hearts, as opposed to infusing stem cells via the circulatory system.

"Most of the stem cell clinical trials were incorrectly designed because they infuse cells into the vasculature," Molkentin explained. "Our results show that the injected material has to go directly into the heart tissue flanking the infarct region. This is where the healing is occurring and where the macrophages can work their magic."

LOOKING TO THE FUTURE

Molkentin and colleagues plan to follow up these findings by looking for other ways to leverage the healing properties of the stem cells and compounds

Triggering an Immune Response



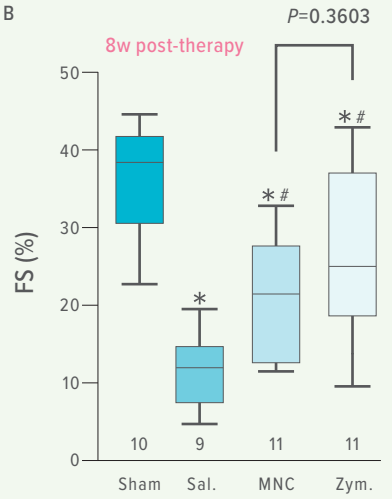
In this microscopic histology image, macrophage immune cells (shown in red and green) flock to the injured region of a damaged mouse heart three days after researchers injected adult heart stem cells within the yellow dotted area. While stem cell therapy did not prompt muscle regeneration, the treatment does appear to help hearts recover from heart attack by triggering an innate immune response that helps the injured area heal with a more optimized scar and improved contractile properties.

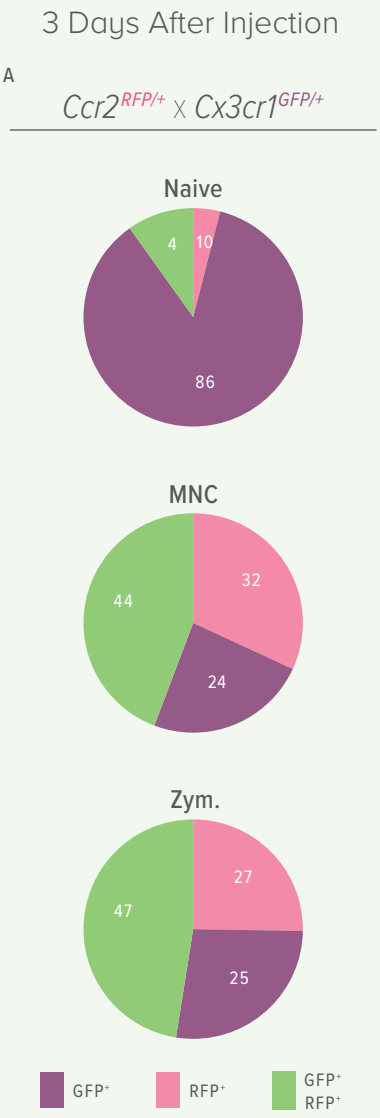
they tested. For example, they plan to explore polarizing macrophages so that they exhibit only their healing-like properties.

Key collaborators included scientists in the Cincinnati Children's Heart Institute, the University of Cincinnati, the Cardiovascular Research Center at Massachusetts General Hospital, and Harvard Medical School.

A Right: This panel shows distribution of CCR2+ and CX3CR1+ subtypes of macrophage in hearts at three days after injection. Pie charts reflect the proportion of RFP (CCR2+)- or GFP (CX-3CR1+)-expressing cells, as well as CCR2+CX3CR1+ double-positive (yellow) cells detected by flow cytometry, as a percentage of total macrophages identified by staining for F4/80 and CD64

B Below: This panel detailing fractional shortening results at eight weeks post-therapy indicates that both cell and inflammatory therapy rejuvenate heart function compared to saline.





Heart Institute: Molecular Cardiovascular Biology

RESEARCH & TRAINING DETAILS	
Faculty	7
Research Fellows & Post Docs	13
Research Graduate Students	12
Total Annual Grant Awards	$6.5M

Vagnozzi RJ, Maillet M, Sargent MA, Khalil H, Johansen AKZ, Schwanekamp JA, York AJ, Huang V, Nahrendorf M, Sadayappan S, Molkentin JD. An acute immune response underlies the benefit of cardiac stem cell therapy. Nature. 2020;577(7790):405-409.

Clinical Trial Success Caps Long Journey for HLH Treatment

IMMUNOBIOLOGY
Alexi Grom, MD / Michael Jordan, MD

The disease hemophagocytic lymphohistiocytosis (HLH) still has no cure. But now it has an approved treatment that appears to help most patients live long enough and well enough to receive crucial stem cell transplants.

The efficacy of the monoclonal antibody emapalumab (Gamifant) was detailed in clinical trial results published in *The New England Journal of Medicine*, The multi-center study was co-authored by Michael Jordan, MD, a member of the Divisions of Immunobiology and Bone Marrow Transplantation and Immune Deficiency, and Alexei Grom, MD, Research Director, Division of Rheumatology.

The biologic, when administered with dexamethasone, achieved its goal of tamping down runaway inflammatory activity while demonstrating less toxicity and fewer side effects than other treatments, such as steroids and chemotherapy.

The *NEJM* paper delved into data from a clinical trial that began in 2013 and officially ended in 2017, although some patients were treated with the drug after the cut-off date. Based on the initial data from the trial, the U.S. Food and Drug Administration approved emapalumab in 2018—the first-ever drug approved specifically for HLH.

The initial trial results suggested that clinicians should consider the drug as the standard of care for "second line" treatment of HLH. But the extended findings also suggest a potential benefit for the drug as a first-line therapy, Jordan says.

STOPPING AN INFLAMMATION TRAIN

HLH is a rare but deadly childhood disease that overstimulates the immune system and causes hyperinflammation, which leads to widespread organ and tissue damage. Clinicians find about 1.2 cases per 1 million individuals per year. For many years, the mortality rate has been about 40%.

Jordan, has been working for years to find a treatment specific to HLH that can block the runaway inflammation. A key step in that effort occurred in 2004, when Jordan's mouse study, published in the journal *Blood*, revealed that the HLH disease process relies on high levels of the protein interferon gamma (IFNg).

Now, emapalumab has shown its ability to block IFNg, which in turn offers improved odds for more children to live with HLH as more of a chronic disease instead of an early cause of death.

"For the first time we have a truly targeted way to treat HLH and a drug with very low toxicity."

—Michael Jordan, MD

ENCOURAGING RESULTS

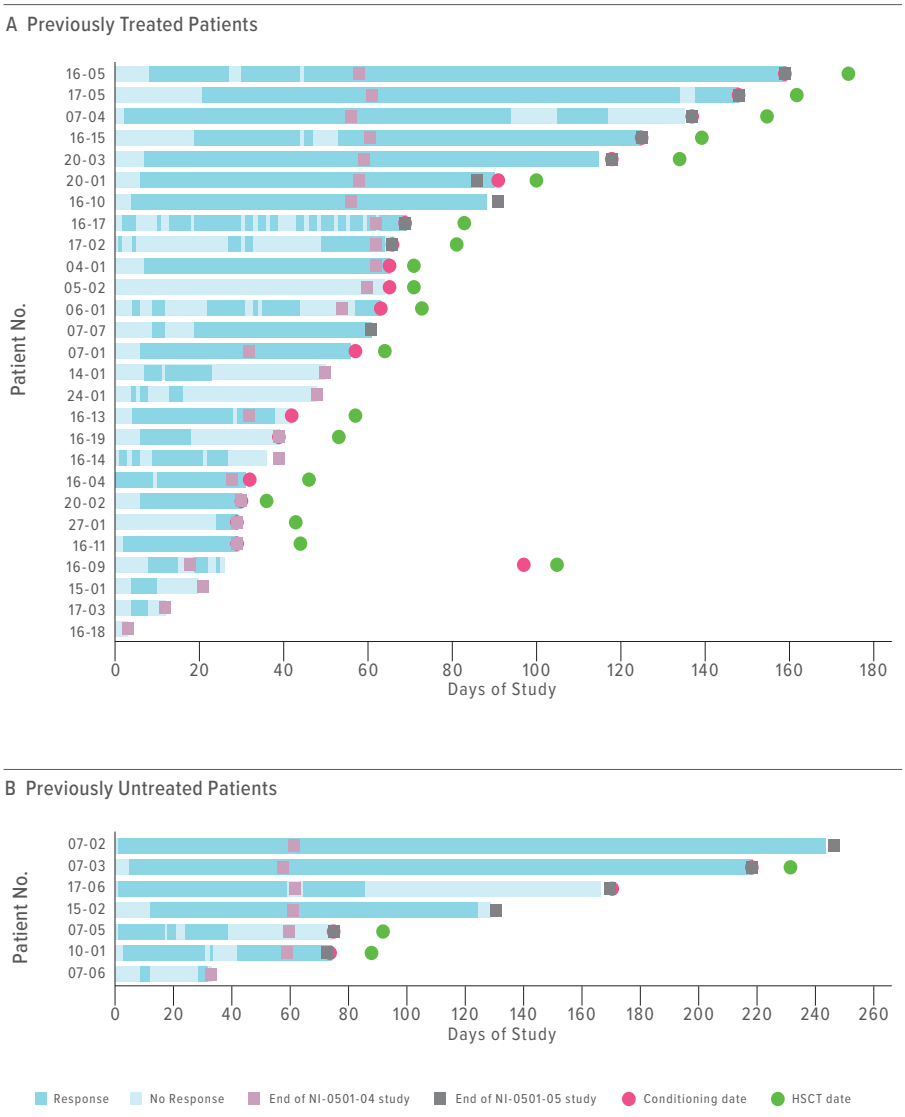
The phase 2–3 clinical trial was performed at 14 sites in Germany, Italy, Spain, the United Kingdom, and the United States. Jordan led the project in conjunction with Franco Locatelli, MD, at the University of Rome.

Overall, 34 patients received emapalumab, including 27 who had received other unsuccessful treatments and seven patients who had not been treated in any other way.

The eight-week treatment began with an emapalumab dose of 1 mg per kilogram of body weight every three days, which was increased over time up to as high as 10 mg per kilogram. Twenty-six patients completed the study.

Investigators found that 63% of the previously treated group and 65% of previously untreated patients responded to emapalumab. This included seven patients who experienced "complete responses," defined as normal spleen and no fever, cytopenia, hyperferritinemia or other abnormalities attributable to hemophagocytic lymphohistiocytosis.

Emapalumab Treatment Results



These swimmer plots show the response status in previously treated patients (Panel A) and previously untreated patients (Panel B) from the day of the first emapalumab infusion (study day 0) until the start of conditioning. The response was considered to be lost on the days when the criteria for an improvement in measures of hemophagocytic lymphohistiocytosis were not met. Patient 16-09 discontinued emapalumab during the study. HSCT denotes hematopoietic stem-cell transplantation.

Of the initial 34 patients, 22 ultimately received hematopoetic stem cell transplant with one-year survival rates exceeding 70%.

"This is a very important advance. For the first time we have a truly targeted way to treat HLH and a drug with very low toxicity," Jordan says.

The clinical trial was funded in large part by the drug maker. However, the research that led up to the trial was funded by a mix of government grants and philanthropy. In fact, participants from several years of 700-mile bike rides from Mississippi to Cincinnati raised more than $1 million to support the work.

HUNT UNDERWAY FOR GENE THERAPY

At the HLH Center of Excellence, Cincinnati Children's has assembled a team of specialists and scientists who continue to work to improve HLH outcomes. In addition to the *NEJM* study results, the team has developed an HLH gene chip for rapid, precise diagnosis and has begun preclinical studies of a potential gene therapy for *PRF1* deficiency.

For emapalumab, more study is needed to track longer-term effectiveness, including to determine whether the drug can reduce or delay the need for stem cell transplants.

"My goal for our work over all these years has been to use scientific exploration and practical medical approaches to make a difference in the lives of these children," Jordan says. "It's been a privilege to help develop this idea from an unexpected laboratory discovery to an approved medicine."

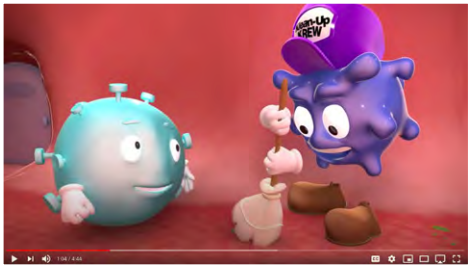
LEARN MORE ABOUT HLH

https://www.cincinnatichildrens.org/service/h/hlh

WATCH A VIDEO ABOUT HLH

https://youtu.be/Vxoy5328MZc

Helping Kids & Parents Understand Science and Treatment of HLH



Immunobiology

RESEARCH & TRAINING DETAILS	
Faculty	13
Joint Appointment Faculty	3
Research Fellows & Post Docs	17
Research Graduate Students	22
Total Annual Grant Awards	$7M
Total Annual Industry Awards	$400,001

Locatelli F, Jordan MB, Allen C, Cesaro S, Rizzari C, Rao A, Degar B, Garrington TP, Sevilla J, Putti MC, Fagioli F, Ahlmann M, Dapena Diaz JL, Henry M, De Benedetti F, Grom A, Lapeyre G, Jacqmin P, Ballabio M, de Min C. Emapalumab in Children with Primary Hemophagocytic Lymphohistiocytosis. N Engl J Med. 2020;382(19):1811-1822.

2020 Scientific Achievements

Investigators here produced more than 2,400 peer-reviewed journal articles, book chapters, and other publications in FY2020. The following pages feature the most significant publication from each of our research divisions.

Transgender AFAB Teens Use a Variety of Contraceptives to Suppress Menses, Provide Protection

Rula Kanj, MD

PUBLISHED JULY 2019

International Journal of Transgenderism

What are the contraceptive practices of transgender youth whose sexual identity is assigned female at birth (AFAB) but who embrace a transmasculine identity?

Researchers in the Division of Adolescent Gynecology reviewed charts of 231 transgender AFAB patients to identify patterns and reasons for contraceptive use among those aged 10 to 25 years old who had begun menstruating but were not pursuing puberty suppression. Half were taking testosterone as part of their transition to a more masculine identity.

Patients were seen at least twice between 2013-2017 at the Transgender Health Clinic. AFAB refers to the practice of assigning gender at birth based on visual identification of female-typical genitalia whereas AMAB is the acronym for assigned male at birth.

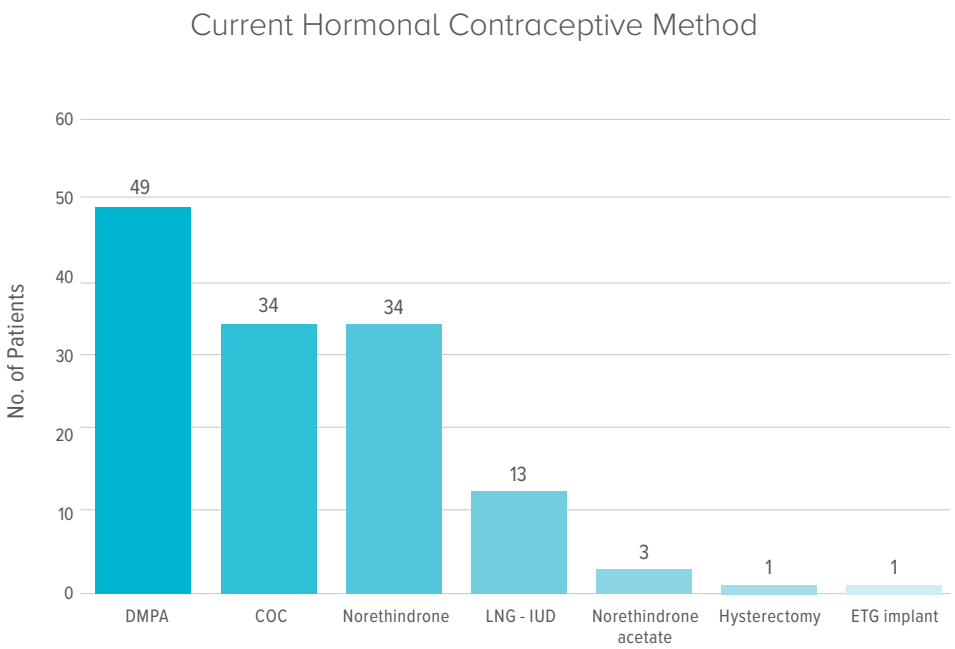
Led by attending physician Rula Kanj, MD, this study found that 59% of the teens were using a hormonal contraceptive method, and of those, 67% relied on it for the indication of menstrual suppression. The most commonly used contraceptive (49 patients) was depot medroxyprogesterone (DMPA), followed by combined oral contraceptives and norethindrone (progestin-only pills; 34 patients each). Another 13 patients relied on a 52 mg levonorgestrel intrauterine device (IUD). Among the 36% of patients (82) who were sexually active, 43% reported sexual intercourse with AMAB partners and/or reported having penile-vaginal intercourse, activities that potentially put them at risk for pregnancy.

Notably, among the 35 patients who were at risk for pregnancy, only 21 were using hormonal contraception. More than half of sexually active patients taking testosterone discontinued the use of hormonal contraceptives once they stopped menstruating. Kanj encourages counseling for these at-risk patients on continued use of barrier methods and hormonal contraception. Kanj says the findings may spur research into favorable side effect profiles of hormonal contraceptives to encourage their long-term use among transmasculine teens.

RESEARCH & TRAINING DETAILS

Joint Appointment Faculty	1

Kanj RV, Conard LAE, Corathers SD, Trotman GE. Hormonal contraceptive choices in a clinic-based series of transgender adolescents and young adults. Int J Transgenderism. 2019;20(4):413-420.


Current Hormonal Contraceptive Method
No. of Patients
60
50
40
30
20
10
0
49
34
34
13
3
1
1
DMPA
COC
Norethindrone
LNG - IUD
Norethindrone acetate
Hysterectomy
ETG implant

Updated Meta-Analysis Shows Real-World Impact of HPV Vaccination

Jessica Kahn, MD, MPH

PUBLISHED AUG. 10, 2019
The Lancet

A systematic review of 65 studies involving data from 60 million people in 14 high-income nations reveals that a decade of vaccination efforts against human papillomavirus (HPV) shows "compelling evidence" of direct benefit from the vaccine—and a herd protection effect in areas with high vaccination rates.

The analysis was produced by the HPV Vaccination Impact Study Group, an investigator collaborative that includes HPV epidemiology expert Jessica Kahn, MD, MPH. "For this analysis, we contributed data from Cincinnati that we have been collecting every three years since 2006 to examine the real-world impact of HPV vaccine introduction, and the meta-analysis findings mirror what we have found in Cincinnati," says Kahn, Director, Division of Adolescent and Transition Medicine.

The meta-analysis reports several powerful findings:

- HPV 16 and HPV 18 decreased 83% in girls ages 13 to 19 and 66% in women ages 20 to 24 after 5 to 8 years of vaccination.
- A 54% reduction occurred in three other HPV types (31, 33, and 45) in girls age 13 to 19, supporting cross-protection against HPV types genetically related to vaccine types.
- Incidence of anogenital warts declined in girls and women from ages 15 to 29 and in boys and men ages 15 to 24.
- Within 5 to 9 years post-vaccination, precancerous lesions decreased 51% in girls ages 15 to 19 and 31% in women ages 20 to 24.

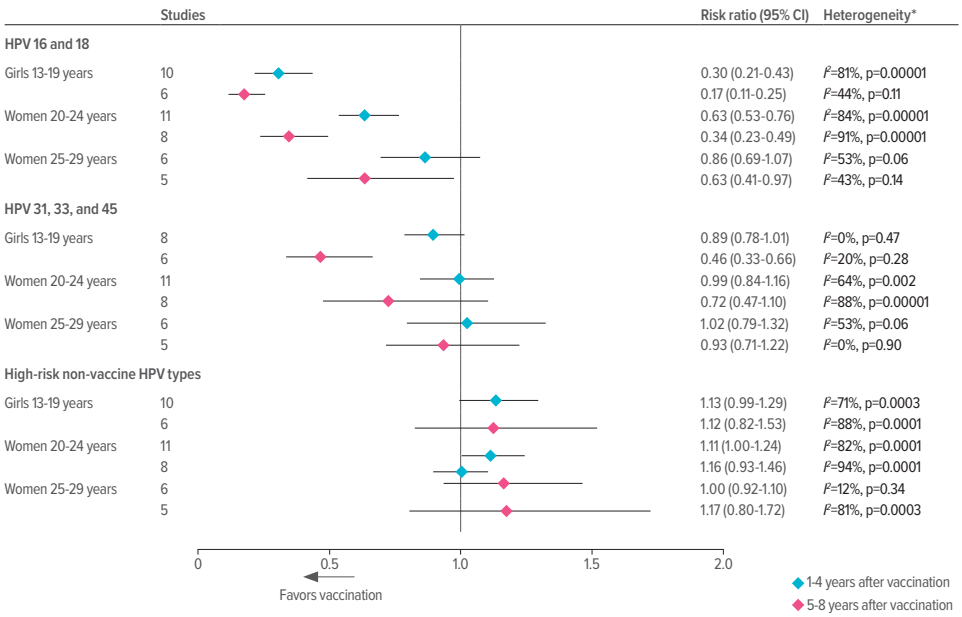
"This analysis was the first to present estimates of the population-level impact of HPV vaccination on pre-cancers and the benefits of vaccinating multiple cohorts of girls and achieving high rates of vaccination coverage," Kahn says. "If public health leaders follow the World Health Organization's call to optimize HPV vaccination as well as cancer screening and treatment, elimination of cervical cancer is within our reach."

RESEARCH & TRAINING DETAILS

Faculty	12
Joint Appointment Faculty	3
Total Annual Grant Awards	$1.1M

Drolet M, Bénard É, Pérez N, Brisson, M, et al, HPV Vaccination Impact Study Group. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. The Lancet. 2019; 394:497-509.

Changes in HPV Prevalence Following Vaccination



HPV=human papillomavirus. *p values are associated with the χ^2 statistic.

AP-1 Transcription Factor a Key Player in T Cell Activation

Masashi Yukawa, PhD

Artem Barski, PhD

PUBLISHED JAN. 6, 2020
Journal of Experimental Medicine

T cells are vital to helping our bodies fight off illness, cancer, and immune disease. Activating them involves the orchestrated opening and closing of chromatin, the material that packages a cell's DNA, which makes some gene functions accessible, while making others inaccessible.

Now a multidisciplinary team of Cincinnati Children's researchers reports uncovering a vital clue about how this process works. Their study, published in the *Journal of Experimental Medicine*, reveals that the transcription factor activator protein 1 (AP-1) directs most of the chromatin remodeling during T cell activation. Further, when AP-1 is inhibited, chromatin opening does not occur and T cells do not form or function correctly.

The involvement of AP-1 is important because this transcription factor also influences and overlaps with risk loci for multiple sclerosis, inflammatory bowel disease, and other allergic disease. For now, the goal for this research is understanding how the epigenome encodes T cell memory, says Artem Barski, PhD, lead investigator on the study. But downstream, this knowledge eventually may help researchers develop ways to manage pathologic immune responses, improve vaccines or find new anti-cancer immune therapies.

Researchers used ChIP-seq and ATAC-seq technologies to analyze all the protein interactions affecting chromatin state. Prior studies have focused on genetic disruptions of individual AP-1 members, but Barski's lab developed an approach of protein electroporation, which "turned out to be amazingly efficient, delivering our dominant-negative protein into almost 100% of cells," says first author Masashi Yukawa, PhD.

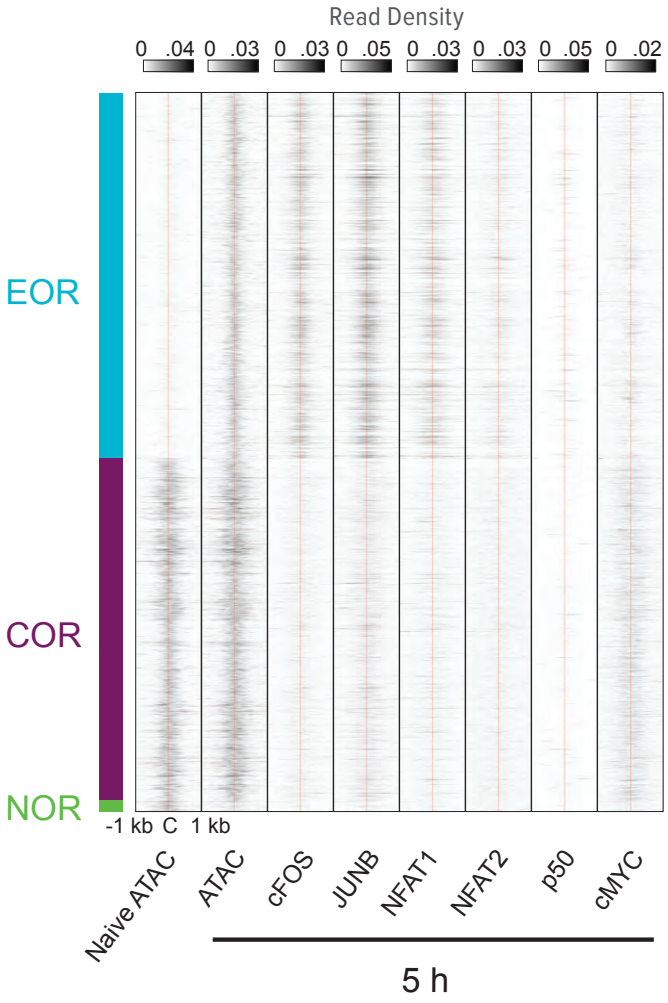
These findings have since been presented at the American Academy of Immunologists and the Cold Spring Harbor Laboratory meetings. Collaborators included researchers from the Center for Autoimmune Genomics and Etiology and the Division of Biomedical Informatics.

RESEARCH & TRAINING DETAILS

Faculty	15
Joint Appointment Faculty	4
Research Fellows & Post Docs	4
Research Graduate Students	3
Total Annual Grant Awards	$3.2M
Total Annual Industry Awards	$259,561

Yukawa M, Jagannathan S, Vallabh S, Kartashov AV, Chen X, Weirauch MT, Barski A. AP-1 activity induced by co-stimulation is required for chromatin opening during T cell activation. J Exp Med. 2020;217(1).

How AP-1 Opens Chromatin



AP-1 and its partner bind to effector open regions (EOR). The fragment density heatmaps show the read density of the ATAC-seq and TF ChIP-seq signal at open chromatin regions. Note that most of the DNA regions opening upon T cell activation (EORs) are bound by FOS and JUNB, the components of AP-1 transcription factor.

Genetic Study Identifies Neurotransmitter Connection Between Surgical Pain and Anxiety Sensitivity

Vidya Chidambaran, MD, MS

PUBLISHED JULY 2019
Journal of Pain

A study of 73 adolescents undergoing spine fusion surgery has identified specific epigenetically enriched pathways that help explain a neurotransmitter connection between chronic postsurgical pain (CPSP) and anxiety sensitivity in children. The multidisciplinary team's analysis of 39 peripheral blood sample genes identified, respectively, 637 and 2,445 associated differentially DNA methylated positions (DMPS) that are associated with CPSP and scores on the Child Anxiety Sensitivity Index (CASI). Specifically, the findings support Gamma aminobutyric acid (GABA) hypofunction and involvement of the dopamine DARPP32 pathway (active in emotion/reward) in anxiety sensitivity and pain.

The findings "have mechanistic as well as translational implications with potential to positively impact outcomes for children undergoing surgery," says lead author Vidya Chidambaran, MD, divisional director of perioperative pain management. Analysis of the gene-gene interaction network revealed participation of pathways in cell signaling, molecular transport, connective tissue development, metabolism, and neurologic diseases.

"The epigenetic findings point to pathways at the intersection of behavioral disorders like anxiety, and persistence of pain 10-12 months after surgery," she explains. "Not only do they have the potential to serve as predictive biomarkers, they also suggest common environmental/external influences on these phenotypes, yielding insight into future research for potential targeted and/or individualized preventive and therapeutic strategies."

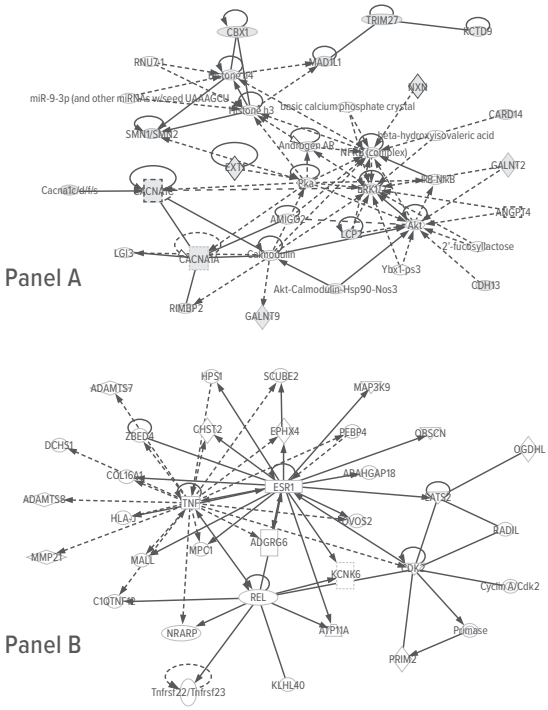
Since the study's July 2019 publication in the *Journal of Pain*, Chidambaran has received additional CCHMC and NIH funding to validate the findings in a bigger cohort and conduct longitudinal methylation studies to understand the effect of pain/opioid use on epigenetic mechanisms underlying acute to chronic pain translations. One of those will be an imaging study to correlate blood epigenetic findings with neurochemical imaging markers in the brain.

RESEARCH & TRAINING DETAILS

Faculty	61
Research Fellows & Post Docs	3
Research Graduate Students	3
Total Annual Grant Awards	$2.6M
Total Annual Industry Awards	$162,998

Chidambaran V, Zhang X, Geisler K, Stubbeman BL, Chen X, Weirauch MT, Meller J, Ji H. Enrichment of Genomic Pathways Based on Differential DNA Methylation Associated With Chronic Postsurgical Pain and Anxiety in Children: A Prospective, Pilot Study. J Pain. 2019;20(7):771-785.

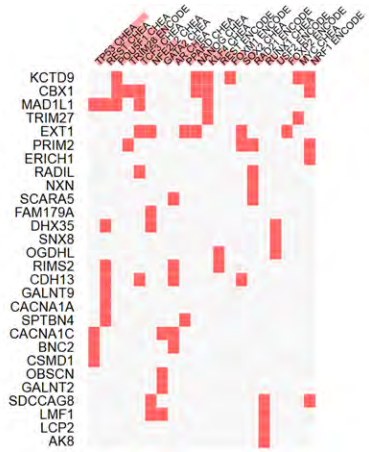
Some Common Neural Networks Suggested by Differential Methylation



LEFT Genes associated with the differentially methylated sites were uploaded to Ingenuity pathway analysis. Based on p-value cutoffs of 10–8, three networks were identified. Two of them were similar in function with several overlapping molecules. Hence, two of the different networks are presented here. The network in panel A is associated with cell signaling, molecular transport, vitamin and mineral msetabolism. It had a p-score of 33 and 14 focus molecules (including CACNA1A, CACNA1C, Calmodulin, ERK1/2, Histone h3, Histone h4, IkB-NfkB, NFkB (complex), miR-9–3p). The network in Panel B is associated with neurological disease, organismal injury and abnormalities, connective tissue development and function; with a p-score of 12, and 6 focus molecules (including ESR1, KCNK6, PRIM2, TNF).

Potential Future Targets For Exploration

RIGHT The results of enrichment analysis using Enrichr are shown here, where for each transcription factor, e.g., REST, its (here ENCODE mapped) targets among genes identified in our study are indicated by red squares (and include in this case *RIMS2*, *CDH13*, *SPTBN4* etc.). Note that statistical significance of the enrichment is indicated by red vertical bars associated with each transcription factor.



Atopic Dermatitis Linked to Higher Allergy Risk Than Parental History

Jocelyn Biagini, PhD

PUBLISHED MAY 2020

The Journal of Allergy and Clinical Immunology

Roughly 10% of American children develop atopic dermatitis (AD), commonly called eczema. While AD has been a known risk factor for asthma development, a lack of cohorts of children with AD has made it difficult to assess how much the skin condition affects allergy sensitization rates.

In a study published in *The Journal of Allergy and Clinical Immunology*, Cincinnati Children's researchers compared sensitization rates between participants of two large studies: the Mechanisms of Progression of Atopic Dermatitis in Children (MPAACH) study, the first pediatric cohort of AD in the U.S. and the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), a high-risk cohort of children with family histories of allergy and/or asthma.

Previous studies have shown that allergy sensitization rates in children with allergic parents are three and a half times higher than those of the general public. The new study shows that having AD presents an even higher risk.

"Rates of parental allergenic disease were similar in each cohort, but we found 50% overall higher sensitization rates in MPAACH compared to CCAAPS, and almost four times increased co-sensitization to aeroallergens plus food allergens," says senior lead author Jocelyn Biagini, PhD.

In another recent publication, Biagini and colleagues further found that increased allergy risk from AD may not depend upon overtly damaged skin. The team found that normal-appearing, non-lesional skin of MPAACH children still shows disease features such as low skin filaggrin, high alarmin expression, and increased *Staphylococcus aureus* colonization.

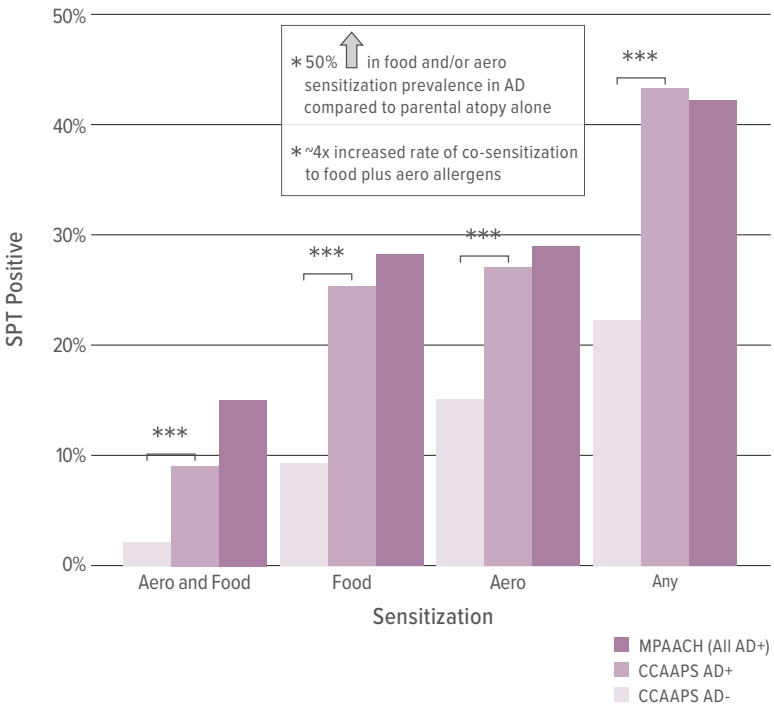
"We are continuing to follow the MPAACH cohort to determine what factors contribute to the progression of AD to other allergic diseases such as food allergy, allergic rhinitis and asthma," Biagini says.

RESEARCH & TRAINING DETAILS

Faculty	6
Joint Appointment Faculty	1
Research Fellows & Post Docs	7
Research Graduate Students	4
Total Annual Grant Awards	$6.1M
Total Annual Industry Awards	$24,827

Kroner JW, Baatyrbek Kyzy A, Burkle JW, Martin LJ, LeMasters GK, Bernstein DI, Lockey JE, Ryan P, Khurana Hershey GK, Biagini Myers JM. Atopic dermatitis independently increases sensitization above parental atopy: The MPAACH study. J Allergy Clin Immunol. 2020;145(5):1464-1466.

Allergy Sensitization Rates



M-PAACH
Mechanisms of Progression of Atopic Dermatitis to Asthma in Children

N=400
N=128 age 1-2 years
All AD +

CCAAPS

AD+ = 222 AD- = 490
All with parental atopy
Age 1-2 years

Sensitization rates are higher in children with atopic dermatitis compared to those with family histories of allergy or asthma.

Childhood Maltreatment Elevates Risk of Pain for Adult Women

Sarah Beal, PhD

PUBLISHED JANUARY 2020
Pain

Adults who experience pain differently—more frequently, intensely, and widespread—have reported higher frequencies of abuse during childhood.

Although specialists and treatment providers have observed these associations for some time, research to explore associations between maltreatment as a child and adult experiences with pain have shown unclear results. Studies have tended to focus on adults who already suffer from pain, relying on self-reports of childhood experiences many years later.

Researchers in the Division of Behavioral Medicine and Clinical Psychology took a unique approach—beginning a study with adolescents and following them into adulthood. The team recruited 477 girls between the ages of 14 to 17 and checked in with them annually until age 19. About half of the participants had a documented history of physical, emotional, or sexual abuse.

Five years later, researchers were able to contact 383 of the participants and ask about their pain experiences. Compared with women who had not experienced childhood maltreatment, those who had reported more pain intensity, more locations of pain, and more likelihood of experiencing pain in the previous week.

"We were able to examine the mechanisms that might explain why some women are experiencing pain and others are not—in this case, elevated post-traumatic stress symptoms," says lead author Sarah Beal, PhD.

The team, including co-authors Susmita Kashikar-Zuck, PhD, and Christopher King, PhD, is preparing a follow-up study to better understand cognitive function, pain processing, and other health behaviors in the same cohort of women.

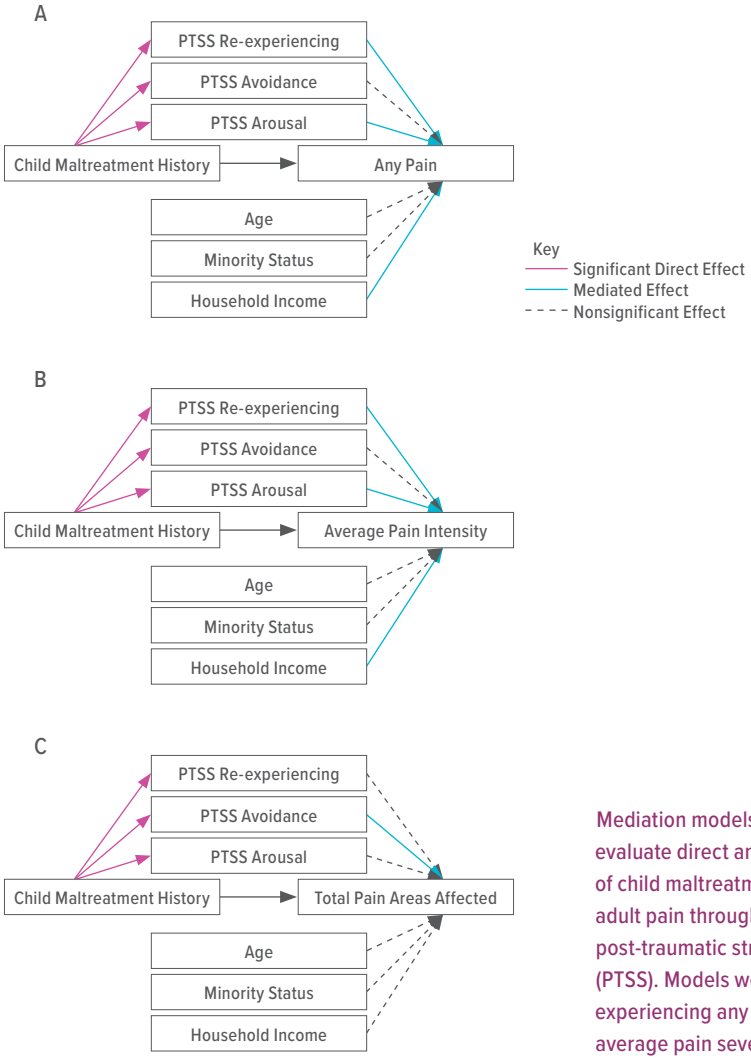
"Our hope is that with better understanding of the processes linking maltreatment to pain and other health outcomes, we can identify opportunities for early intervention to help women who experience maltreatment to lead healthier and more productive lives in adulthood," says Beal.

RESEARCH & TRAINING DETAILS

Faculty	57
Joint Appointment Faculty	1
Research Fellows & Post Docs	16
Research Graduate Students	6
Total Annual Grant Awards	$13.3M

Beal SJ, Kashikar-Zuck S, King C, Black W, Barnes J, Noll JG. Heightened risk of pain in young adult women with a history of childhood maltreatment: a prospective longitudinal study. Pain. 2020;161(1):156-165.

Models Linking Maltreatment and Pain



Mediation models estimated to evaluate direct and indirect effects of child maltreatment on young adult pain through adolescent post-traumatic stress symptoms (PTSS). Models were estimated for experiencing any pain in adulthood (A), average pain severity ratings (B), and total pain locations (C).

Air Pollution Linked to Spikes in Psychiatric Emergency Visits

Cole Brokamp, PhD

PUBLISHED SEPT. 25, 2019
Environmental Health Perspectives

What do air pollution and mental health have in common? For children, short-term increases in air pollution could lead to exacerbations of anxiety, suicidality, bipolar disorder, and PTSD.

While previous evidence has linked exposure to particulate matter with psychiatric exacerbations in adults, researchers in the Division of Biostatistics and Epidemiology are the first to study this association in children.

The team focused on PM2.5 particles, which measure less than 2.5 micrometers in diameter, can enter the brain or bloodstream through the lungs, and have been shown to cause inflammation throughout the body with short-term exposure.

First, the team analyzed emergency department visits at Cincinnati Children's for psychiatric issues from 2011-2015. Next, they paired the data with estimated PM2.5 exposure at residential addresses.

Researchers found that psychiatric visits would spike one to two days after a rise in exposure to PM2.5. Children living in disadvantaged neighborhoods were more susceptible to these effects when compared to other children, especially for disorders related to anxiety and suicidality.

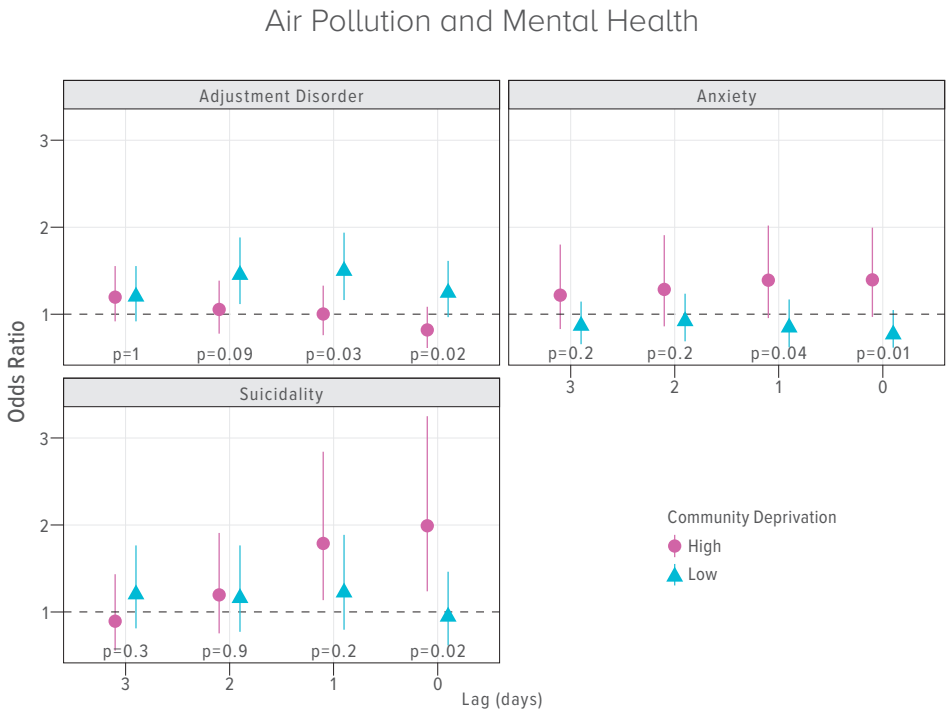
"More research is needed to confirm these findings, but it could lead to new prevention strategies for children experiencing symptoms related to a psychiatric disorder," says lead author Cole Brokamp, PhD. "The fact that children living in high-poverty neighborhoods experienced greater health effects of air pollution could mean that pollutants and neighborhood stressors can have synergistic effects on psychiatric symptom severity and frequency."

To better understand the biological mechanisms behind these associations, researchers plan to replicate the study in a nationwide population and focus on children with severe anxiety.

RESEARCH & TRAINING DETAILS

Faculty	21
Research Fellows & Post Docs	2
Research Graduate Students	13
Total Annual Grant Awards	$13.9M

Brokamp C, Strawn JR, Beck AF, Ryan P. Pediatric Psychiatric Emergency Department Utilization and Fine Particulate Matter: A Case-Crossover Study. Environ Health Perspect. 2019;127(9):97006.



When air pollution spikes, so do emergency visits related to suicide and anxiety, especially among children in disadvantaged neighborhoods. These graphs show the odds ratios and 95% confidence intervals for associations between a 10-µg/m^3 increase in PM2.5 and pediatric psychiatric emergency department visits (stratified by community deprivation from conditional logistic regression models adjusted for temperature, humidity, and holidays).

Eculizumab Improves Survival When Stem Cell Transplant Patients Develop High-Risk TA-TMA

Sonata Jodele, MD

Stella Davies, MBBS, PhD, MRCP

PUBLISHED MARCH 26, 2020
Blood

Transplant-associated thrombotic microangiopathy (TA-TMA) is one of the most dangerous complications that can occur in patients receiving hematopoietic stem cell transplant (HSCT). It occurs in about 30% of patients, and when untreated, can have a mortality rate exceeding 80%.

Closer study of TA-TMA in recent years has revealed that an over-activated complement system drives severe organ damage, especially in the kidney. This information prompted a multidisciplinary team of experts at Cincinnati Children's to explore whether the complement blocking drug eculizumab could help.

The research was led by first author Sonata Jodele, MD, senior author Stella Davies, MBBS, PhD, MRCP, and 12 co-authors from several divisions at Cincinnati Children's.

The team reported encouraging results from treating 64 HSCT recipients with a high risk for TA-TMA with the drug. At one year post-transplant, the survival rate for treated patients improved to 66%; up from 16% in a previously reported untreated cohort.

Patients who responded received a median of 11 doses of eculizumab, and their TA-TMA resolved within a median of 66 days. Those who did not respond tended to have more severe complement activation, and some had intestinal bleeding that limited the drug's effectiveness.

The team noted that treatment with eculizumab started only after multi-organ damage had occurred, suggesting that earlier detection of high-risk TA-TMA could further improve survival rates.

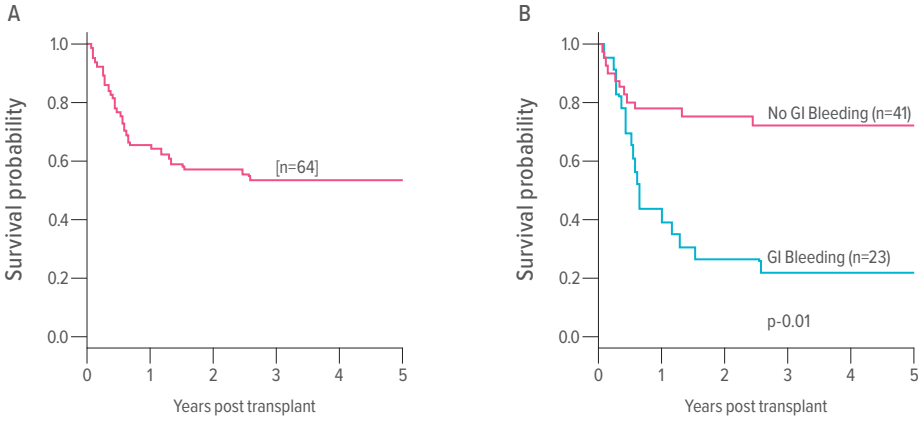
"We were quite excited to see a strong response to this treatment, but the outcomes are not yet ideal," Jodele says. "Now we hope to determine whether a combination of complement blockers and targeting other endothelial injury pathways may assist those who do not respond to eculizumab alone."

RESEARCH & TRAINING DETAILS

Faculty	15
Joint Appointment Faculty	2
Total Annual Grant Awards	$1.7M
Total Annual Industry Awards	$192,727

Jodele S, Dandoy CE, Lane A, Laskin BL, Teusink-Cross A, Myers KC, Wallace G, Nelson A, Bleesing J, Chima RS, Hirsch R, Ryan TD, Benoit S, Mizuno K, Warren M, Davies SM. Complement blockade for TA-TMA: lessons learned from a large pediatric cohort treated with eculizumab. Blood. 2020;135(13):1049-1057.

Treating High-Risk TA-TMA



These charts depict outcomes for 64 stem cell transplant patients who were treated with eculizumab for high-risk transplant-associated thrombotic microangiopathy.

Blood Stem Cells Use Mitochondria to Limit Self-Renewal Activity

Marie-Dominique Filippi , PhD

PUBLISHED MARCH 5, 2020
Cell Stem Cell

Hematopoietic stem cells (HSCs) are programmed to renew themselves to sustain life-long production of blood and immune cells. However, HSCs can divide only a limited number of times.

Understanding how HSCs control the pace of their activity could help scientists better manage blood diseases and improve hematopoietic stem cell transplant outcomes.

Now a team of experts at Cincinnati Children's has uncovered an important clue about how HSC cellular memory works. "We propose that HSCs use mitochondria as a natural checkpoint to remember their divisional history and limit their self-renewal ability," the co-authors state.

The study was led by co-first authors Ashwini Hinge, PhD, Jingyi He, MD, James Bartram, PhD candidate, and senior author Marie-Dominique Filippi, PhD.

The team found that each time HSCs divide, their energy-producing mitochondria become increasingly dysfunctional. This in turn serves as a form of cellular memory that helps prevent HSCs from excessive replication. Mechanistically, the team reports that this process is controlled by the loss of activity of the mitochondrial fission regulator protein Drp1.

"There are multiple clinical implications from this finding. On the one hand, since overcoming this 'block' could lead to cancer, restoring this memory could be a way to reduce outgrowth," Filippi says. "On the other hand, if we can pharmacologically manipulate this 'memory', we could help keep 'young' HSCs even after division and thus improve the outcome of transplantation."

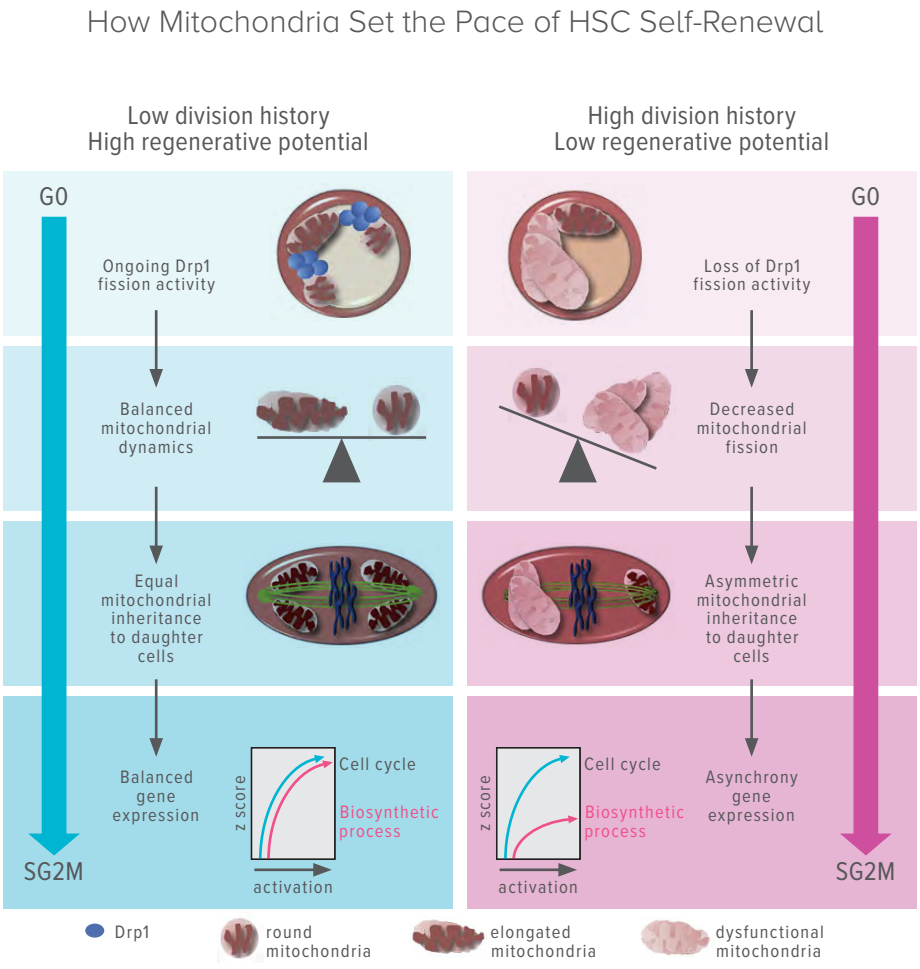
The high-resolution microscopy work involved in this study was difficult, Filippi says, and was made possible by "tremendous" help from Matt Kofron, PhD, Director, Confocal Imaging Core. Co-authors Lee Grimes, PhD, and Nathan Salomonis, PhD, were instrumental in the molecular analysis of single cells.

Among several next steps, the team is exploring several pharmacological avenues to help maintain Drp1 functions.

RESEARCH & TRAINING DETAILS

Faculty	29
Joint Appointment Faculty	17
Research Fellows & Post Docs	21
Research Graduate Students	31
Total Annual Grant Awards	$12.7M
Total Annual Industry Awards	$289,227

Hinge A, He J, Bartram J, Javier J, Xu J, Fjellman E, Sesaki H, Li T, Yu J, Wunderlich M, Mulloy J, Kofron M, Salomonis N, Grimes HL, Filippi MD. Asymmetrically Segregated Mitochondria Provide Cellular Memory of Hematopoietic Stem Cell Replicative History and Drive HSC Attrition. Cell Stem Cell. 2020;26(3):420-430 e426.



This graphic illustration explains how an increase in dysfunctional mitochondria instructs HSCs to stop self-renewing.

Clinical Trial Success Leads to FDA Approval for Selumetinib for Children with Inoperable Plexiform Neurofibromas

Brian Weiss, MD

PUBLISHED MARCH 18, 2020
The New England Journal of Medicine

Children who develop NF1-related plexiform neurofibromas can experience disfigurement, weakness, loss of mobility and serious pain as these non-cancerous tumors grow. In some anatomical locations, these tumors can become life-threatening.

Now, years of work at Cincinnati Children's, the National Cancer Institute and other medical centers to develop a medication to treat this rare disease have finally paid off.

The drug selumetinib was approved on April 10, 2020, by the US Food and Drug Administration for use in this population shortly after phase 2 clinical trial results were reported in March in *The New England Journal of Medicine*.

Brian Weiss, MD, Director of the Neuroblastoma Program for the Cancer and Blood Diseases Institute at Cincinnati Children's, co-authored the NCI-led study.

The researchers tracked 50 children who received two daily doses of selumetinib. Overall, 37 of the 50 children (74%) showed at least a partial response in tumor volume reduction, with 28 children (56%) showing a durable response. In addition, children reported less pain and improved quality of life.

"This drug is not a cure," Weiss says. "However, the tumor volume reduction and associated pain relief have provided the first effective medical therapy for children with NF1. It was very exciting to be involved with this project."

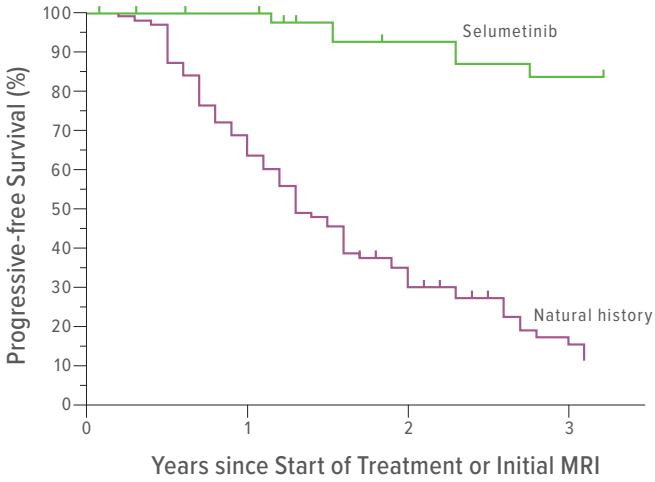
Clinical studies had been in the works since 2016, when the potential benefit of the drug was revealed through mouse-based studies led by Nancy Ratner, PhD, Co-Director of the Rasopathy Program at Cincinnati Children's.

RESEARCH & TRAINING DETAILS

Faculty	27
Joint Appointment Faculty	3
Research Fellows & Post Docs	7
Research Graduate Students	3
Total Annual Grant Awards	$7.2M
Total Annual Industry Awards	$2.2M

Gross AM, Wolters PL, Dombi E, Baldwin A, Whitcomb P, Fisher MJ, Weiss B, Kim A, Bornhorst M, Shah AC, Martin S, Roderick MC, Pichard DC, Carbonell A, Paul SM, Therrien J, Kapustina O, Heisey K, Clapp DW, Zhang C, Peer CJ, Figg WD, Smith M, Glod J, Blakeley JO, Steinberg SM, Venzon DJ, Doyle LA, Widemann BC. Selumetinib in Children with Inoperable Plexiform Neurofibromas. N Engl J Med. 2020;382(15):1430-1442.

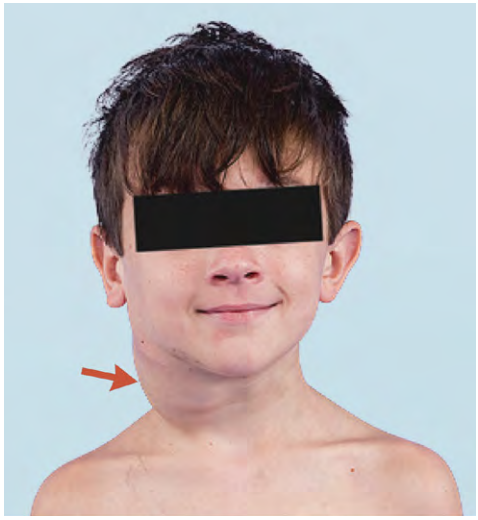
Selumetinib Success Story



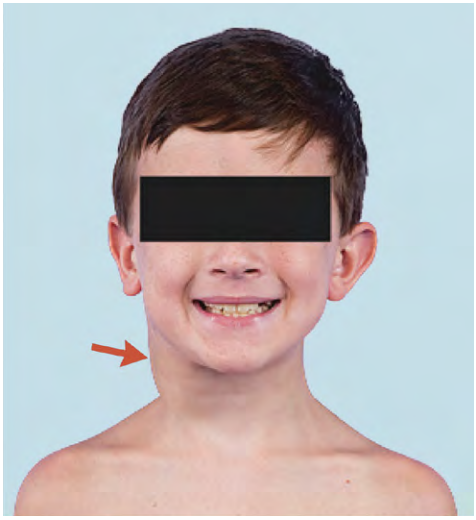
LEFT At 3 years of follow-up, the progression-free survival was 15% in the natural history group and 84% in the selumetinib group.

BELOW These photos depict the tumor size reduction achieved after selumetinib treatment

Patient 2 at Baseline



Patient 2 before Cycle 13



Novel CAR-NK Cell Technology Targets Lupus and Beyond

Seth Reighard, PhD

Stephen Waggoner, PhD

PUBLISHED APRIL 21, 2020
Cell Reports Medicine

The revolution in cellular immunotherapy that has transformed cancer care may soon show new applications against lupus and other autoimmune diseases, thanks to a breakthrough involving natural killer (NK) cells.

A team of Cincinnati Children's scientists led by Seth Reighard, PhD, Stephen Waggoner, PhD, and Hermine Brunner, MD, MSc, MBA, reports early success at engineering NK cells to express chimeric antigen receptors (CAR), which allows them to target specific cell types involved in autoimmune disease.

In laboratory testing of human cells and a humanized mouse model of lupus, these CAR-NK cells targeted a specific harmful population of T cells, known as T follicular helper cells (Tfh), without harming other cell types.

"This is the first method to specifically remove an otherwise intractable population of harmful cells," Waggoner says. "We think targeting them will be safe and clinically beneficial in multiple diseases. Our approach started with lupus because the disease is a leading cause of death in young women for which a cure is presently lacking."

Systemic lupus erythematosus affects 20-150 per 100,000 people in the U.S. and ranks among the five leading causes of death among African American and Hispanic women, aged 15-34.

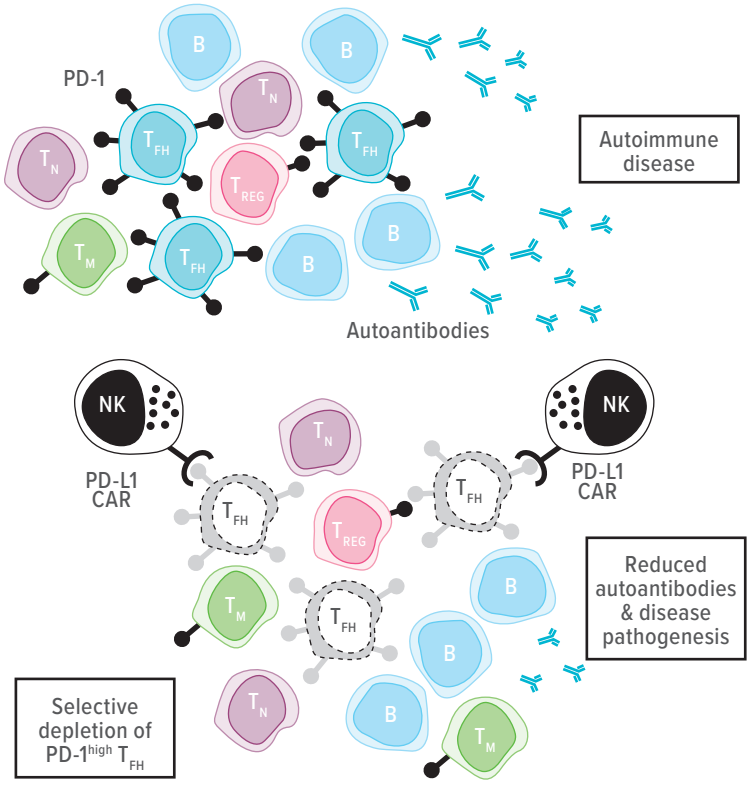
In addition to potential improvement in lupus outcomes, the co-authors say this discovery may also open doors to new treatments for other diseases that involve aberrant Tfh responses, including Sjögren syndrome, juvenile dermatomyositis, multiple sclerosis, type 1 diabetes, and rheumatoid arthritis.

RESEARCH & TRAINING DETAILS

Faculty	11
Joint Appointment Faculty	5
Research Fellows & Post Docs	11
Research Graduate Students	11
Total Annual Grant Awards	$7.2M

Reighard SD, Cranert SA, Rangel KM, Ali A, Gyurova IE, de la Cruz-Lynch AT, Tuazon JA, Khodoun MV, Kottyan LC, Smith DF, Brunner HI, Waggoner SN. Therapeutic Targeting of Follicular T Cells with Chimeric Antigen Receptor-Expressing Natural Killer Cells. Cell Rep Med. 2020;1(1):100003.

CAR-NK Cells Put the Brakes on Autoimmune Disease



This graphical abstract depicts how CAR-NK cells can target a population of dysfunctional T follicular helper (Tfh) cells without harming other types of T-cells.

Decision Support Platform Facilitates Morphine Precision Dosing in Neonates

Kevin Dufendach, MD, MS

Sander Vinks, PharmD, PhD

RESEARCH & TRAINING DETAILS

Faculty	3
Joint Appointment Faculty	3
Research Fellows & Post Docs	5
Research Graduate Students	4
Total Annual Grant Awards	$426,661

Vinks AA, Punt NC, Menke F, Kirkendall E, Butler D, Duggan TJ, Cortezzo DE, Kiger S, Dietrich T, Spencer P, Keefer R, Setchell KDR, Zhao J, Euteneuer JC, Mizuno T, Dufendach KR. Electronic Health Record-Embedded Decision Support Platform for Morphine Precision Dosing in Neonates. Clin Pharmacol Ther. 2020;107(1):186-194.

PUBLISHED OCT. 16, 2019
Clinical Pharmacology & Therapeutics

Managing pain in neonatal patients—most commonly with the opioid morphine—is a delicate balancing act. Rapid physiological changes, life-sustaining procedures, and patients' inability to describe their symptoms can make it difficult to provide individualized morphine dosing.

To help providers make data-informed decisions, experts at Cincinnati Children's developed NeoRelief, a decision support platform embedded in the electronic health record (EHR).

Traditionally, the process of morphine dosing is iterative—from a wide range of starting doses, adjustments are made empirically based on clinical response, side effects, pain scores, and levels of sedation. Because neonates vary in their ability to clear morphine, they experience a wide range of exposures, which are poorly predicted by dose alone.

The team, led by Kevin Dufendach, MD, MS, and first author Sander Vinks, PharmD, PhD, tackled this challenge with a user-friendly approach to decision support. NeoRelief translates morphine dose into a pharmacokinetic profile and exposure. Simultaneously, the application depicts markers of response and clinical events in the form of pain scores, heart rate, and respiratory rate.

A visual dashboard of this feedback is accessible directly from the EHR, providing actionable information at the time of medication ordering and facilitating precision dosing for each individual patient. Researchers expect that NeoRelief will improve pain management and reduce the risk of harm from side effects and opioid dependence.

"This project demonstrates our first successful build of an EHR-integrated clinical decision support application," Dufendach says. "Next, we will measure the effect of implementing this clinical decision support application into clinical care. Our hypothesis is that regular use of this tool will result in fewer *pro re nata* (PRN) doses of morphine and lower total morphine exposure in neonates."

NeoRelief Application as Displayed in the Electronic Health Record

TOP This landing page graphically presents the Neonatal Pain, Agitation, and Sedation Scale (NPASS), morphine dose (infusion and pro re nata doses), heart rate, and breathing frequency. NPASS scores and dosing events are summarized chronologically in table format to be viewed over different selectable time frames. **BOTTOM** A second screen summarizes the NPASS data, the doses administered (infusion "drip" and "bolus" doses), and the model-based translation of the dosing regimen into a morphine concentration time profile. The symbol size and colors represent the severity of the NPASS: score 0–3 (green), 4–5 (shades of orange), and 6–7 (shades of red).

PERSEVERE-II Risk Model Predicts Severe Acute Kidney Injury in Pediatric Septic Shock

Natalja Stanski, MD

Hector Wong, MD

PUBLISHED APRIL 2020

American Journal of Respiratory and Critical Care Medicine

When septic shock strikes in pediatric patients, every second counts—serious complications like acute kidney injury (AKI) can set in quickly. What if we could predict which patients are most at risk before AKI occurs?

A first-of-its-kind tool can help identify these patients early on, allowing for aggressive protection strategies. The Pediatric Sepsis Biomarker Risk Model (PERSEVERE-II), developed by researchers at Cincinnati Children's, draws from biomarkers and clinical data to personalize care.

Sepsis-associated AKI is common, but the complex disease process is poorly understood. Providers must rely on prevention and supportive care, leaving patients with a lack of viable therapeutic options—and up to five times higher odds of mortality.

To better understand these patients and their needs, researchers collected clinical and laboratory data from 379 children admitted with septic shock to 14 pediatric ICUs. The project was led by Natalja Stanski, MD, and senior author Hector Wong, MD.

Using biomarkers and platelet counts obtained within 24 hours of diagnosis, PERSEVERE-II assigned patients into risk categories. On day three of septic shock, researchers compared these results with the development of AKI. They found that PERSEVERE-II was able to predict severe AKI and identify patients who are likely to recover.

"Our study is the first to utilize biomarkers specific to sepsis immune dysregulation, as opposed to biomarkers specific to kidney tubular injury, to predict the development of sepsis-associated AKI," Stanski says. "We believe this reframing is what allowed our model to be so successful."

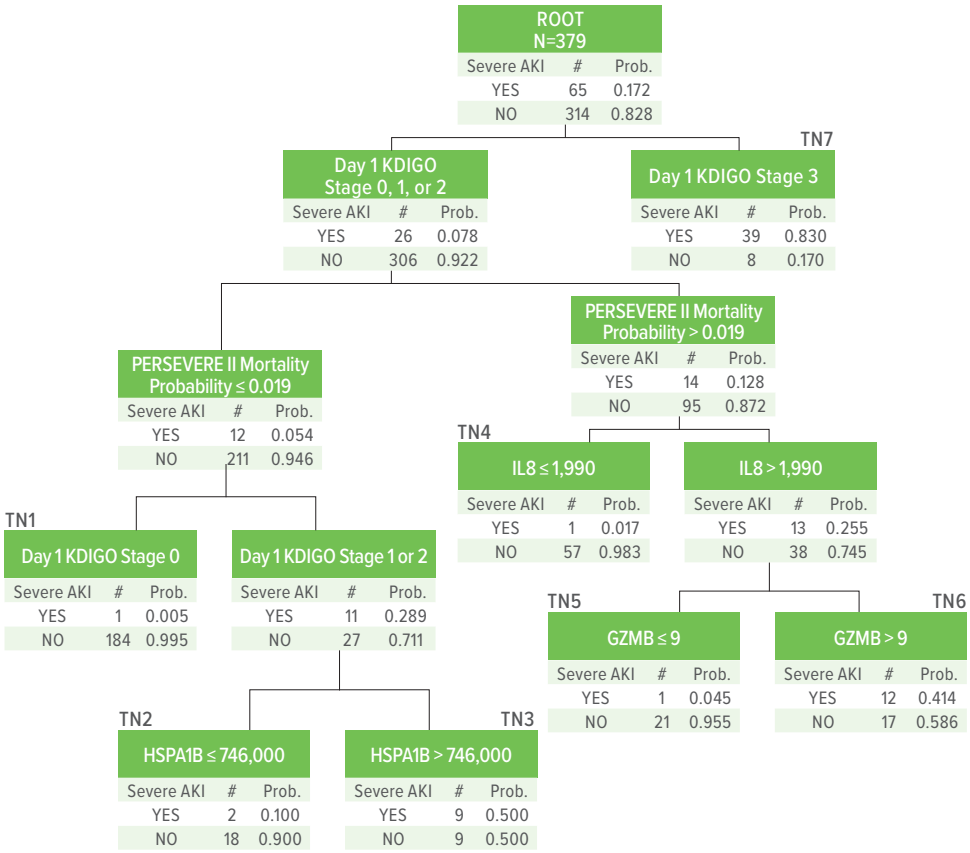
Next, researchers plan to improve the tool with new risk assessment factors and utilize its predictions to inform enrollment in clinical trials aimed at treating sepsis-associated AKI.

RESEARCH & TRAINING DETAILS

Faculty	16
Joint Appointment Faculty	1
Research Fellows & Post Docs	2
Total Annual Grant Awards	$2.9M

Stanski NL, Stenson EK, Cvijanovich NZ, Weiss SL, Fitzgerald JC, Bigham MT, Jain PN, Schwarz A, Lutfi R, Nowak J, Allen GL, Thomas NJ, Grunwell JR, Baines T, Quasney M, Haileselassie B, Wong HR. PERSEVERE Biomarkers Predict Severe Acute Kidney Injury and Renal Recovery in Pediatric Septic Shock. Am J Respir Crit Care Med. 2020;201(7):848-855.

Estimating the Risk of Kidney Injury from Severe Pediatric Sepsis



This chart shows the derived decision tree for estimating the risk of severe sepsis-associated acute kidney injury on Day 3 of septic shock.

‘I Just Want to Be Treated Like a Normal Person,’ Say Transgender Youths About Dental Care

Scott Schwartz, DDS, MPH

PUBLISHED SEPTEMBER 2019

The Journal of the American Dental Association

One of the first studies to examine the experiences of transgender youths with their oral healthcare providers finds mostly positive feedback and areas for opportunity and attentiveness. Youths who identify as transgender report minimal difficulties receiving adequate dental care, but the study identifies strategies for providers to create an environment that is comfortable and safe for the gender-diverse patients and their caregivers, especially around insurance issues, and stress and anxiety related to care.

Pediatric dentist Scott Schwartz, DDS, MPH, says the study grew out of knowledge that transgender youths can encounter discrimination from some healthcare providers. Others are known to exhibit orally detrimental behaviors, including bulimia, to control their weight and body image.

Data was captured in 20-minute interviews with the teen dental patients and their caregivers. One of the biggest challenges was staying vigilant to changing terminology used to describe the transgender population to make sure the researchers were communicating effectively, says Schwartz.

“It is imperative that we provide these patients with a safe place to receive oral healthcare and to promote methods for the best care for their mouths,” he says. “The results of the study facilitated the development of strategies for the oral health team to provide culturally competent care to transgender youths and their families.”

Schwartz was selected to present a pre-conference course on difficult conversations with adolescent patients at the 2018 American Academy of Pediatric Dentistry Annual Session. Follow-up research will explore two novel topics: the use and impact of puberty blocker medications to delay the onset of irreversible body changes in this population, and preferences for elective oral and maxillofacial procedures to alter their appearance to be more aligned with their gender identity.

RESEARCH & TRAINING DETAILS

Faculty	7
Total Annual Grant Awards	$200,000

Macdonald DW, Grossoehme DH, Mazzola A, Pestian T, Schwartz SB. “I just want to be treated like a normal person”: Oral health care experiences of transgender adolescents and young adults. J Am Dent Assoc. 2019;150(9):748-754.

Recommendations for Improving Comfortability for Transgender Patients

Provide separate selections for "Sex at Birth" and "Gender Identity."
Provide separate selections for "Legal Name" and "Chosen Name."
Ask for patient specific pronouns or how patient would like to be addressed.
Be cautious in making assumptions about gender. For example: avoid "dude" or "darling."
Connect patients and families to local resources if possible.
Post a rainbow flag or sticker, serving as a sign of acceptance and comfort to patients and families.

Maleness, Higher Parent-Reported Inattention Make Children More Likely to Receive ADHD Medication, Not Race

Kelly Kamimura-Nishimura, MD, MS

PUBLISHED OCTOBER 2019
The Journal of Pediatrics

Attention deficit/hyperactivity disorder (ADHD) affects 8 to 12% of school-aged children in the U.S., making it the most common neurodevelopmental disorder in childhood. Current guidelines recommend behavioral therapies and/or stimulant medication, yet as few as half of children diagnosed with ADHD receive medication. While many have speculated about which factors influence the likelihood of mediation prescription, a retrospective cohort study of 577 children presenting for ADHD at 50 community-based practices took a more comprehensive look.

"Pediatricians are less likely to prescribe ADHD medications to children with certain sociodemographic characteristics and ADHD symptom profiles," explains lead researcher Kelly Kamimura-Nishimura, MD, MS, Division of Developmental and Behavioral Pediatrics.

The study evaluated 31 possible predictors of medication prescription, including several factors highlighted in previous studies such as male sex, white race, younger latency age, severity of symptoms, urban residence of the patient, as well as age of provider. This study also explored the roles of income, health insurance, and other comorbidities.

Even after correcting for higher rates of male ADHD diagnosis, boys were still more likely to receive medication. Higher inattention scores and living in a neighborhood with higher medical expenditures also increased the likelihood of medication prescription. However—contrary to the researchers' initial hypothesis—factors such as the child's race or physician characteristics did not relate to frequency of medication prescription. Researchers used the geographic information system Alteryx Designer to retrieve and map out the sociodemographic data. Findings have since been presented at the American Academy of Child and Adolescent Psychiatry annual meeting. A crucial next step for the research will be developing strategies to "minimize barriers to receiving evidence-based treatment for children with ADHD from diverse populations," Kamimura-Nishimura says.

RESEARCH & TRAINING DETAILS

Faculty	19
Research Fellows & Post Docs	2
Total Annual Grant Awards	$4.5M
Total Annual Industry Awards	$25,000

Kamimura-Nishimura KI, Epstein JN, Froehlich TE, Peugh J, Brinkman WB, Baum R, Gardner W, Langberg JM, Lichtenstein P, Chen D, Kelleher KJ. Factors Associated with Attention Deficit Hyperactivity Disorder Medication Use in Community Care Settings. J Pediatr. 2019;213:155-162 e151.

Multivariable Regression Results Predicting Whether Children were Prescribed ADHD Medication

Predictor	Regression Estimate	Odds Ratio	*p* value
Patient gender	.30	1.34	.02
Inattention score (P)	.06	1.06	< .0001
Average Household Expenditure for Medical Services (GIS[Z]; in hundreds of dollars)	.11	1.11	.005
Inattention score (T)	.03	1.03	.06
Hyperactivity-Impulsivity Score (P)	.003	1.00	.39
Academic Impairment Score (P)	.04	1.04	.34
Academic Impairment Score (T)	.03	1.03	.41
Participation in Activities (P)	.04	1.04	.27
Organization of Materials (T)	-.01	.99	.46
Following Directions (T)	.19	1.20	.09
Assignment Completion (T)	-.14	.87	.16

Notes: N = 577; GIS = geographical information system; Z = zip code; P = parent; T = teacher

Observational Study Questions the Routine use of Antibiotics for Pediatric Pneumonia

Matthew Lipshaw, MD, MS

PUBLISHED APRIL 2020
Pediatrics

Younger children with pneumonia, especially those who are well enough to be treated outside of the hospital, are unlikely to have a bacterial infection and may not need routine treatment with antibiotics, according to experts with the Division of Emergency Medicine.

The prospective cohort study of 294 children ages 3 months to 18 years found no distinct difference in treatment failure—defined as hospitalization after being discharged from the ED, a return ED visit with to initiate or change antibiotics, or antibiotic change within 7-15 days of the ED visit—between children who were prescribed antibiotics and those who were not. Quality-of-life measures as reported by the pediatric patients' parents also were similar.

The findings call into question the common practice of prescribing antibiotics for pediatric pneumonia in children, given the high prevalence of a viral cause for community-acquired pneumonia. Studies elsewhere also have identified low levels of bacterial pneumonia in the pediatric population, including research that used blood and nasopharyngeal polymerase chain reaction testing of pediatric patients; 14% of the pneumonia cases were bacterial, and 73% were viral in nature.

"Currently, there is no reliable way to differentiate viral from bacterial pneumonia," says Matthew Lipshaw, MD, MS, who participated in the study with emergency medicine colleagues Richard Ruddy, MD, and Michelle Eckerle, MD, and Samir Shah, MD, MSCE, from the Division of Hospital Medicine. "Further work is needed to determine which children with pneumonia are more likely to have bacterial disease and which are likely to develop complications without antibiotics."

Follow-up studies will involve a multi-center randomized, controlled trial to compare treatment with antibiotics vs. placebo in children at low risk of complications from community-acquired pneumonia.

RESEARCH & TRAINING DETAILS

Faculty	43
Joint Appointment Faculty	3
Total Annual Grant Awards	$4.1M

Lipshaw MJ, Eckerle M, Florin TA, Crotty EJ, Lipscomb J, Jacobs J, Rattan MS, Ruddy RM, Shah SS, Ambroggio L. Antibiotic Use and Outcomes in Children in the Emergency Department With Suspected Pneumonia. Pediatrics. 2020;145(4).

Symptoms After Discharge Based on Phone Follow-up

	Not Treated With or Prescribed Antibiotics	Treated With or Prescribed Antibiotics	p[a]	OR (95% CI)	OR (95% CI), Adjusted[b]
N	147	147	-	-	-
Parental report of symptoms since discharge					
Presence of fever, *n* (%)	56 (38.1)	62 (42.2)	.552	1.2 (0.74-1.9)	1.2 (0.65-2.2)
Days of fever, median (IQR)	2 (1-3.25)	2 (1-3)	.82	0.94 (0.75-1.2)[c]	1.0 (0.73-1.4)[c]
Days of cough, median (IQR)	7 (3-7)	7 (4-7)	.97	1.0 (0.91-1.1)[c]	1.0 (0.91-1.2)[c]
Cough compared with discharge, *n* (%)			.43		
Worse	4 (3.7)	3 (2.4)		-	-
About the same	29 (26.9)	25 (20.2)		-	-
Better	49 (45.4)	69 (55.6)		-	-
All better	26 (24.1)	27 (21.8)		-	-
Presence of difficulty breathing, *n* (%)	49 (33.3)	38 (25.9)	.20	0.70 (0.42-1.2)	0.56 (0.27-1.1)
Presence of wheezing, *n* (%)	53 (36.1)	42 (28.6)	.21	071 (0.43-1.2)	0.80 (0.41-1.5)
Presence of rapid breathing, *n* (%)	37 (25.2)	40 (27.2)	.79	1.1 (0.66-1.9)	1.3 (0.33-1.7)
Presence of runny nose, *n* (%)	103 (70.1)	95 (64.6)	.38	0.78 (0.48-1.3)	1.4 (0.71-2.9)
Presence of vomiting, *n* (%)	23 (15.6)	22 (15.0)	.99	0.95 (0.50-1.8)	1.1 (0.46-2.5)
Presence of diarrhea, *n* (%)	30 (20.4)	25 (17.0)	.55	0.80 (0.44-1.4)	1.1 (0.53-2.4)
Presence of abdominal pain, *n* (%)	19 (12.9)	22 (15.0)	.736	1.2 (0.61-2.3)	1.4 (0.58-3.2)

Two-Day Hospital Program Reduces Readmissions for Children Newly Diagnosed With Type 1 Diabetes

Sarah Lawson, MD

PUBLISHED MARCH 2, 2020
JAMA Network Open

When children are diagnosed with type 1 diabetes, they often are admitted to a hospital even if they are not especially sick at the time. In our institution this standard of care often resulted in at least a 48-hour inpatient stay,

At the time of diagnosis, children require close observation during initial insulin therapy, families need education to manage the drug, and social support is needed to live with the condition, says Sarah Lawson, MD, Division of Endocrinology. However, admitting children early in their disease course who are well at the time of diagnosis can cause confusion and anxiety for families. And when those children are not facing complications such as diabetic ketoacidosis, insurance coverage denial rates for the hospital admission can reach 80%.

In a recent quality improvement study published in *JAMA Network Open*, Lawson detailed an elegant solution launched at Cincinnati Children's: the shift to a "day hospital" program. The new two-day model provides supervision for families learning how to care for diabetes and manage insulin, while retaining access to the inpatient pharmacy, food services, fluid replacement, visits from rounding physicians, and bedside nurse support. Families can also go home for a night of practice between the two days of the program.

Lawson and colleagues compared outcomes for 96 patients in the day hospital program to the previous hospital admission approach. Day hospital charges averaged $2,800 vs. $24,103 for inpatient care. The time spent in the hospital dropped from 48 to 15 hours. But the 30-day readmission rate dropped to zero compared with an industry-wide 15% average. One year later, the readmission rate for day hospital graduates was 3% compared to 24% for the traditional approach. The new insurance denial rate: 0%.

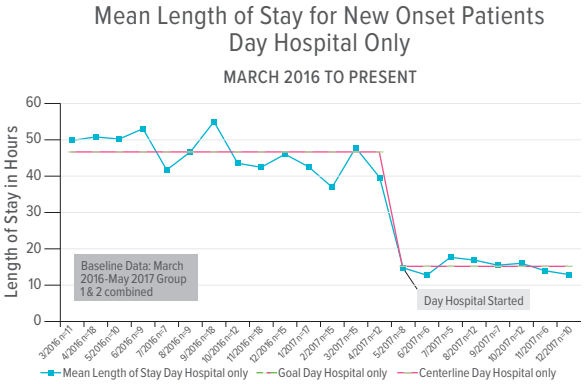
These results have since been presented at the Pediatric Endocrine Society and Cincinnati Children's Grand Rounds. The team also created a digital book, "Diabetes Day Hospital Program Development," to provide to other hospitals.

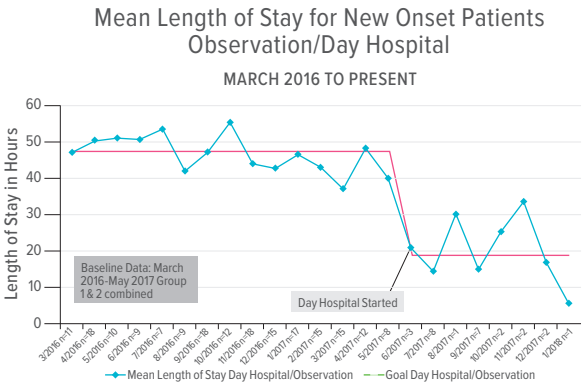
RESEARCH & TRAINING DETAILS

Faculty	17
Joint Appointment Faculty	3
Research Fellows & Post Docs	1
Total Annual Grant Awards	$1.5M
Total Annual Industry Awards	$442,856

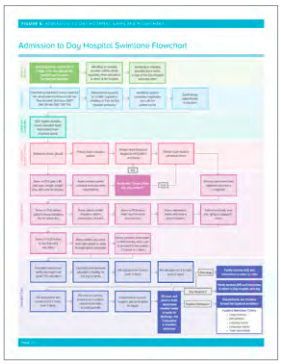
Lawson S, Redel JM, Smego A, Gulla M, Schoettker PJ, Jolly M, Mostajabi F, Hornung L. Assessment of a Day Hospital Management Program for Children With Type 1 Diabetes. JAMA Netw Open. 2020;3(3):e200347.

A Fresh Approach to Diabetes Care





Transition to day hospital program dramatically decreased hospital length of stay for new onset type 1 diabetes patients.



Childhood Maltreatment Increases Risks of Suicide Attempts in Low-income Postpartum Mothers

Robert Ammerman, PhD, ABPP

PUBLISHED NOVEMBER 2019
Child Abuse & Neglect

Asking young, low-income mothers about prior suicide attempts and maltreatment during their own childhoods can serve as key indicators of the need for additional support and mental health treatment to prevent future suicides and to address underlying major depressive disorders (MDD).

Data from a clinical and psychological examination of 170 low-income, young, depressed mothers evolved from Every Child Succeeds' (ECS) in-home treatment program for postpartum depression. Published November 2019 in *Child Abuse & Neglect*, the study focused on suicide risks and histories of childhood maltreatment trauma, both of which are key predictors of suicide in this vulnerable population.

"Results showed that mothers with prior suicide attempts had increased levels of childhood maltreatment experiences," says Robert T. Ammerman, PhD, ABPP, Scientific Director of ECS. Among postpartum mothers generally, 20% of deaths are linked to suicide, a cause of death that ranks second among all deaths of 10- to 24-year-olds and has risen by 2% annually from 2006-2014. Among the subjects in the study, 31.8% of mothers with major depressive disorder reported previous suicide attempts, with an average age of 14 for the first attempt and two lifetime attempts. Mothers with more suicide attempts had more MDD symptoms, overall more MDD episodes, and earlier age of their first depressive episode. A previous suicide attempt was associated with greater childhood trauma, more current MDD symptoms, and a diagnosis of post-traumatic stress disorder (PTSD); no association was found for intimate partner violence.

"Conducting community-based research is difficult," Ammerman notes. "The mothers who participated in the study are often overlooked in research because they are difficult to engage in the research process. From the perspective of equity and representation, it is important that we seek to involve underserved mothers in research studies to ensure that their concerns and needs are adequately considered and addressed."

RESEARCH & TRAINING DETAILS

Faculty	1

Ammerman RT, Scheiber FA, Peugh JL, Messer EP, Van Ginkel JB, Putnam FW. Interpersonal trauma and suicide attempts in low-income depressed mothers in home visiting. Child Abuse Negl. 2019;97:104126.

Logistic Regression Predicting Suicide Attempt Group Membership

	Estimate	S.E.	Est/SE	*p*-value	Odds Ratio
MDD Symptoms	0.51	0.20	2.55	0.01	1.66
Age of 1st Episode	-0.14	0.05	-2.57	0.01	0.87
CTQ	0.03	0.01	2.84	0.00	1.03
MDD Episodes	0.06	0.08	0.77	0.44	1.06
PCL-S	0.00	0.02	0.03	0.98	1.00
ISEL-Tangible	-0.03	0.04	-0.75	0.46	0.97
SNI-NN	-0.05	0.03	-1.52	0.13	0.96

Note: CTQ=Childhood Trauma Questionnaire, PCL-S=PTSD Checklist-Specific, ISEL=Interpersonal Support Evaluation List, SNI-NN=Social Network Index-Network Number

Increased Screen Use in Preschoolers Correlates with Lower White Matter Integrity

John Hutton, MD, MS

PUBLISHED JAN. 1, 2020
JAMA Pediatrics

The study was one of the most-discussed findings of the year from Cincinnati Children's. When researchers led by John Hutton, MD, MS, reported the first evidence linking screen time and brain development in preschoolers, the findings sparked headlines in *The New York Times*, *Wall Street Journal*, CNN, Fox News and other media—plus a call from Ohio's First Lady, Fran DeWine.

The MRI-based study found significant associations between higher screen-based media use and lower micro-structural integrity in major white matter tracts (the brain's "wiring") along with lower cognitive abilities supported by these tracts, specifically vocabulary, rhyming, processing speed, and composite early literacy skills.

Despite the ubiquity of digital technology, "the human brain is essentially an analog organ that has evolved over millennia to process the real world in a multi-sensory way and to learn in social contexts involving other humans, particularly language," explains Hutton, Director of the Reading & Literacy Discovery Center at Cincinnati Children's.

While older children may be able to adapt, the American Academy of Pediatrics and World Health Organization recommend limiting screen time for young children to reduce risks of language delay, poor sleep, and impaired academic performance.

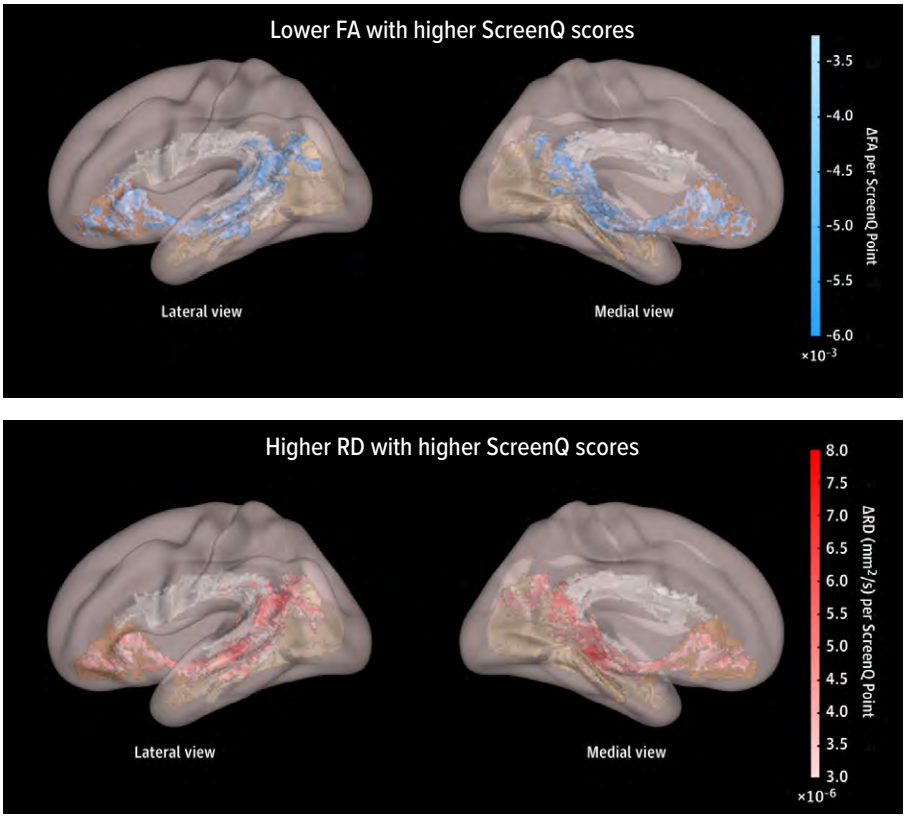
Getting 49 young children to sit still for an MRI was "a major challenge," Hutton says. But thanks to the skilled efforts of imaging staff, the team gathered the data they needed. Researchers quantified screen use with ScreenQ, a novel tool developed by Hutton and colleagues.

While some news reporters asked whether the white matter changes were signs of "brain damage," a more likely explanation is displacement of more constructive experiences at this critical age. "Children with more screen time may spend less time engaging in multi-sensorial play, using their imaginations, playing outside, or reading and talking with caregivers," Hutton says.

RESEARCH & TRAINING DETAILS

Faculty	18
Joint Appointment Faculty	1
Research Fellows & Post Docs	3
Research Graduate Students	2
Total Annual Grant Awards	$2.5M
Total Annual Industry Awards	$162,798

Hutton JS, Dudley J, Horowitz-Kraus T, DeWitt T, Holland SK. Associations Between Screen-Based Media Use and Brain White Matter Integrity in Preschool-Aged Children. JAMA Pediatr. 2019;174(1):e193869.



Diffusion tensor MRI imaging (DTI) reveals how white matter areas that support language and literacy can be affected by screen time. Higher screen time (as measured by ScreenQ scores) tracked with lower fractional anisotropy (FA) and higher radial diffusivity (RD) measures, suggesting reduced white matter organization and transmission efficiency. Both analyses controlled for child age, gender and household income level.

Study Finds Evidence of Hypertension Risk Factors in Children as Young as 11

Elaine Urbina, MD, MS

PUBLISHED MAY 4 2020
Hypertension

A novel study of hypertension in teens aged 11 to 19 years old has uncovered subclinical and metabolic changes at levels that might warrant intervention in childhood and adolescence to address risk factors that can lead to cardiovascular disease later in life. Heart Institute researchers compared echocardiogram results for left ventricular strain and diastolic function—two precursors of heart failure in adults—in 346 pediatric subjects classified into low-, mid- and high-risk blood pressure levels. Among the findings: Teens in the mid- and high-risk categories showed greater adiposity, lower HDL and higher glucose and insulin levels compared to teens in the low-risk group. They also showed significantly lower ejection fraction and peak global longitudinal strain, indicating reduced systolic function and higher E/e' ration indicating diastolic dysfunction.

"Previously, it was thought that high blood pressure-related cardiac damage took years to develop," says Preventive Cardiology Director Elaine Urbina, MD, MS. "This is one of the first studies to demonstrate reduced systolic and diastolic cardiac function at the higher range of blood pressure in otherwise healthy youths, even though the mean value is still within the normal range. Data suggests that appropriate early intervention, including diet, weight loss, and possibly medication to control BP, may prevent permanent damage that leads to heart failure in adulthood."

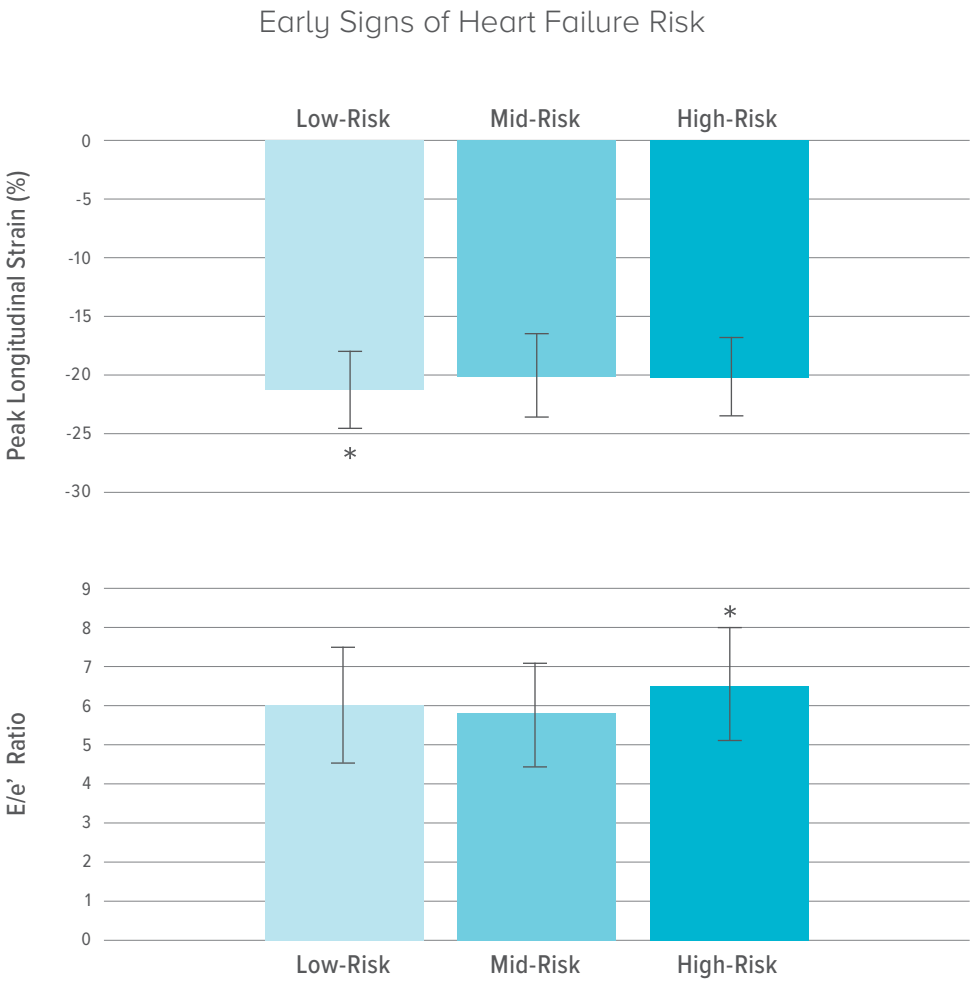
Since the study was published, lead author and former cardiology fellow Andrew Tran, MD, and Urbina have presented study data at pediatric academic, hypertension, and nephrology conferences in the U.S., Poland and Italy.

A basic science arm of the same study led to a gene expression hypothesis that hypertension may lead to upregulation of hsa-miR-30e-5p, an RNA precursor, which in turn favors the upregulation of vasohibin (VASH-1), a protein coding gene. Follow-up research will explore the importance of VASH-1 in animal models and its role in progression of cardiac disease damage.

RESEARCH & TRAINING DETAILS

Faculty	53
Joint Appointment Faculty	2
Total Annual Grant Awards	$2.9M
Total Annual Industry Awards	$330,437

Tran AH, Flynn JT, Becker RC, Daniels SR, Falkner BE, Ferguson M, Hanevold CD, Hooper SR, Ingelfinger JR, Lande MB, Martin LJ, Meyers K, Mitsnefes M, Rosner B, Samuels JA, Urbina EM. Subclinical Systolic and Diastolic Dysfunction Is Evident in Youth With Elevated Blood Pressure. Hypertension. 2020;75(6):1551-1556.



These bar graphs show two indicators revealing that blood pressure-related damage can occur in teens even when hypertension appears to be within a normal range.

How to Help Infants with Congenital Heart Disease Avoid 'Limping' to Transplantation

Kyle Riggs, MD

David L. S. Morales, MD

PUBLISHED JUNE 2020

The Journal of Thoracic and Cardiovascular Surgery

While families of children with heart failure often expect a heart transplant to provide decades of survival, the actual likelihood of post-transplant survival for some patients—especially infants with congenital heart disease (CHD)—can decline sharply based on surprisingly common risk factors, according to heart experts at Cincinnati Children's.

"We were surprised to find that a patient with CHD awaiting transplant while being mechanically ventilated as their only modifiable risk factor had a 1-year survival of only 75% after receiving a transplant, because such a patient would not commonly be considered a high-risk candidate," the co-authors state. "Even more concerning was that if that patient had renal dysfunction, 1-year survival approached 60%, and it was even less than 60% if the patient was also an infant."

A team led by Kyle Riggs, MD, and David L. S. Morales, MD, reviewed survival data for more than 4,100 pediatric heart transplants performed between 2000 and 2017. They compared cases according to "modifiable risk factors" (MRFs), such as ventilator dependency, kidney dysfunction, or liver dysfunction.

Without any MRFs, one-year survival can be over 90%, and reaches 95% in many cases. However, 36% of patients had at least one MRF. Survival for an infant with CHD and two MRFs dropped to 58%. These risk factors are common; occurring in up to 4 in 10 patients listed as status 1A.

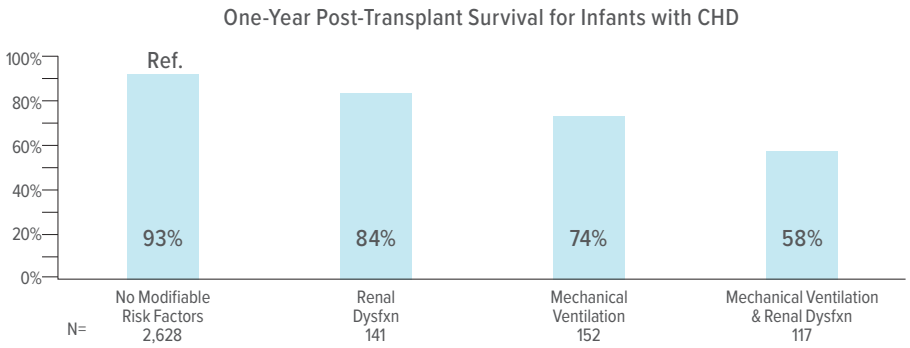
Morales and colleagues suggest that these findings will enable families to be provided with realistic expectations regarding post-transplant survival. The findings also encourage providers to use ventricular assist devices (VADs) more often to allow children with MRFs to enjoy the same post-transplant survival outlook as others without them.

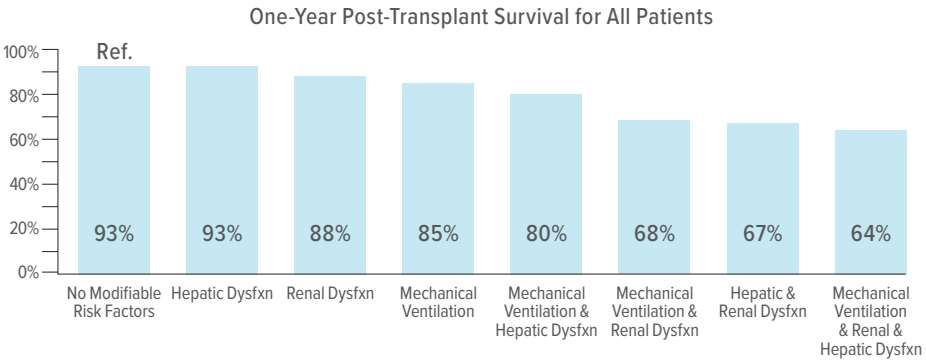
"Children should not limp to transplant but approach it in their best possible state to maximize each organ and their outcomes," Morales says.

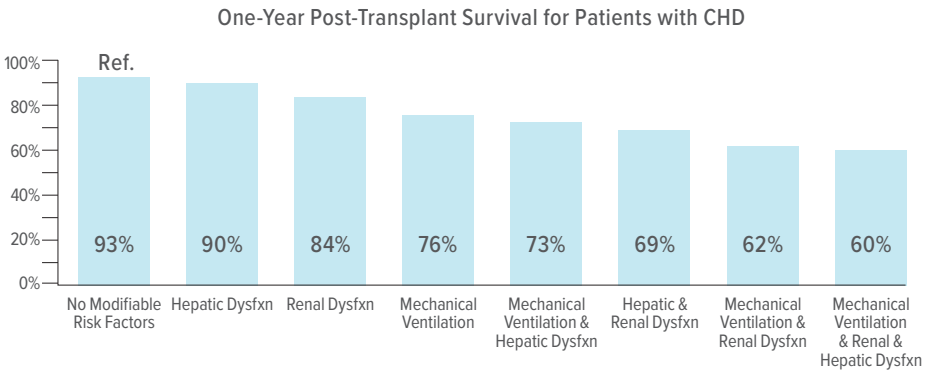
RESEARCH & TRAINING DETAILS

Faculty	8
Total Annual Grant Awards	$433,981
Total Annual Industry Awards	$125,000

Riggs KW, Zafar F, Lorts A, Chin C, Bryant R, 3rd, Tweddell JS, Morales DLS. The reality of limping to pediatric heart transplantation. J Thorac Cardiovasc Surg. 2020;159(6):2418-2425 e2411.







These charts show how much heart transplant survival can be affected by relatively common risk factors.

Constant Pulse Oximetry Monitoring Too Much for Infants with Bronchiolitis

Patrick Brady, MD, MSc

Amanda Schondelmeyer, MD, MSc

PUBLISHED APR. 21, 2020
JAMA

When infants with bronchiolitis do not need supplemental oxygen, they also generally do not need constant measurement of their blood oxygen levels, according to a multi-institutional team of physicians.

Acute viral bronchiolitis is the No. 1 cause of infant hospitalization in the U.S. Treatment includes fluids, suctioning, and supplemental oxygen when necessary. Yet despite recommendations against continuous pulse oximetry monitoring from the American Academy of Pediatrics and the Society of Hospital Medicine, many hospitals still use continuous monitors non-stop.

The result can be an increase in "alarm fatigue" triggered by excessive numbers of false alarms from an unnecessary form of monitoring.

The study was based on information from 56 hospitals in the U.S. and Canada that participate in the Pediatric Research in Inpatient Settings (PRIS) Network. The team found that 46% of infants with bronchiolitis who were not receiving supplemental oxygen were still being monitored via continuous pulse oximetry. The unneeded monitoring ranged from as low as 6% to as high as 82%.

Raising awareness of this wide variation in practice is a first step toward phasing out a common source of false alarms.

The study involved researchers from Children's Hospital of Philadelphia, Boston Children's Hospital, Cincinnati Children's and other institutions. Amanda Schondelmeyer, MD, MSc, was senior author and Patrick Brady, MD, MSc, was a co-author.

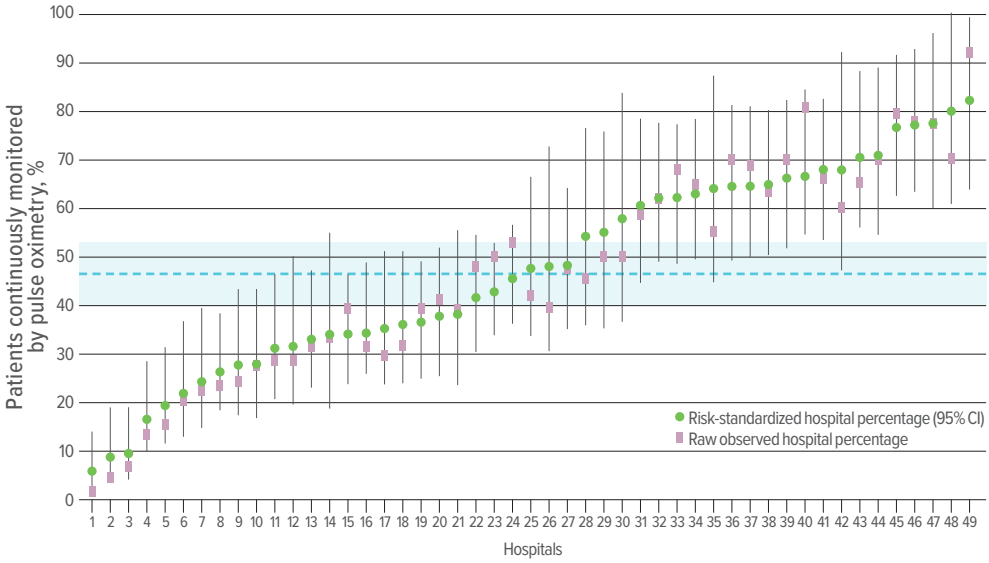
While this study involved infants with bronchiolitis, similar analysis is occurring with other common conditions that may involve excessive monitoring. In July 2020, in *Pediatrics*, Schondelmeyer and colleagues published a set of expert recommendations regarding pulse oximetry monitoring for children hospitalized with mild to moderate asthma and several other conditions.

RESEARCH & TRAINING DETAILS

Faculty	48
Joint Appointment Faculty	6
Total Annual Grant Awards	$570,727

Bonafide CP, Xiao R, Brady PW, Landrigan CP, Brent C, Wolk CB, Bettencourt AP, McLeod L, Barg F, Beidas RS, Schondelmeyer A, Pediatric Research in Inpatient Settings N. Prevalence of Continuous Pulse Oximetry Monitoring in Hospitalized Children With Bronchiolitis Not Requiring Supplemental Oxygen. JAMA. 2020;323(15):1467-1477.

Continuous Pulse Oximetry Use in Patients with Bronchiolitis Not Receiving Any Supplemental Oxygen or Nasal Cannula Flow



No. of observations 61 67 60 82 91 59 58 154 62 29 63 35 89 24 61 165 98 79 61 63 23 75 200 100 62 33 61 33 32 24 75 205 56 111 40 50 64 71 70 67 100 35 95 70 92 94 44 57 25

This chart indicates the wide range of variation in continuous pulse oximetry monitoring at 49 hospitals

Discovery Links *Gpr63* Mutation to Microcephaly Severity

Rolf Stottmann, PhD

PUBLISHED NOV. 15, 2019
PLoS Genetics

Scientists have known that disruption of primary cilia function during embryonic development can lead to microcephaly, based on studies of mice with a mutated form of the gene *Ttc21b*. However, the severity of the brain size loss has varied when this mutation is maintained in different inbred strains of mice, possibly because of influence from unknown "background" genes.

Now, a team of genetic experts at Cincinnati Children's led by first author John Snedecker, PhD, and senior author Rolf Stottmann, PhD, has isolated a gene mutation that appears to be a key contributor to the severity of microcephaly.

The hunt began with a Quantitative Trait Locus (QTL) analysis to determine what other gene mutations beyond *Ttc21b* may be contributing to differential forebrain size. The team chose to use B6 and FVB mice for this project because these strains have been used in medical studies for decades and their genomics have been deeply documented.

The QTL produced 253 potential gene candidates, which meant the team faced a lengthy mapping process to identify which ones actually played a causative role. However, using CRISPR-Cas9 genome editing, the team whittled the field down to one gene of interest: an orphan G-protein coupled receptor, *Gpr63*.

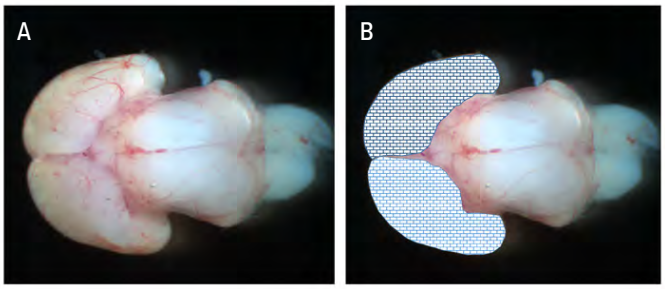
The team ultimately found a SNP in *Gpr63* (rs13477613) that differed between B6 and FVB mice. Further testing demonstrated the SNP alters localization to the cilium, where it interacts with *Ttc21b*, resulting in more severe brain size reduction in the FVB mice.

"We found that the *Gpr63* mutation is the likely causal variant affecting brain size," Stottmann says. "This is significant because the approach taken here may be quite useful in understanding modifier effects in any number of structural birth defects."

RESEARCH & TRAINING DETAILS

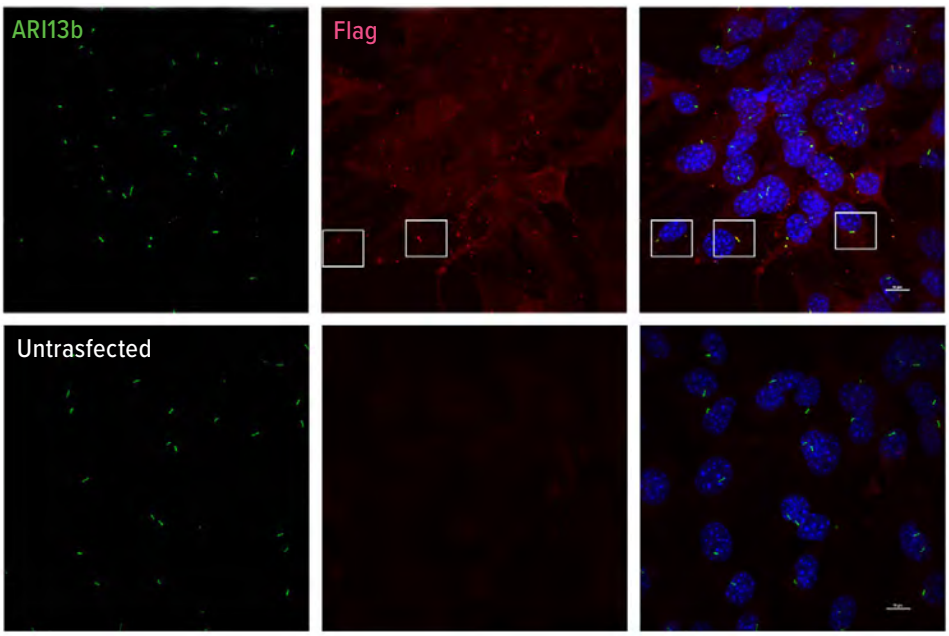
Faculty	31
Joint Appointment Faculty	5
Research Fellows & Post Docs	14
Research Graduate Students	7
Total Annual Grant Awards	$4M
Total Annual Industry Awards	$1.3M

Snedeker J, Gibbons WJ, Jr., Paulding DF, Abdelhamed Z, Prows DR, Stottmann RW. Gpr63 is a modifier of microcephaly in Ttc21b mouse mutants. PLoS Genet. 2019;15(11):e1008467.



Shaded areas denote locations measured in mouse models to determine forebrain size.

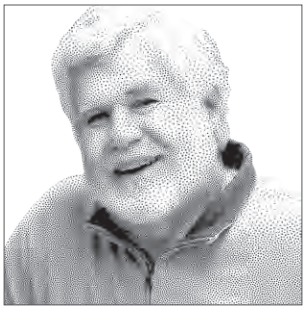
GPR63 Expression Across Mouse Models



This color enhanced confocal microscope image indicates *GPR63* expression with ciliary localization.

Chimeric Hemagglutinin Shows Promise as Possible 'Universal' Flu Vaccine

Monica McNeal, MS



David I. Bernstein, MD

RESEARCH & TRAINING DETAILS

Faculty	22
Research Fellows & Post Docs	8
Research Graduate Students	8
Total Annual Grant Awards	$15.1M
Total Annual Industry Awards	$9.5M

Bernstein DI, Guptill J, Naficy A, Nachbagauer R, Berlanda-Scorza F, Feser J, Wilson PC, Solorzano A, Van der Wielen M, Walter EB, Albrecht RA, Buschle KN, Chen YQ, Claeys C, Dickey M, Dugan HL, Ermler ME, Freeman D, Gao M, Gast C, Guthmiller JJ, Hai R, Henry C, Lan LY, McNeal M, et.al. Immunogenicity of chimeric haemagglutinin-based, universal influenza virus vaccine candidates: interim results of a randomised, placebo-controlled, phase 1 clinical trial. Lancet Infect Dis. 2020;20(1):80-91.

PUBLISHED JANUARY 2020
The Lancet Infectious Diseases

Vaccine experts at Cincinnati Children's collaborated with a large team of scientists from the Icahn School of Medicine at Mount Sinai and several other institutions to take a significant step forward in the quest for a universal flu vaccine.

The team tested a novel approach employing what they call chimeric hemagglutinin (cHA). The idea is based on deeper study of the hemagglutinin protein, which is found on the outer shell of influenza viruses and helps the virus get inside host cells. While the "head" of this protein varies widely from strain to strain, the "stalk" varies less.

The new cHA-based approach focuses on prompting the body's immune defenses to focus on that stalk. The team tested several potential cHA-based formulations. They found that an inactivated vaccine combined with an adjuvant induced significant antibody response, but a live attenuated version did not.

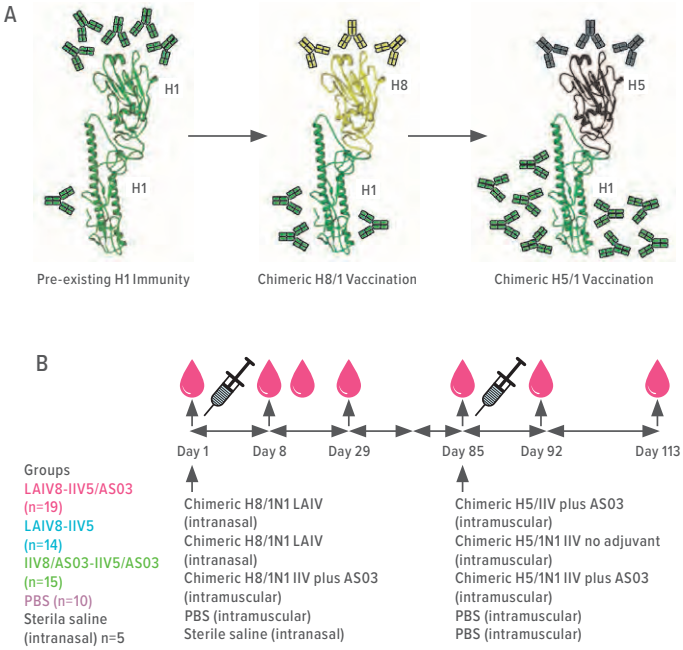
The vaccine induced a broad antibody response against several circulating human influenza viruses—and to avian and bat influenza virus subtypes. The co-authors also say the strong response induced by the inactivated formulation with adjuvant suggests that a one-dose vaccine may be enough to respond to future influenza pandemics.

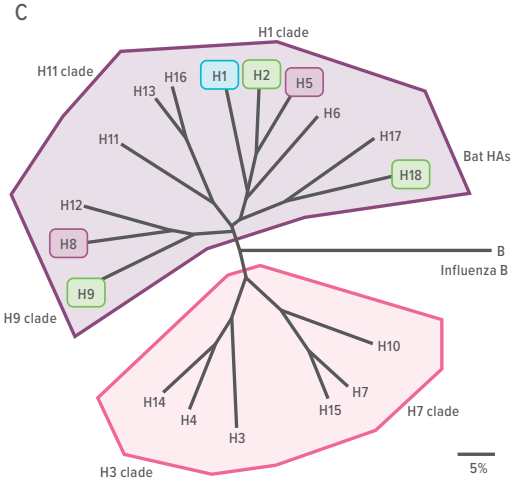
Cincinnati Children's co-authors on the study included first author David I. Bernstein, MD, Monica McNeal, MS, Michelle Dickey, MSN, Kristen Buschle, MSN

Chimeric HA Vaccination Regimens & Trial Design

A. Vaccination strategy. Adults have pre-existing antibodies targeting both the membrane-distal head domain (top) and the membrane-proximal stalk domain (bottom) of H1 HA (green) due to previous exposure to influenza viruses. Vaccination with a chimeric H8/1 construct is expected to elicit some antibodies against the head domain (yellow), to which humans are naive, while substantially boosting H1 stalk antibodies.

B. Vaccination and blood collection schedule.





C. This phylogenetic tree, based on percentage amino acid difference, was constructed to illustrate the evolutionary distance of the antigens used for the ELISA analysis. The H1 (blue) stalk domain was used in the vaccines. H2 is closely related to H1, whereas H9 and H18 (all highlighted in green) are distantly related HAs within influenza A group 1. HA subtypes that donated heads to the vaccine constructs (H5 and H8) are shown in purple. Group 1 HAs are shaded in purple and group 2 in pink. IIV=inactivated influenza vaccine. LAIV=live-attenuated influenza vaccine. PBS=phosphate-buffered saline. HA=haemagglutinin.

Optimizing Growth and Development of Collaborative Learning Health Systems

Michael Seid, PhD

David Hartley, PhD, MPH

PUBLISHED NOV. 13, 2019
Learning Health Systems

Solving the puzzle of improving health outcomes requires participation by everyone who matters—from patients, clinicians, and researchers to health systems and other community organizations. Collaborative learning health systems (CLHSs) bring people and organizations together, facilitating collaboration and generating new knowledge. But what is the best way to develop and optimize these systems?

According to a study from researchers in Pulmonary Medicine and the James M. Anderson Center for Health Systems Excellence, it is by using an actor-oriented organizational architecture. This organizational framework is composed of three elements—actors (people, organizations, and databases); a commons where they create and share resources; and structures, protocols, and processes that facilitate collaboration.

Researchers led by Michael Seid, PhD, David Hartley, PhD, MPH, and Peter Margolis, MD, PhD, aimed to describe and measure implementation of these elements in ImproveCareNow, an existing CLHS. The team traced changes in actor-oriented organizational architecture between 2010 and 2016, identifying measures of actors, the commons, and methods that have streamlined member participation. Resulting data showed how ImproveCareNow made changes in the three elements over time—the first quantitative description of an actor-oriented organizational scheme in a CLHS. The findings demonstrate that this small set of factors can provide a conceptual framework for development and optimization.

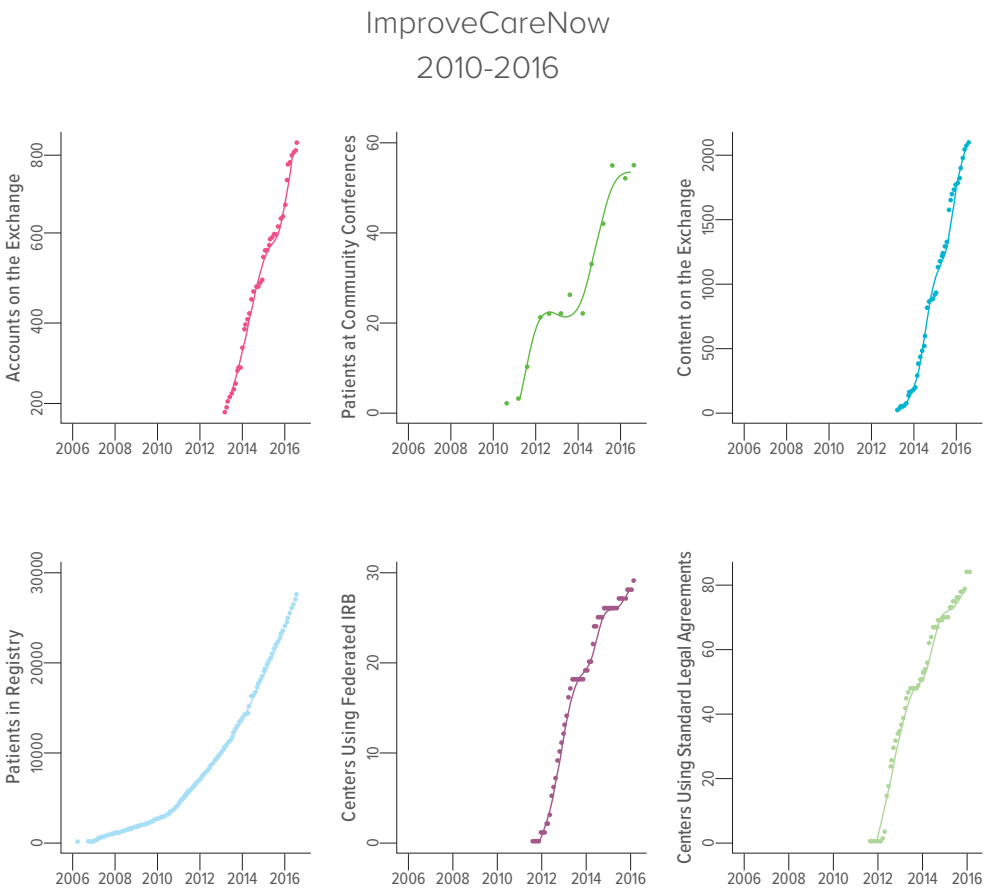
Since publication, the research team has developed a computational model that can be used to simulate the effects of different interventions.

"Next, we are embarking on a program of research designed to increase the effectiveness, efficiency, and scale of CLHSs," Seid says. "Learning networks hold great promise for transforming the health system and improving outcomes. With 7,000 rare diseases, we need to scale this model and increase its effectiveness."

RESEARCH & TRAINING DETAILS

Faculty	10
Joint Appointment Faculty	25
Total Annual Grant Awards	$8.5M

Seid M, Hartley DM, Dellal G, Myers S, Margolis PA. Organizing for collaboration: An actor-oriented architecture in ImproveCareNow. Learn Health Syst. 2020;4(1):e10205.



This graph shows changes over time in six actor-oriented architecture measures for ImproveCareNow (ICN), including steep increases in numbers of accounts on the ICN Exchange (the commons), patients at community conferences, content on the Exchange, patients in the Registry, and centers using a federated Institutional Review Board (IRB) and standard legal agreements.

Maternal Adverse Childhood Experiences Associated with Offspring Healthcare Use

Robert Allan Shapiro, MD

PUBLISHED AUGUST 2019
Journal of Pediatrics

When a child experiences potentially traumatic events, the negative effects on wellbeing can last into adulthood. If they grow up to become a parent, can these adverse childhood experiences (ACEs) affect how they support healthcare services for their children?

For mothers in particular, the answer may be yes, according to a study led by researchers in the Mayerson Center for Safe and Healthy Children.

"The practice of pediatrics is multi-generational," says Robert Allan Shapiro, MD, corresponding author and Director of the Mayerson Center. "Identifying tools that help us better understand our patients' parents could help us improve the health of our patients."

In this study, researchers explored parental exposure to ACEs and patients' healthcare use by age 2. The cohort included 454 patients at a large suburban pediatric primary care practice whose mother, father, or both completed an ACE survey.

Using multivariable negative binomial regression, the research team modeled the association between self-reported parental ACEs and the number of missed well-child visits, sick visits, and delayed or missed immunizations.

For each additional maternal ACE, the team found a significant 12% increase in the rate of missed well-child visits. For these patients, ACE exposure of mothers was associated with worse adherence to preventive healthcare visits early in life.

In partnership with Beech Acres Parenting Center, the research team has developed a program called Parent Connext aimed at preventing and reducing the impact of ACEs on children. The program empowers pediatricians to screen for parenting and family psychosocial concerns. On-site parenting specialists are also available to provide individualized coaching to parents related to these concerns.

Ongoing research seeks to examine the intervention's effect on healthcare utilization.

RESEARCH & TRAINING DETAILS

Faculty	2
Joint Appointment Faculty	8
Total Annual Grant Awards	$1.1M

Eismann EA, Folger AT, Stephenson NB, Brownrigg ME, Shapiro RA, Macaluso M, Gillespie RJ. Parental Adverse Childhood Experiences and Pediatric Healthcare Use by 2 Years of Age. J Pediatr. 2019;211:146-151.

Adjusted IRR for Missed Well-Child Visits by Parental ACE Exposure

Variables	IRR (95% CI)	
	Maternal* (n=345)	Paternal† (n=147)
ACEs ‡		
≥1	1.12 (1.03-1.22)§	1.00 (0.79-1.26)
<1 (Ref)	—	—
≥2	1.49 (1.02-2.18)§	0.91 (0.42-1.97)
<2 (Ref)	—	—
≥3	1.60 (1.04-2.47)§	0.77 (0.28-2.07)
<3 (Ref)	—	—
Child Sex		
Female	1.08 (0.77-1.51)	1.55 (0.88-2.72)
Male (Ref)	—	—
Payer Source		
Public	2.32 (1.65-3.27)¶	2.65 (1.49-4.72)¶
Private (Ref)	—	—
Preterm Birth		
<37 Weeks	1.51 (0.85-2.68)	1.36 (0.59-3.14)
≥37 Weeks (Ref)	—	—

Ref, Reference category
* There were 29 participants (7.8%) excluded from analysis because of missing data on preterm birth.
† There were 9 (5.8%) participants excluded from analysis because of missing data on preterm birth.
‡ Each cutoff-specific relative risk was adjusted for the other variables in the model. The IRRs shown for child sex, payer source, and preterm birth were derived from the model that used an ACE risk cutoff of ≥1.
§ P ,< .05.
¶ P < .01.

This table shows the adjusted incident rate ratio (IRR) for missed well-child visits by parental adverse childhood experience (ACE) exposure. Higher maternal ACE exposure was significantly associated with an increased risk for missed well-child visits.

‘NINJA’ Program Decreases Acute Kidney Injury in Multi-Hospital Study

Stuart Goldstein, MD

PUBLISHED NOV. 1, 2019
Kidney International

For children admitted to the hospital, nephrotoxic medications (NTMx) can commonly lead to acute kidney injury (AKI). More than 80% of non-critically ill hospitalized children receive a NTMx; between 10% and 49% of children who survive AKI develop chronic kidney disease.

In hospitals without systematic kidney function surveillance, AKI due to medications often goes unnoticed. In fact, various studies show that serum creatinine levels—commonly assessed to detect kidney function decline—are measured at least every four days for only 50-60% of children receiving multiple NTMx.

In 2011, Cincinnati Children’s physicians implemented the Nephrotoxic Injury Negated by Just-in-time Action (NINJA) program to screen all non-critically ill hospitalized patients for high NTMx exposure and obtain daily serum creatinine levels in those patients. The NINJA program decreased NTMx-associated acute kidney injury by 64%.

The NINJA program, funded by the Agency for Health Research and Quality, was implemented at nine other pediatric institutions between 2015 and 2017, which accounted for a combined 638,695 inpatient hospital days. AKI prevalence declined, on average, by eight cases per 1,000 patient days.

“The study shows that the improvements we found at Cincinnati Children’s can be realized by other institutions, even though they may be of different size and makeup and have different resources than here,” says lead author Stuart Goldstein, MD, Director, Center for Acute Care Nephrology.

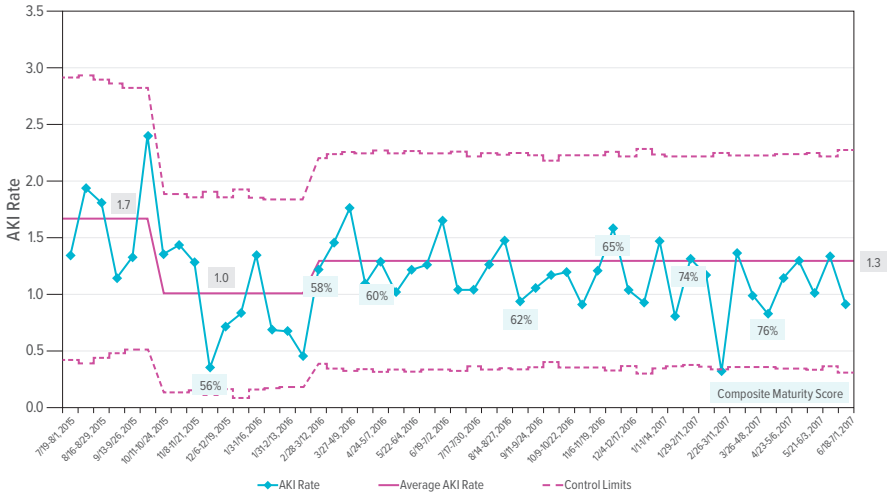
Using NINJA, the hospitals demonstrated a significant and sustained 23.8% decrease in NTMx-AKI rates. Moreover, researchers noted that NINJA’s trigger to alert the healthcare team to increasing NTMx burden likely also helped focus their attention on deciding which medications were necessary and which could be discontinued or substituted with less nephrotoxic alternatives. Researchers are working with more centers in a mentorship program called CUSTOM NINJA to accelerate its adoption.

RESEARCH & TRAINING DETAILS

Faculty	11
Joint Appointment Faculty	5
Research Fellows & Post Docs	8
Total Annual Grant Awards	$1.5M
Total Annual Industry Awards	$1M

Goldstein SL, Dahale D, Kirkendall ES, Mottes T, Kaplan H, Muething S, Askenazi DJ, Henderson T, Dill L, Somers MJG, Kerr J, Gilarde J, Zaritsky J, Bica V, Brophy PD, Misurac J, Hackbarth R, Steinke J, Mooney J, Ogrin S, Chadha V, Warady B, Ogden R, Hoebing W, Symons J, Yonekawa K, Menon S, Abrams L, Sutherland S, Weng P, Zhang F, Walsh K. A prospective multi-center quality improvement initiative (NINJA) indicates a reduction in nephrotoxic acute kidney injury in hospitalized children. Kidney Int. 2020;97(3):580-588.

Acute Kidney Injury Rates
Per 1000 Patient Days Over the Two Years of Study



Biweekly average rates of acute kidney injury (AKI) development as measured by patient number with AKI per 1,000 non–critically ill patient hospital days. AKI rates decreased from 1.7 to 1.3 AKI per 1,000 patient days over the course of the study as revealed by eight consecutive weekly rates below the baseline rate, representing a 99.7% likelihood that a special cause was present. Each data point represents a 14-day interval. The percentages noted in the blue boxes reflect the composite maturity score for the collaborative.

Medical Marijuana Poses Drug-Drug Interaction Risk with Tuberous Sclerosis Complex Medications

Daniel Ebrahimi-Fakhari, MD

David Neal Franz, MD

PUBLISHED APR. 1, 2020
Pediatric Neurology

Day-to-day life for people with tuberous sclerosis complex (TSC) has been significantly improved by the recent FDA approvals of everolimus and sirolimus, drugs that help reduce the size of tumors called astrocytomas and reduce the seizures that often come with the condition.

However, a growing number of people with epilepsy and related conditions are using cannabidiol—the key ingredient of medical marijuana—as a potential seizure controller. Now, a study led by first author Daniel Ebrahimi-Fakhari, MD, and David Neal Franz, MD, reports that taking medical marijuana with either of these drugs can be a dangerous combination for people with TSC.

The researchers reviewed the cases of 25 people with TSC who took cannabidiol in combination with either everolimus (18 people) or sirolimus (7 people). Marijuana increased the activity of the TSC medications in 76% of the cases—but not always with beneficial outcomes.

"Some patients experienced doubling or tripling of their mechanistic target of rapamycin (mTOR) inhibitor trough following the addition of cannabidiol," Franz says. "In some cases this resulted in clinical toxicity, including aphthous ulcers and intercurrent infections."

Less severe adverse events occurred in 10 of 25 patients, including diarrhea, drowsiness, mouth sores, acne, ankle swelling, sinusitis, and abdominal pain. Doctors reduced dose levels of the mTOR inhibitors before serious adverse events occurred.

It is possible that combination therapy might eventually prove beneficial to TSC patients who do not achieve good results with everolimus or sirolimus alone. However, the effects of cannabidiol remain under-studied, Franz says.

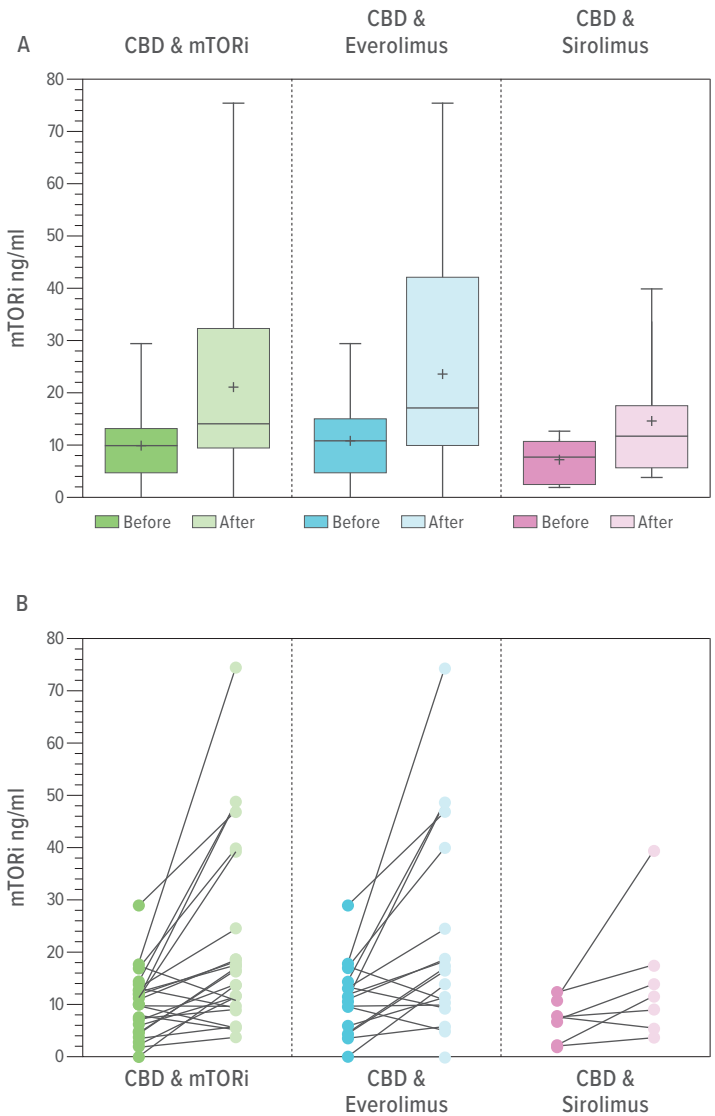
For now, clinicians should be aware of this potential drug-drug interaction and should consider reducing dosing of everolimus or sirolimus before initiating cannabidiol treatment in patients with TSC.

RESEARCH & TRAINING DETAILS

Faculty	36
Joint Appointment Faculty	2
Research Fellows & Post Docs	4
Research Graduate Students	6
Total Annual Grant Awards	$3.9M
Total Annual Industry Awards	$1.6M

Ebrahimi-Fakhari D, Agricola KD, Tudor C, Krueger D, Franz DN. Cannabidiol Elevates Mechanistic Target of Rapamycin Inhibitor Levels in Patients With Tuberous Sclerosis Complex. Pediatr Neurol. 2020;105:59-61.

mTOR Inhibitor Levels
Before and After Cannabidiol Treatment



These charts depict mTOR inhibitor levels before and after cannabidiol treatment. (A) Box plot indicating median and min/max values. (B) Individual levels before and after treatment with cannabidiol.

Diffusion Tensor Imaging Shows Promise as Monitoring Tool After Spina Bifida Fetal Surgery

Francesco Mangano, DO

Weihong Yuan, PhD

PUBLISHED APRIL 2020
Child's Nervous System

Fetal surgery has emerged as a potentially superior method for correcting myelomeningocele (MMC), the most severe form of spina bifida. When successful, this surgery can reduce the risk of children being born with hydrocephalus or with paralysis.

Now, clinicians have a more effective tool for evaluating the success of fetal surgery and for predicting the need for further procedures.

A team led by Francesco Mangano, DO, FACS, FAAP, FACOS, and Weihong Yuan, PhD, reports that an MRI scanning process called diffusion tensor imaging (DTI) can detect abnormalities in the brain's white matter among fetal surgery patients that do not appear in children without spina bifida.

Specifically, the imaging revealed lower fractional anisotropy values and higher mean diffusivity values in the fetal surgery group. This information can be useful in deciding whether a patient needs a shunt as a follow-up procedure.

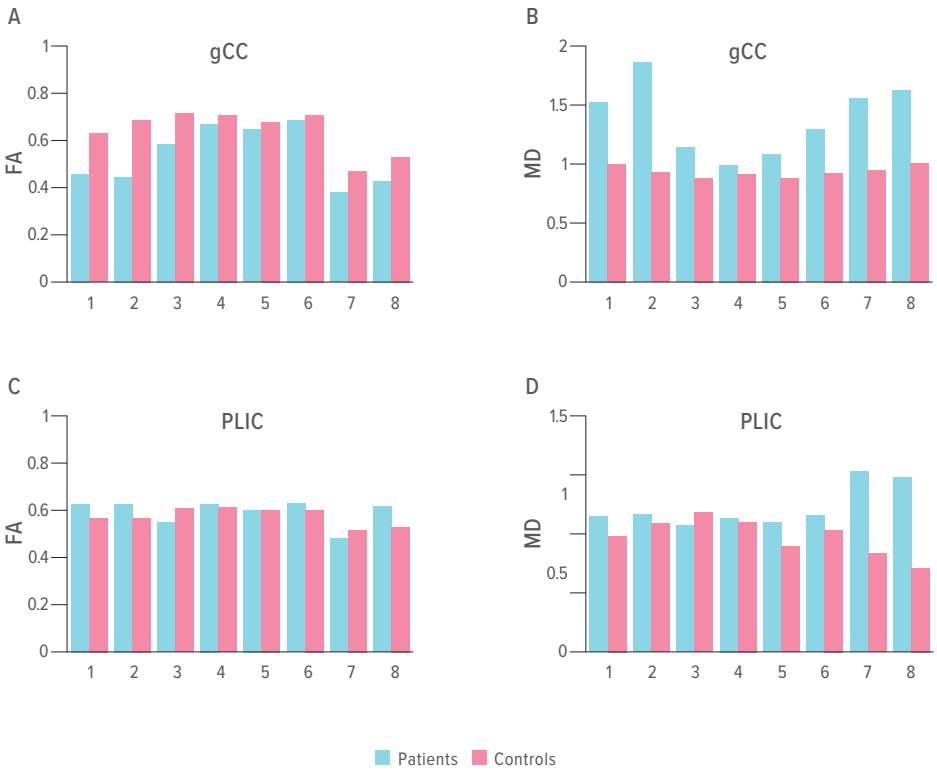
"The sensitivity of DTI in detecting white matter abnormality, as shown in the present study, may help to serve as an imaging biomarker for assessing hydrocephalus and improve and optimize decision making for the treatment of hydrocephalus in this patient population," the co-authors state.

RESEARCH & TRAINING DETAILS

Faculty	7
Research Fellows & Post Docs	1
Research Graduate Students	3
Total Annual Grant Awards	$234,477

Mangano FT, Stevenson CB, Nagaraj U, Conley A, Yuan W. Abnormal anisotropic diffusion properties in pediatric myelomeningocele patients treated with fetal surgery: an initial DTI study. Childs Nerv Syst. 2020;36(4):827-833.

Diffusion Tensor Imaging Values



These bar charts compare DTI values for 8 pediatric patients with fetal MMC repair and 8 age-matched controls. FA = fractional anisotropy. MD = mean diffusivity

Metabolism Affected by Fat Cells that Sense Sunlight

Richard Lang, PhD

PUBLISHED JAN. 21, 2020
Cell Reports

Scientists at Cincinnati Children's who were studying how mice control their body temperature made a discovery that may shed new light on the often-unhealthy consequences of modern life.

A team led by Richard Lang, PhD, Director of the Visual Systems Group, has shown that fat cells deep under the skin possess opsins that both sense and respond to a specific wavelength of visible sunlight.

Changing the exposure level of this 480-nanometer wavelength of blue light influences an internal fat-burning response that mice employ when exposed to chilly temperatures—about 40° F.

The team went on to show that this light response is controlled by the gene *OPN3*. When light exposure occurs, the OPN3 protein prompts white fat cells to release fatty acids into the bloodstream. In this mouse study, brown fat cells then oxidize the fatty acids to generate heat.

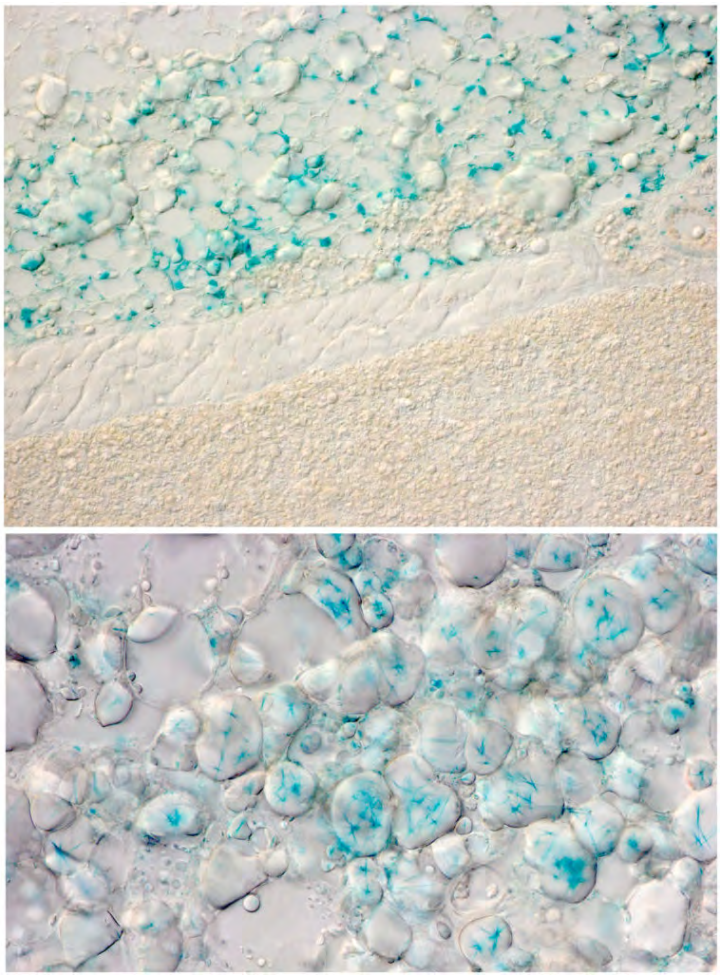
This data prompted the team to conclude that sunlight is required for normal energy metabolism. They also note that this blue wavelength of sunlight is found only in low amounts in typical indoor lighting.

"We are conducting further study to confirm that this light-OPN3 adipocyte pathway exists in humans. If so, there are potentially broad implications for human health," Lang says. "Our modern lifestyle subjects us to unnatural lighting spectra, exposure to light at night, shift work, and jet lag, all of which result in metabolic disruption. Based on the current findings, it is possible that insufficient stimulation of the light-OPN3 adipocyte pathway is part of an explanation for the prevalence of metabolic deregulation in industrialized nations where unnatural lighting has become the norm."

RESEARCH & TRAINING DETAILS

Faculty	1
Research Fellows & Post Docs	2
Research Graduate Students	5
Total Annual Grant Awards	$711,732

Nayak G, Zhang KX, Vemaraju S, Odaka Y, Buhr ED, Holt-Jones A, Kernodle S, Smith AN, Upton BA, D'Souza S, Zhan JJ, Diaz N, Nguyen MT, Mukherjee R, Gordon SA, Wu G, Schmidt R, Mei X, Petts NT, Batie M, Rao S, Hogenesch JB, Nakamura T, Sweeney A, Seeley RJ, Van Gelder RN, Sanchez-Gurmaches J, Lang RA. Adaptive Thermogenesis in Mice Is Enhanced by Opsin 3-Dependent Adipocyte Light Sensing. Cell Rep. 2020;30(3):672-686 e678.



These fluorescent micrographs show expression of the *OPN3* gene (in blue) in white fat cells of mice in two locations. The upper panel shows interscapular white adipocytes (above a layer of muscle and above brown adipose tissue). The lower panel shows white adipocytes from the inguinal adipose depot.

Nerve Transfers Restore Shoulder Function in Most Brachial Plexus Cases

Kevin Little, MD

PUBLISHED JULY 2019
Journal of Hand Surgery

A study of 73 children who received spinal accessory nerve-to-suprascapular nerve transfer (SAN-SSN) at Cincinnati Children's for brachial plexus birth injuries reveals that most patients recovered enough shoulder function that they did not need further procedures. Brachial plexus birth injuries affect approximately 1.5 children per 1,000 live births in the United States and can lead to permanent neurological deficits in up to 30% of affected children.

In this study, first author David Segal, MD, and senior author Kevin Little, MD, reviewed outcomes at one year after patients received an SAN-SSN procedure. They also extended the review to three years post-surgery for many of those studied.

They report that 76.7% of the patients receiving SAN-SSN recovered enough function to prevent tendon transfers and corrective osteotomies. Forty-three patients (58.9%) obtained functional shoulder motion of at least one of three planes (abduction/flexion/external rotation).

The rate of patients who achieved functional abduction motion grew from 12.3% to 39.7%; functional forward flexion motion improved from 12.3% to 41.1%, and external rotation motion improved the most, from 2.7% to 39.7%.

The team was surprised to see the favorable forward flexion outcomes because the transferred nerve does not directly control this motion. "This significant improvement may underscore how rotator cuff strength, augmented by the SAN-SSN transfer, plays a role in all shoulder movements," Little says.

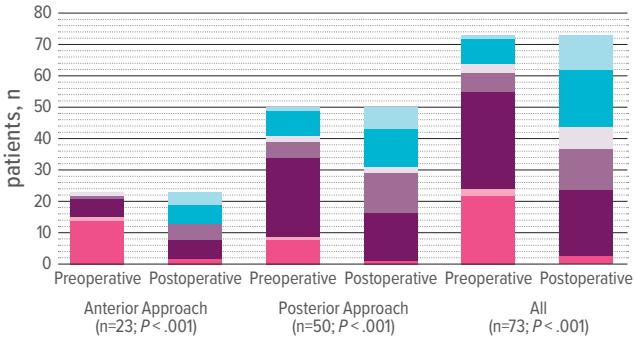
The amount of regained motion also improved across time for most patients. Among the 47 patients who were followed for three years, those obtaining at least one functional AMS score increased to 66%.

"With this evidence of reduced need for more-extensive secondary procedures, SAN-SSN may become the first line procedure for shoulder reconstruction in brachial plexus birth injuries," Little says.

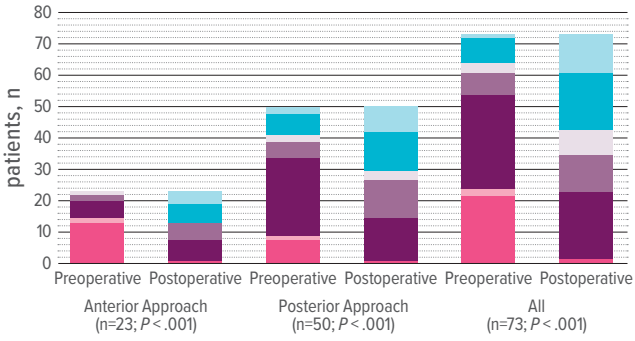
RESEARCH & TRAINING DETAILS

Faculty	15
Research Graduate Students	4
Total Annual Grant Awards	$475,601

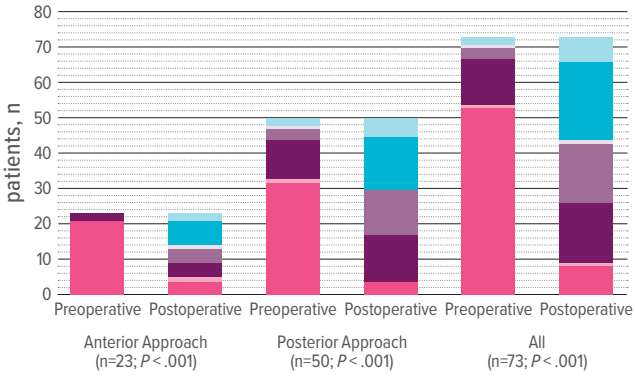
Segal D, Cornwall R, Little KJ. Outcomes of Spinal Accessory-to-Suprascapular Nerve Transfers for Brachial Plexus Birth Injury. J Hand Surg Am. 2019;44(7):578-587.



A. Shoulder abduction active movement scale (AMS) scores before and following SAN-SSN nerve transfer in brachial plexus patients, divided by the surgical approach.



B. Shoulder forward flexion AMS scores before and following SAN-SSN nerve transfer in brachial plexus patients, divided by the surgical approach.



C. Shoulder external rotation AMS scores before and following SAN-SSN nerve transfer in brachial plexus patients, divided by the surgical approach.

Novel Mutations Detected at Work in Rare Histiocytoses Cases

Jennifer Picarsic, MD

PUBLISHED DEC. 25, 2019
Nature Medicine

Histiocytoses are a collection of rare disorders that share a common trait of excess accumulation of dendritic cells that can lead to tumor formation across many areas of the body. According to the Histiocytosis Association of America, 1 in 200,000 U.S. children per year are born with histiocytosis.

Most of these disorders are now known to be driven by mutations in the mitogen-activated protein kinase (MAPK) pathway mapping to the BRAF and MEK1 and MEK2 kinases in the majority. However, the developmental origins for many groups within this disease category are not yet known.

Now a multi-institutional team of scientists—including co-author Jennifer Picarsic, MD, who serves as Co-Director of the Langerhans Cell Histiocytosis Center—has detailed a new collection of kinase mutations linked to histiocytic neoplasms. The project included experts from Memorial Sloan Kettering Cancer Center, Children's Hospital of Pittsburgh, and centers in Belgium, Spain and France.

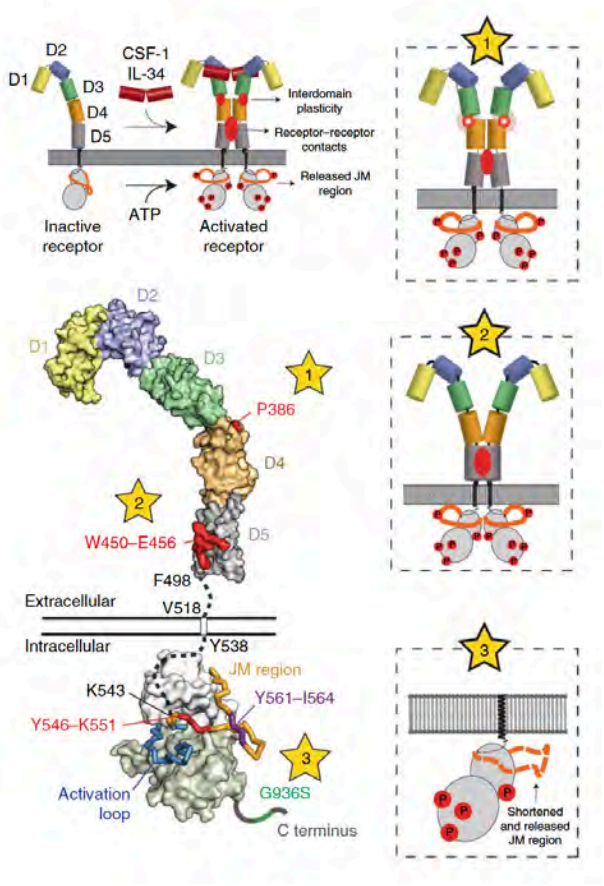
The team performed extensive analysis of 270 patients that uncovered a series of activating receptor tyrosine kinase (RTK) alterations. Key discoveries included finding activating mutations in CSF1R and rearrangements in NTRK, RET and ALK. Adult patients with some of these newly identified mutations showed dramatic responses to the RET inhibitor selpercatinib and the ALK inhibitor crizotinib. Meanwhile, another patient with refractory Langerhans Cell Histiocytosis (LCH) benefitted from the MEK1/2 inhibitor trametinib.

"These findings further support the genetic diversity found in the histiocytic neoplastic lesions and show that with a robust testing platform, we can identify those who may benefit from kinase-inhibitor medications, which have not traditionally been prescribed for these conditions," Picarsic says. The Langerhans Cell Histiocytosis Center, co-directed by Ashish Kumar, MD, PhD, is one of the few centers worldwide capable of providing inhibitor-based therapy as a first-line treatment based on the patient's unique mutational profile.

RESEARCH & TRAINING DETAILS

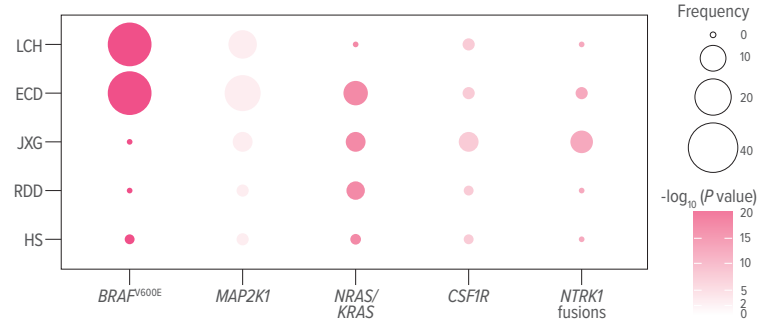
Faculty	24
Joint Appointment Faculty	1
Research Fellows & Post Docs	3
Total Annual Grant Awards	$921,256

Durham BH, Lopez Rodrigo E, Picarsic J, Abramson D, Rotemberg V, De Munck S, Pannecoucke E, Lu SX, Pastore A, Yoshimi A, Mandelker D, Ceyhan-Birsoy O, Ulaner GA, Walsh M, Yabe M, Petrova-Drus K, Arcila ME, Ladanyi M, Solit DB, Berger MF, Hyman DM, Lacouture ME, Erickson C, Saganty R, Ki M, Dunkel IJ, Santa-Maria Lopez V, Mora J, Haroche J, Emile JF, Decaux O, Geissmann F, Savvides SN, Drilon A, Diamond EL, Abdel-Wahab O. Activating mutations in CSF1R and additional receptor tyrosine kinases in histiocytic neoplasms. Nat Med. 2019;25(12):1839-1842.



Left: Structural mapping of CSF-1R mutations and proposed impact on CSF-1R activation. Top left: Binding of CSF-1 or IL-34 to autoinhibited CSF-1R leads to receptor dimerization and activation hallmarked by conformational switching in the extracellular domains and receptor-receptor contacts to elicit phosphorylation of intracellular domains. Expulsion of the juxtamembrane (JM) region is a prerequisite to activate CSF-1R. Lower left: Structural mapping of mutations to crystal structures of the extracellular and intracellular segments of human CSF-1R (stars 1–3). Proposed mechanistic consquences of these mutations are elaborated via three insets with the corresponding star number.

Below:Frequency and statistical enrichment of kinase mutations (x-axis) across histologic subtypes of histiocytic neoplasms (y-axis; LCH (n=67); ECD (n=80); JXG (n=24); RDD (n=8); HS (n=5)). Two-sided p-values, Fisher's exact test.



Longer-Lived Mouse Model Improved Tool for Biliary Atresia Research

Sujit Mohanty, DVM, PhD

Greg Tiao, MD

PUBLISHED APRIL 2020
Hepatology

In recent years, biliary atresia (BA) research has been hampered because the primary mouse model of the disease had a 14-day lifespan. But now, a new method of inducing a biliary atresia-like state in mice has resulted in longer survival times and more opportunity to study potential medications.

Biliary atresia is the leading cause of liver transplantation for children. Inflammation from the condition results in end-stage liver disease and, without surgical intervention, leads to death by 2 years of age. Experts have long suspected that a prenatal viral infection might trigger the bile duct blockages the condition induces.

So far, scientists have used a rhesus rotavirus to induce biliary obstruction that parallels human biliary atresia. But the liver damage is so extensive that mice die within 14 days. The Cincinnati Children's team—led by first and corresponding author Sujit Mohanty, DVM, PhD, and senior author Greg Tiao, MD—generated an RRV-TUCH rotavirus reassortant that resulted in longer-lived mouse models.

Their study indicates that the new mouse model shows increased cholangiocyte proliferation, extensive liver fibrosis, and partial bile duct obstruction that better mimic the disease progression seen in humans. Importantly, the team compared genetic data from patients with BA and found that the new mouse model shares an expression pattern involving several genes linked to human BA.

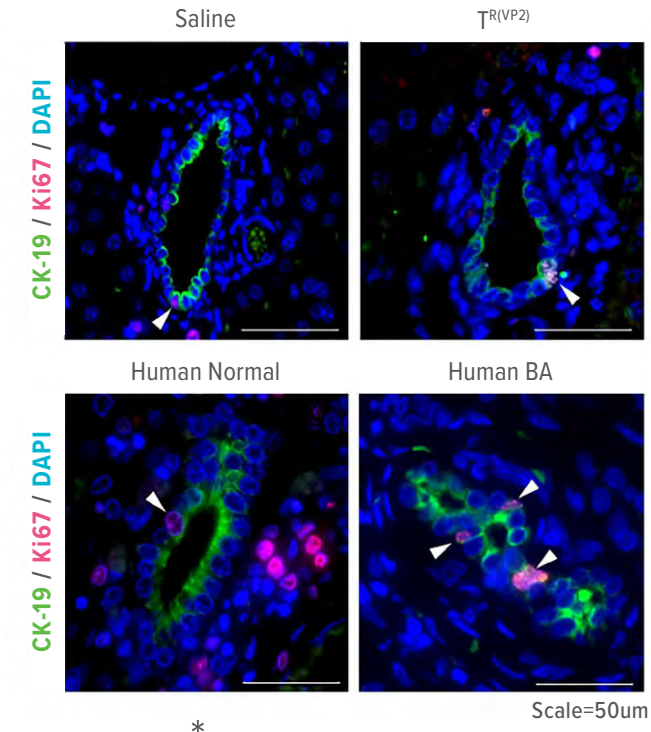
"This model of rotavirus-induced neonatal fibrosis will provide an opportunity to study disease pathogenesis and has potential to be used in preclinical studies to identify therapeutic targets that may alter the course of biliary atresia," the co-authors say.

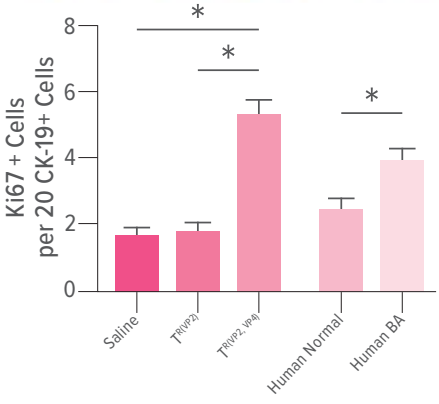
RESEARCH & TRAINING DETAILS

Faculty	25
Joint Appointment Faculty	2
Research Fellows & Post Docs	6
Total Annual Grant Awards	$4.6M
Total Annual Industry Awards	$75,475

Mohanty SK, Lobeck I, Donnelly B, Dupree P, Walther A, Mowery S, Coots A, Bondoc A, Sheridan RM, Poling HM, Temple H, McNeal M, Sestak K, Bansal R, Tiao G. Rotavirus Reassortant-Induced Murine Model of Liver Fibrosis Parallels Human Biliary Atresia. Hepatology. 2020;71(4):1316-1330.

Human Biliary Atresia Liver Samples Show Increased Ki67+ and CK-19+ Cells





These five fluorescent microscope images show that human BA liver samples (bottom row) also demonstrate increased Ki67+ (red) and CK-19+ cells (green) compared with healthy controls, similar to mice inoculated the new virus reassortant (top row). The sixth panel shows the total number of Ki67+ cells per 20 CK-19+ cells.

Helping Preterm Infants Fight Lung Infections May Start by Reinforcing Gut Microbiota

Katherine Oherle

Hitesh Deshmukh, MD, PhD

PUBLISHED FEBRUARY 2020
Immunity

Clinicians have worked for years to protect the underdeveloped lungs of preterm infants from devastating infections. Now, experts at Cincinnati Children's report early signs of progress, in mice, at adjusting the gut-lung development axis to help preterm infants build healthier immune systems.

A team led by first author Katherine Oherle and senior author Hitesh Deshmukh, MD, PhD, has shed new light on the mechanisms at work as the lung's alveoli begin to build their immune defenses. They found that the lung air sacs of preterm infants lack type 3 innate lymphoid cells crucial to responding to infection. They also found that production of these lymphoid cells depends on biological cues from commensal bacteria from the gut, specifically via production of the growth hormone IGF1.

Deleting pulmonary IGF1 in the lungs of newborn mice interrupted the development of type 3 innate lymphoid cells and made the mice susceptible to lung infections and pneumonia. The team also confirmed that a similar process occurs in humans.

The findings suggest that treating lungs directly with IGF1, or by stimulating healthy gut microbiota to generate IGF1, could help preterm infants develop stronger lungs. Both concepts will be evaluated in further studies.

"This study gives us important new information that helps us develop new and cost-effective methods to boost innate lung immunity in preterm babies. This could help them develop lifelong pulmonary resistance to respiratory infections," Deshmukh says.

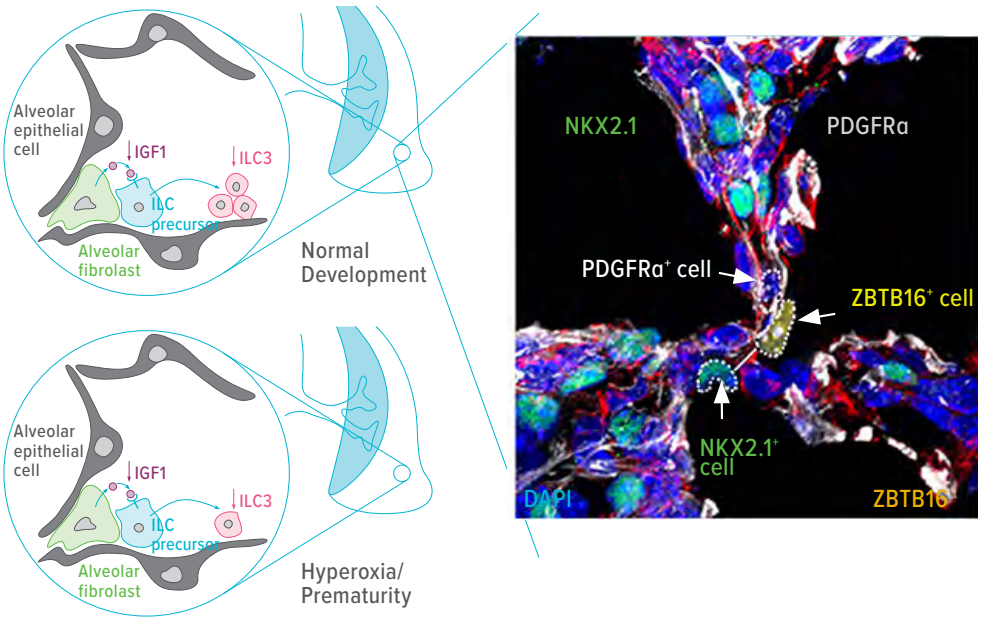
This discovery builds upon previous findings from Deshmukh and colleagues published in *Nature Medicine* (2014) and *Science Translational Medicine* (2017) that established the connection between commensal bacteria and lung immunity and warned of the long-term harm that can follow aggressive antibiotic regimens for premature infants.

INSTITUTE RESEARCH & TRAINING DETAILS

Faculty	58
Joint Appointment Faculty	1
Research Fellows & Post Docs	8
Research Graduate Students	6
Total Annual Grant Awards	$12.6M
Total Annual Industry Awards	$530,254

Oherle K, Acker E, Bonfield M, Wang T, Gray J, Lang I, Bridges J, Lewkowich I, Xu Y, Ahlfeld S, Zacharias W, Alenghat T, Deshmukh H. Insulin-like Growth Factor 1 Supports a Pulmonary Niche that Promotes Type 3 Innate Lymphoid Cell Development in Newborn Lungs. Immunity. 2020;52(2):275-294.

How Healthy Gut Microbiota
Support Healthy Lung Development



This graphical abstract depicts how signals from commensal gut bacteria influence production of type 3 innate lymphoid cells crucial to responding to infection.

Primary Decidual Zone Formation Requires Scribble For Pregnancy Success In Mice

Jia Yuan

Xiaofei Sun

PUBLISHED NOV. 28, 2019
Nature Communications

One of the early events following blastocyst implantation occurs when stromal cells differentiate into decidual cells that support embryo development. In mice and rats, this process begins in an area called the primary decidual zone (PDZ).

Sudhansu K. Dey, PhD, and colleagues at Cincinnati Children's have devoted years to studying the genetic and cellular mechanisms at work in this early stage of pregnancy and have identified key genes involved in the process. Now, Dey and co-authors Jia Yuan and Xiaofei Sun report another critical genetic finding.

The Scribble (*Scrib*) gene produces a protein that's involved in various functions including cell polarity, cell adhesion, and cell proliferation. Dey and colleagues reveal that *Scrib* interacts with *Vangl2* during pregnancy to contribute to embryo development in an unexpected way.

Other studies have shown that *Scrib* expressed in the epithelium has not been essential to successful pregnancy. However, this paper shows that *Scrib* expression rapidly increases in stromal cells around the embryo after attachment and is critical for PDZ initiation and formation. This process contributes to crypt-glands assembly that leads to pregnancy success.

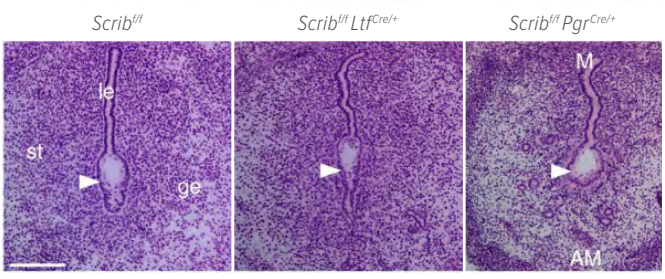
"Our observations of marginal adverse effects on pregnancy success after epithelial deletion of *Scrib* as opposed to severe subfertility with the deletion of stromal *Scrib* suggest that *Scrib* has an important and unique role in the stromal compartment in early pregnancy," the co-authors say.

One next step for this line of research is to determine whether the PDZ formed during embryo implantation in mice also forms during implantation in humans.

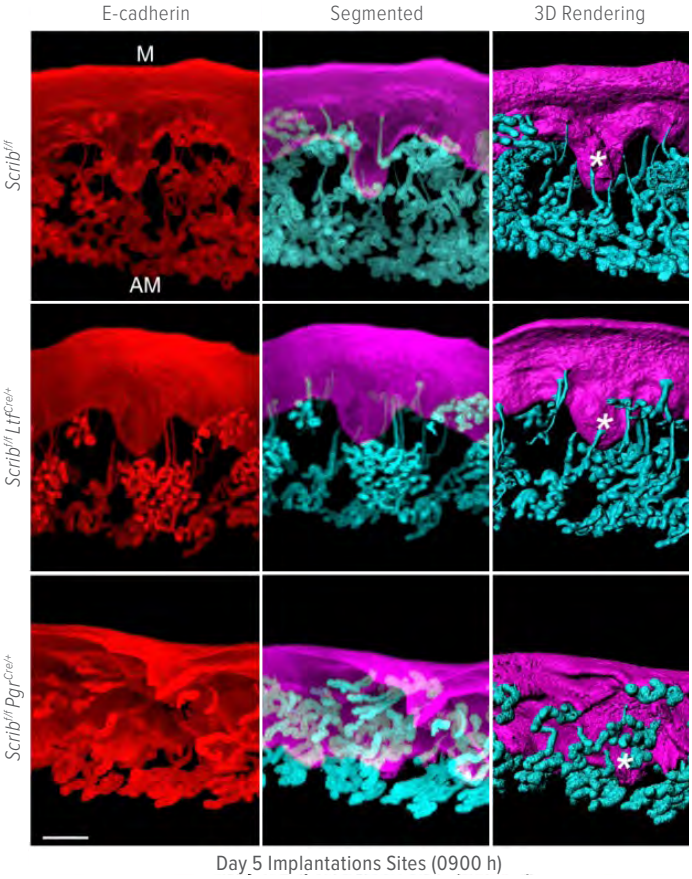
RESEARCH & TRAINING DETAILS

Faculty	6
Joint Appointment Faculty	1
Research Fellows & Post Docs	12
Total Annual Grant Awards	$2.1M

Yuan J, Aikawa S, Deng W, Bartos A, Walz G, Grahammer F, Huber TB, Sun X, Dey SK. Primary decidual zone formation requires Scribble for pregnancy success in mice. Nat Commun. 2019;10(1):5425.



Day 5 Implantations Sites (0900 h)



Day 5 Implantations Sites (0900 h)

These panels show how implantation goes wrong without the involvement of the *Scrib* protein in stromal cells. The top row shows histology of day 5 of implantation sites in each genotype. Scale bar, 200 µm. Arrowheads indicate the location of embryos. The next panels show 3D imaging of day 5 implantation sites in *Scrib*$^{f/f}$ (top row), *Scrib*$^{f/f}$*Ltf*$^{Cre/+}$ (middle), and *Scrib*$^{f/f}$*Pgr*$^{Cre/+}$ females (bottom), with aberrant crypt-gland structure in *Scrib*$^{f/f}$*Pgr*$^{Cre/+}$ females.

* indicate the location of blastocysts.
M=mesometrial pole,
AM= antimesometrial pole,
le=luminal epithelium,
ge=glandular epithelium,
st=stroma.

Summing Up a 12-Year Study of Early Childhood TBI

Shari Wade, PhD

PUBLISHED MAY 2020
Journal of Head Trauma Rehabilitation

The Ohio Head Injury Outcomes (OHIO) study was a 12-year investigation of longitudinal outcomes for children aged 3 to 7 years who suffered complicated mild to moderate and severe Traumatic Brain Injury (TBI).

"This publication synthesizes more than 50 papers reflecting cutting edge findings about influences on recovery following early childhood TBI," says Shari Wade, PhD, Director of Research, Division of Rehabilitation Medicine and principle investigator of the study.

The OHIO study allowed investigators to explore the complex interactions between social-environmental influences (such as parenting and discipline practices) and children's cognitive, social, and emotional recovery. Supported by two R01 NICHD awards, an Ohio EMS grant, and other ancillary awards, the work also allowed investigators to examine the neural substrates of language, attention and working memory in these children. Other work focused on collecting genetic data that could shed further light on ways to improve long-term recovery.

The OHIO study included three follow-up assessments within the first 18 months of injury, another follow-up at 39 months post-injury, and a comprehensive follow-up as children transitioned to middle school, a period of heightened expectation for self-control. Investigators compared outcomes to children who sustained non-TBI orthopedic injuries.

Among only a handful of studies looking at long-term outcomes , the OHIO study was able to assess TBI outcomes on genetics, comorbid characteristics, and parenting—as well as academic outcomes.

Researchers found certain factors, such as positive home environment, largely mitigated the effects of TBI on everyday functioning. These observations led to a trial of a responsive parenting skills intervention now being used at Sick Kids in Toronto to support positive development in children with congenital heart disease and perinatal stroke.

RESEARCH & TRAINING DETAILS

Faculty	10
Joint Appointment Faculty	1
Research Fellows & Post Docs	1
Research Graduate Students	3
Total Annual Grant Awards	$1M

Petranovich CL, Smith-Paine J, Wade SL, Yeates KO, Taylor HG, Stancin T, Kurowski BG. From Early Childhood to Adolescence: Lessons About Traumatic Brain Injury From the Ohio Head Injury Outcomes Study. J Head Trauma Rehabil. 2020;35(3):226-239.

Study Measures and Assessments

Domain/ Construct	Measure/ Method	Source	Assessment	Time Point Collected
Adaptive, behavioral, and social-emotional functioning				
Real world functioning	CAFAS[79]	Parent, interview	Lab	82mo
Child behavior	CBCL/TRF[80,81]	Parent, teacher	Lab/school	All time points
Child social competence	HCSBS/SSBS[82]	Parent, teacher	Lab/school	All time points
Victimization	Schwartz Report of Victimization[83]	Child, parent, teacher	Lab/school	82mo
Neuropsychological functioning				
Executive functions in daily life	BRIEF[35]	Parent, teacher, self-report	Lab/school	All time points
Attentional control	ANT, TEA-Ch Walk/Don't Walk[84,85]	Child	Lab	82mo
Planning/problem solving	IGT, Tower of London, D-KEFS Verbal Fluency[86-88]	Child	Lab	82mo
Working memory	TEA-Ch Code Transmission[85]	Child	Lab	82mo
	TEA-Ch Creature Counting	Child	Lab	82mo
Processing speed	WISC-IV Processing Speed Index[89]	Child	Lab	82mo
Language pragmatics	CASL Pragmatics, Discourse[90]	Child	Lab	Baseline and 6,12,18,82 mo
Global cognitive ability	WASI[91]	Child	Lab	82mo
Academic achievement	Woodstock Johnson Tests of Achievement-3rd Ed.[92]	Child	Lab	Baseline and 12,82mo
Memory	Verbal Paired Associates[93]	Child	Lab	82mo
Social problem solving	Dodge SIP-SR Stories[94]	Child	Lab	82mo
Family/Environment				
Parent psychological functioning	SCL-90[95]	Parents	Lab	82mo
Injury-related burden	FBII[96]	Parent interview	Lab	All time points
Family functioning	FAD[97]	Parents	Lab	All time points
Caregiving coping	COPE[98]	Parents	Lab	Baseline and 6,12,18,82 mo
Stresses and interpersonal	LISRES-A[99]	Parent interview	Lab	All time points
Marital/partner relations	Relationships Interactions Questionnaire[100]	Parents	Lab	Baseline and 6,12,18,82mo
Parenting practices	Parenting Practices Questionnaire[101]	Parents	Lab	All time points
DNA saliva collection	Oragene Collection Kit	Child	Home	82mo

Abbreviations: ANT, Attention Network Test; BRIEF, Behavior Rating Inventory of Executive Function; CAFAS, Child and Adolescent Functional Assessment Scale; CASL, Comprehensive Assessment of Spoken Language; CBCL, Child Behavior Checklist;D-KEFS, Delis-Kaplan Executive Function System; Dodge SIP-SR, Dodge Social Information Processing-Self-Report;FAD, Family Assessment Device; FBII, Family Burden of Injury Interview; HCSBS, Home and Community Social Behavior Scales; IGT, Iowa Gambling Tast; LISRES-A, Life Stressors and Social Resources Inventory-for Adults; SCL-90, Symptom Checklist-90; SSBS, School Social Behavior Scales; TEA-Ch, Test of Everyday Attention for Children; TRF, Teacher's Report Form; WASI, Wechsler Abbreviated Scale of Intelligence, WISC-IV, Wechsler Intelligence Scale for Children–Fourth Edition.

Studies of commonly used outcome measures following pediatric TBI: Main effects, moderators, and other significant main effects.

Study Clarifies Role of Hyaluronan in Cleft Palate Formation

Yu Lan, PhD

PUBLISHED SEPT. 11, 2019
Journal of Dental Research

Cleft palate is a common birth defect impacting about 1 in 1,000 live births. Even with surgical treatment, many individuals face long-term health implications.

In mammals, during embryonic development the palate arises from the maxillary process and grows downward to form a pair of palatal shelves flanking the developing tongue. These shelves then reorient horizontally above the tongue, grow towards each other and fuse at the middle to become the palate.

"Most cleft palate cases result from disruption or failure in palatal shelf reorientation," says Yu Lan, PhD. "But the developmental mechanism driving palatal shelf elevation is not well understood."

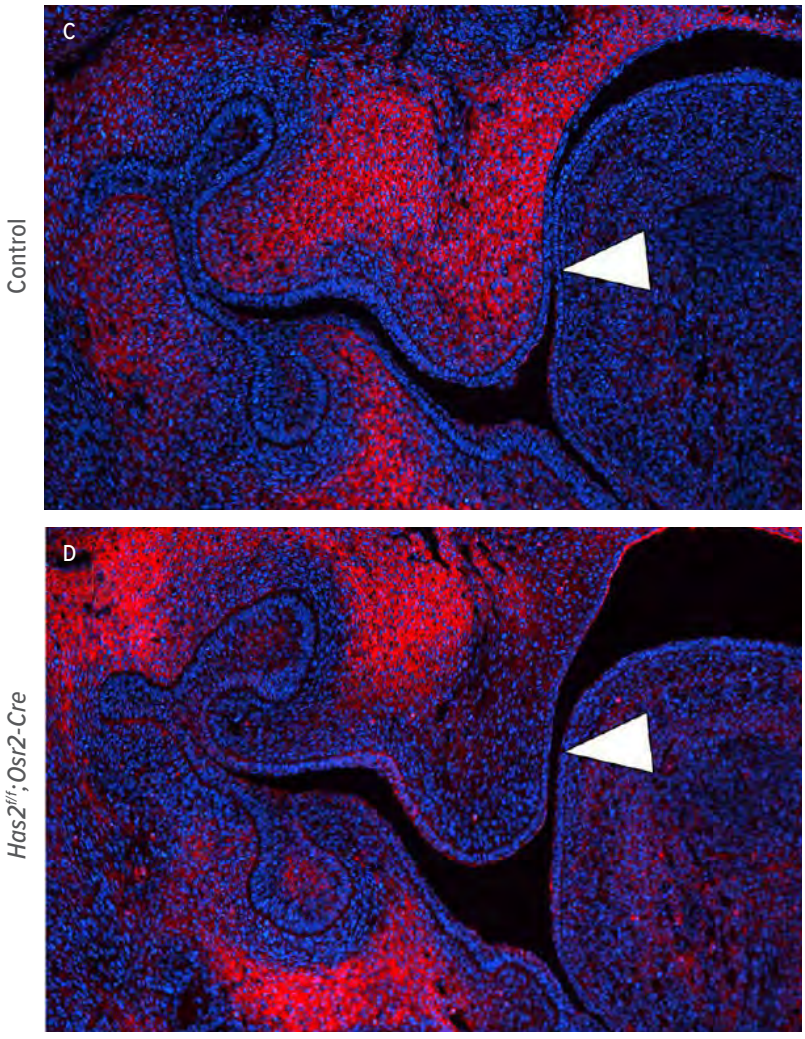
A prevailing hypothesis suggested a region-specific accumulation of hyaluronan plays a major role in PS elevation. A study led by Lan clarifies how the process works. Using multiple lines of mouse models combined with embryonic maxillary explant culture assays, the study showed that *Has2*, one of three hyaluronan synthases in mammals, is responsible for hyaluronan synthesis and accumulation in the developing palatal shelves. The team further demonstrated that inactivating *Has2* throughout the craniofacial mesenchyme caused cleft palate and micrognathia, but specific inactivation of *Has2* in the palatal mesenchyme cells did not block palatal shelf elevation. However, the experiment contradicts the longstanding prevailing theory of a direct role for hyaluronan in palatal shelf elevation.

"We are happy our results represent a major milestone in the field of palate development research," says Lan, lead author on the study. The results and conclusions have been corroborated by independent study by other researchers at University of Washington, and work continues at Cincinnati Children's to better understand the mechanisms regulating palatal shelf elevation and palate development using other mutant mouse models.

RESEARCH & TRAINING DETAILS

Faculty	4
Joint Appointment Faculty	1

Lan Y, Qin C, Jiang R. Requirement of Hyaluronan Synthase-2 in Craniofacial and Palate Development. J Dent Res. 2019;98(12):1367-1375.



Panel D shows the result of loss of hyaluronic acid (HA) accumulation in the palatal mesenchyme in *Has2*$^{f/f}$*;Osr2-Cre* mutant embryos compared to control (panel C).

Potential Biomarker Isolated for Children with Combined ADHD and Autism Spectrum Disorders

Ernest Pedapati, MD, MS

PUBLISHED NOV. 13, 2019
Translational Psychiatry

Nearly one in two children diagnosed with autism spectrum disorder (ASD) also is diagnosed with attention deficit hyperactivity disorder (ADHD). Children with both diagnoses (ASD+) tend to have more severe symptoms, with higher rates of medication use and intensive treatments. What's more, studies indicate that the ADHD symptoms often go under-recognized and less frequently treated in children with autism.

Now a brain structure biomarker may help clinicians improve their diagnosis and treatment of children with ASD+.

In a study supported by a national award from the American Academy of Child and Adolescent Psychiatry, Cincinnati Children's physicians used transcranial magnetic stimulation (TMS) to compare the brain signatures of 29 youths with ASD+ to 20 youths with autism but not ADHD (ASD-).

"We found that children with autism and ADHD had a very different brain signature than children with autism alone," says lead author Ernest Pedapati, MD, MS, who holds joint appointments in the Divisions of Psychiatry and Neurology.

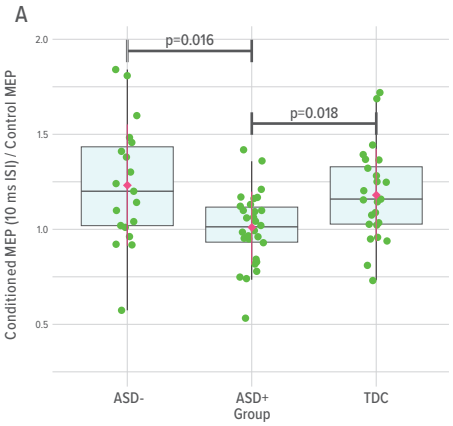
Children with ASD+ showed a marked reduction in intracortical facilitation (ICF) compared to ASD-. Children with decreased ICF also showed worsened inattention and executive function. Interestingly, ICF not only results from the cerebral cortex commonly associated with ADHD, but, notes Pedapati, "also deeper structures of the brain that are involved in movement, emotion, and motivation." These findings concerning ICF could suggest several subcortical neural circuits specifically relevant to ASD+ symptoms.

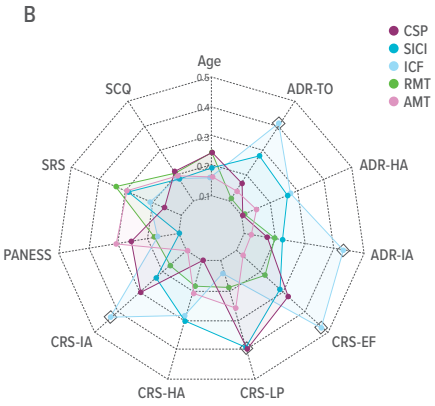
The study is part of a larger dataset tracking how common ADHD treatments work in the brains of children with ASD. Cincinnati Children's co-authors included Steve Wu, MD, Donald Gilbert, MD, MS, and Craig Erickson, MD, MS.

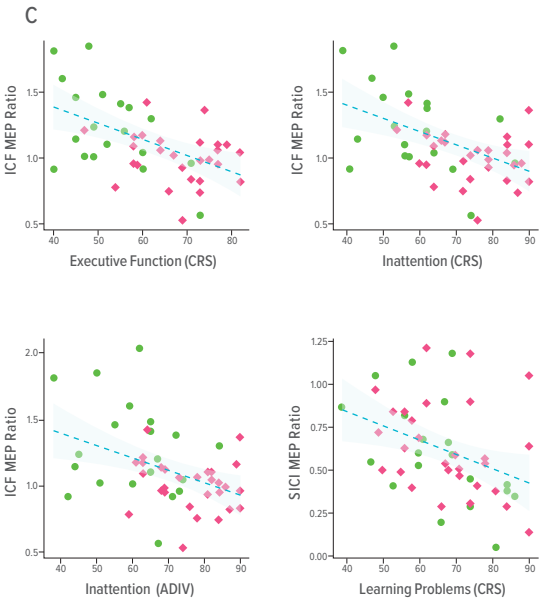
RESEARCH & TRAINING DETAILS

Faculty	22
Joint Appointment Faculty	2
Total Annual Grant Awards	$2.1M
Total Annual Industry Awards	$625,294

Pedapati, E.V., Mooney, L.N., Wu, S.W. et al. Motor cortex facilitation: a marker of attention deficit hyperactivity disorder co-occurrence in autism spectrum disorder. Translational Psychiatry 9, 298 (2019).







A. Bracket lines indicate significant post-hoc comparisonsmotor evoked potential (MEP). Larger ratios of ICF indicate greater paired pulse facilitation. KEY: Circles: Individual subject average ICF, Red Diamond: Overall group average, Whiskers: Group standard deviation, Boxplot notch: Group median, Boxplot edges: Upper and lower quartiles.

B. Radar plots of Spearman correlation coefficients between resting motor physiology measures (ICF, SICI, CSP, RMT) and various clinical measures. KEY: Black outlined diamonds represent significant correlations.

C. Scatter plots of significant relationships (following FDR correction) between subject symptom severity and TMS measures. KEY: Green circles = ASD−, Red diamond = ASD+, Higher clinical scores indicate more severe ADHD symptoms

New Cystic Fibrosis Medications Also Help Recover Dysfunction in Other Inflammatory Pathways

Assem Ziady, PhD

Matthew Siefert

PUBLISHED AUG. 1, 2019
Journal of Clinical Investigation

Cystic fibrosis (CF) is a genetic disease that impacts multiple organs and is known to be caused by loss of function of the gene *CFTR*. The disease causes chronic inflammation that contributes to many pathologies, including potentially fatal lung tissue damage. Now, a research team at Cincinnati Children's reports that medications recently approved to compensate for the loss of *CFTR* function also impact pathways related to inflammation.

Using multiple models and primary cells from 12 CF patients and six non-CF control subjects, the researchers became the first to identify a direct relationship between *CFTR* and Nrf2, an important regulator of antioxidant and anti-inflammatory signaling. Using super-clinical doses of approved pharmaceuticals for *CFTR*, researchers found dysfunction in Nrf2 can also be corrected in a *CFTR*-dependent fashion.

"Multiple approaches were used and all pointed to a relationship between the primary defect in CF and a major regulator of inflammatory signaling, a very strong and novel finding both in the fields of cystic fibrosis and redox biology, where Nrf2 is more of a focus of study," says lead author Assem Ziady, PhD, Division of Pulmonary Medicine.

The work also identified the mechanisms involved when correcting loss of *CFTR* influences inflammatory signaling. Since publication, new drugs have been approved that better correct *CFTR* than those available at the time of the original research.

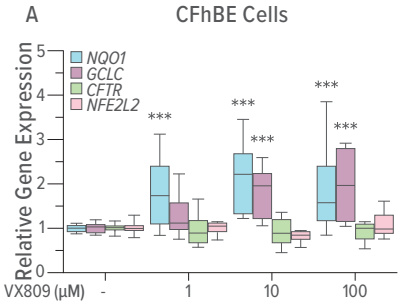
"We are interested in whether, at clinical doses, new and improved therapies correct sufficient levels of *CFTR* to correct anti-inflammatory and anti-oxidant responses in CF," says Matthew Siefert, co-first author on the study.

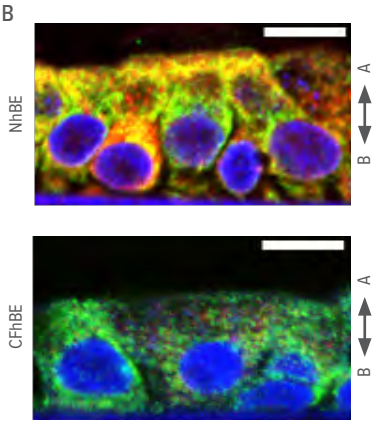
The lab is evaluating whether these newer therapies are more efficient at correcting Nrf2 dysfunction and dysregulated inflammatory signaling in CF. They also are looking at *CFTR*-independent Nrf2 activators as potential co-therapies for CF.

RESEARCH & TRAINING DETAILS

Faculty	35
Joint Appointment Faculty	7
Research Fellows & Post Docs	11
Research Graduate Students	7
Total Annual Grant Awards	$11.9M
Total Annual Industry Awards	$1.4M

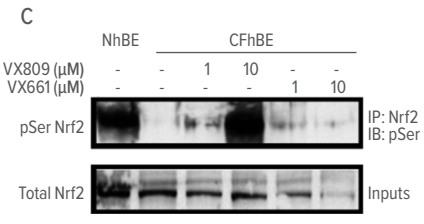
Borcherding DC, Siefert ME, Lin S, Brewington J, Sadek H, Clancy JP, Plafker SM, Ziady AG. Clinically-approved CFTR modulators rescue Nrf2 dysfunction in cystic fibrosis airway epithelia. J Clin Invest. 2019;129(8):3448-3463.

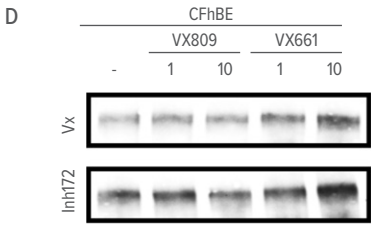




A. *CFTR* modulation dose-dependently increases Nrf2 activity. Gene expression of *CFTR*, *NFE2L2 (Nrf2)*, and *Nrf2*- regulated genes *GCLC* and *NQO1* in primary CF human bronchial epithelial cells, after incubation with DMSO control or the indicated doses of VX809 for 48 hours, determined by real-time quantitative PCR (qPCR). Data presented as fold changes versus untreated cells; calculated from cycle threshold measurements and normalized to 18S rRNA for n=3 independent experiments and 3 donors. Data are expressed as box-and-whisker plots. Horizontal bars indicate the median, box borders indicate 25th and 75th percentiles, and whiskers indicate 5th and 95th percentiles. *P < 0.05, **P < 0.01, ***P < 0.001 vs. DMSO control cells by 1-way ANOVA and Dunnett's multiple-comparisons test.

B. Representative immuno-fluorescent images of coronal sections of non-CF or CF human bronchial epithelial cells stained for *CFTR* (red) and Nrf2 (green), with colocalization of Nrf2 and *CFTR* in yellow.





C & D. *CFTR* modulation increases Nrf2 phosphorylation and interaction with CBP. Non-CF and CF cells were treated with the indicated doses of VX809 or VX661 for 48 hours. (A and B) Cell lysates were immunoprecipitated at 4°C with anti-Nrf2 antibody, then subjected to Western blot analysis with anti-phosphoserine antibody (A); or with anti-CBP antibody, then subjected to Western blot analysis with anti-Nrf2 antibody (B). Representative of 4 independent experiments with 3-4 donors per condition.

High Air Pollution Exposure Linked to Structural Brain Changes in Children

Travis Beckwith, PhD

Kim Cecil, PhD

PUBLISHED JAN. 24, 2020
PLOS One

When newborns are exposed during their first year of life to high levels of traffic-related air pollution (TRAP), reductions in gray matter volume and cortical thickness could be detected at age 12, according to a study led by experts at Cincinnati Children's.

"The results of this study, though exploratory, suggest that where you live and the air you breathe can affect how your brain develops," says Travis Beckwith, PhD, lead author of the study. "While the percentage of loss is far less than what might be seen in a degenerative disease state, this loss may be enough to influence the development of various physical and mental processes."

Beckwith and Kim Cecil, PhD, with the Cincinnati Children's Imaging Research Center, led a research team that used magnetic resonance imaging to obtain anatomical brain images from 147 children at age 12 who were involved in the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS). This study had recruited volunteers prior to the age of six months to examine early childhood exposure to TRAP and health outcomes.

The team divided the group into low and high-exposure cohorts based of their place of residence and pollution data from 27 air sampling sites in the Cincinnati area. The study found that specific regions in the frontal and parietal lobes and the cerebellum were affected with decreases on the order of 3% to 4%. These areas are involved in motor control and sensory perception.

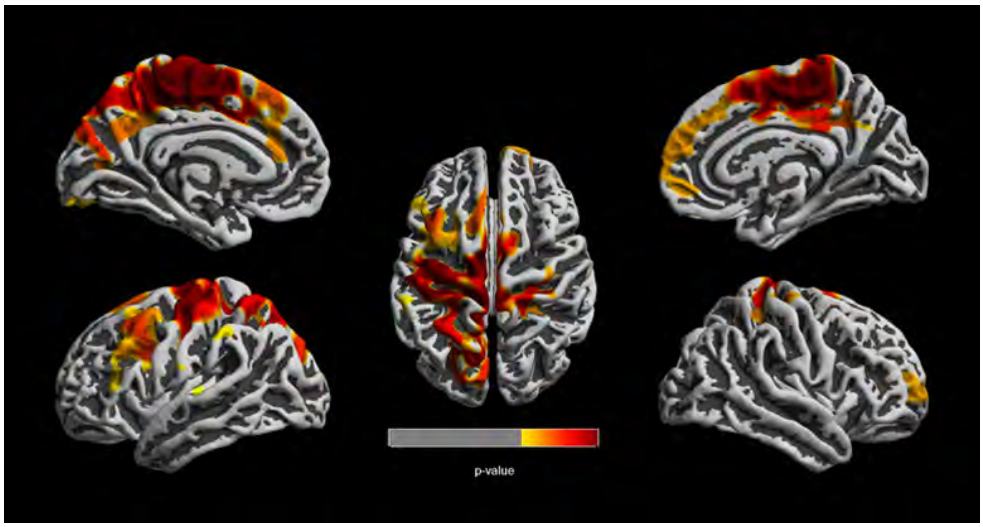
Previous studies of TRAP suggest that it contributes to neurodegenerative diseases and neurodevelopmental disorders. This work supports that TRAP changes brain structure early in life.

RESEARCH & TRAINING DETAILS

Faculty	50
Joint Appointment Faculty	3
Research Fellows & Post Docs	3
Total Annual Grant Awards	$2.3M

Beckwith T, Cecil K, Altaye M, Severs R, Wolfe C, Percy Z, Maloney T, Yolton K, LeMasters G, Brunst K, Ryan P. Reduced gray matter volume and cortical thickness associated with traffic-related air pollution in a longitudinally studied pediatric cohort. PLoS One. 2020;15(1):e0228092.

Brain Regions Adversely Affected by Air Pollution



These renderings obtained from brain imaging of 12-year-old children show regions in red, orange and yellow that are most affected by traffic related air pollution (TRAP). The darker the color, the stronger the effect.

Hearing Study May Change the Standard Audiogram

David Moore, PhD

Lina Motlagh Zadeh, PhD

PUBLISHED NOVEMBER 2019

Proceedings of the National Academy of Sciences

The inability to understand speech in a noisy setting is one of the first signs of age-related hearing loss. A study of 116 adults with "normal hearing" has discovered a possible reason for their self-reported difficulty understanding speech in noisy environments.

Around 60% of the listeners were less than 30 years old, yet more than half of these 20-somethings had at least some impaired extended high frequency (EHF) hearing and 34% reported difficulty following a conversation in background noise.

David Moore, PhD, Director of the Communication Sciences Research Center, points out that EHF hearing, beyond the range routinely tested in hearing clinics, contributes to speech recognition.

"The most important clinical implication of this study is by using EHF audiometry, we may be able to detect in childhood who is going to have the most common form of hearing loss later in life and take steps to prevent that from happening," says Moore.

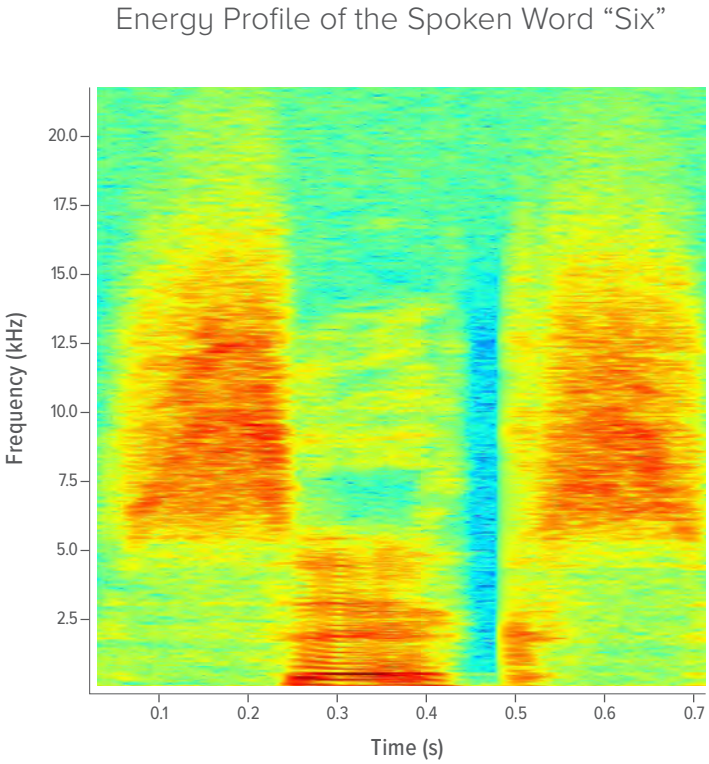
Lead author Lina Motlagh Zadeh, PhD, earned her doctorate degree based on this study. Since then, follow-up papers have called for EHF measurement to be incorporated into the standard hearing test. Another team member, Lisa Hunter, PhD, FAAA, Scientific Director of Research in the Division of Audiology, has received an NIH R01 grant that includes study of EHF as a possible biomarker for antibiotic-induced hearing loss in children with cystic fibrosis. That research will be conducted with colleagues in the Divisions of Pulmonary Medicine and Clinical Pharmacology.

Moore's team is developing a smartphone app that can serve as an EHF-sensitive home hearing test. The technology also can support automated and remote fitting of hearing aids particularly in low- and middle-income countries.

RESEARCH & TRAINING DETAILS

Faculty	6
Joint Appointment Faculty	10
Research Fellows & Post Docs	2
Research Graduate Students	10
Total Annual Grant Awards	$1.6M

Motlagh Zadeh L, Silbert NH, Sternasty K, Swanepoel W, Hunter LL, Moore DR. Extended high-frequency hearing enhances speech perception in noise. Proc Natl Acad Sci U S A. 2019;116(47):23753-23759.



The “sound spectrogram,” or energy profile, across time of the spoken digit “six,” shows that much of the sound energy (in red) of fricative consonants (such as “s” and “x”) is above the 8 kHz limit of audiometry. A healthy young person with good hearing can hear up to 20 kHz. Without the energy between 8-20 kHz, distinguishing between “six” and “sis” would be difficult.

Serious Lung Complication in sJIA Linked to Biologics

Grant Schulert, MD

PUBLISHED OCT. 29, 2019
Arthritis & Rheumatology

For thousands of children living with systemic juvenile idiopathic arthritis (sJIA), a class of medications known as "biologics" have produced dramatic, life-changing improvements.

Now, however, experts at Cincinnati Children's have documented 18 cases of a rare and potentially fatal lung complication that they call "systemic JIA-associated lung disease" or (sJIA-LD).

The children experiencing the lung problems tended to be less than 2 years old when their sJIA was diagnosed. Their use of biologics often failed to push their disease into remission, and eight of the 18 experienced adverse reactions to the medications. Importantly, 80% of the children with lung disease also had a past brush with macrophage activation syndrome (MAS), another dangerous complication of sJIA.

The 18 children identified here have been added to a national collection that exceeds 100 cases. The good news, early identification and aggressive supportive care appears to sharply reduce the risk of dying from this condition.

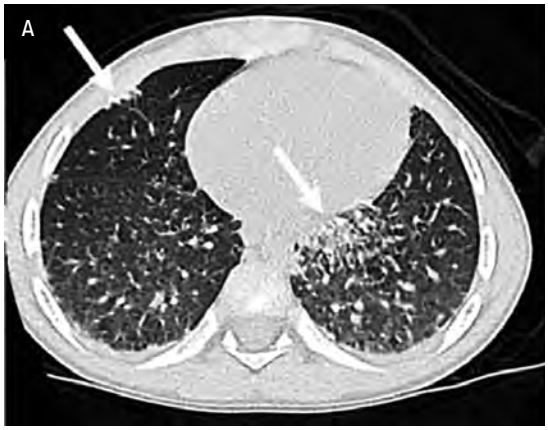
"The doctors taking care of these patients need to be more aware of this complication and have a very high index of suspicion for it," says lead author Grant Schulert, MD, PhD. "Similarly, parents and families of these patients need to be talking to their doctors about this lung disease and making sure that their doctors are screening for it."

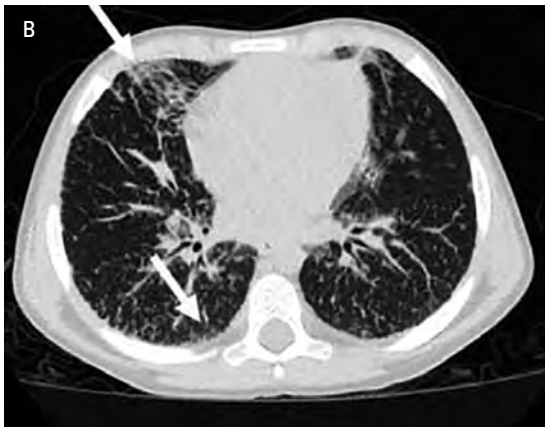
Schulert and colleagues are continuing to study the complication and plan to identify a more-refined set of symptoms for doctors and families to watch for.

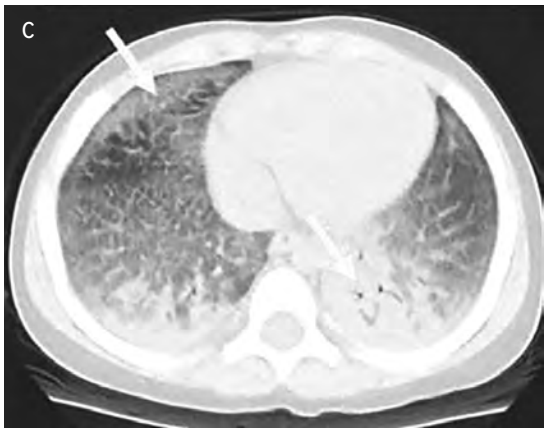
RESEARCH & TRAINING DETAILS

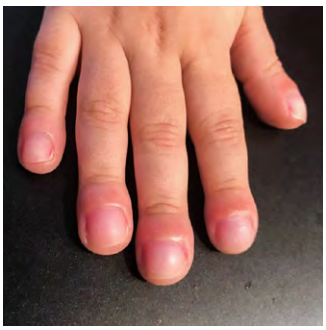
Faculty	12
Joint Appointment Faculty	2
Total Annual Grant Awards	$1.8M
Total Annual Industry Awards	$657,986

Schulert GS, Yasin S, Carey B, Chalk C, Do T, Schapiro AH, Husami A, Watts A, Brunner HI, Huggins J, Mellins ED, Morgan EM, Ting T, Trapnell BC, Wikenheiser-Brokamp KA, Towe C, Grom AA. Systemic Juvenile Idiopathic Arthritis-Associated Lung Disease: Characterization and Risk Factors. Arthritis Rheumatol. 2019;71(11):1943-1954.









Above Vikram Boutele, age 7, was diagnosed with sJIA shortly after his first birthday. His family moved from San Francisco to Cincinnati to receive care from rheumatology experts at Cincinnati Children's

Below "Clubbing" is an unusual form of inflammation that can occur at the fingertips of children affected by systemic JIA-associated lung disease.

Left From top to bottom these CT scans show increasing levels of severity for children with systemic JIA who experience a rare lung complication. Experts at Cincinnati Children's are urging families and doctors who see these patients to be vigilant about early symptoms of lung malfunction. Early intervention may prevent the most severe effects.

Big Data Techniques Help Identify Best Strategies for Improving Sport-Relevant Skills

Christopher DiCesare, PhD

Gregory Myer, PhD

PUBLISHED MAY 2020

Medicine & Science in Sports & Exercise

A unique analysis of biomechanical data sheds light on the connection between organized coordination patterns involved in sport-relevant movements, the anatomical structures that support them, and the task-relevant factors that influence and constrain an athlete's ability to perform.

Based on 15 years of 3D motion analysis of whole-body movement data collected from adolescent athletes performing the drop vertical jump (DVJ), researchers in the Division of Sports Medicine found that only a few successful DVJ coordination strategies—each with their own distinct performance outcomes—are possible. Lead researcher Christopher DiCesare, PhD, and Gregory Myer, PhD, Director of Research, say the findings broaden the understanding of movement patterns and risks.

"This approach can simplify the screening process and allow for easier interpretation of the underlying mechanisms that contribute to injury risk," DiCesare says. "If we know that better strategies exist for athletes than are observed when we screen them, we can develop biofeedback and neuromuscular training strategies that will allow them to optimize sport performance while simultaneously reducing injury risk." Data were aggregated from previous studies of 780 adolescent athletes, most of them females. Drop, land, and jump tasks involved three specific movement profiles; a similar analysis of the single leg drop landing produced its own distinct, task-specific profiles.

The biggest challenge was controlling for the vast amount of "noisy" biomechanical data due to the inherent variability in human movement, according to Myer.

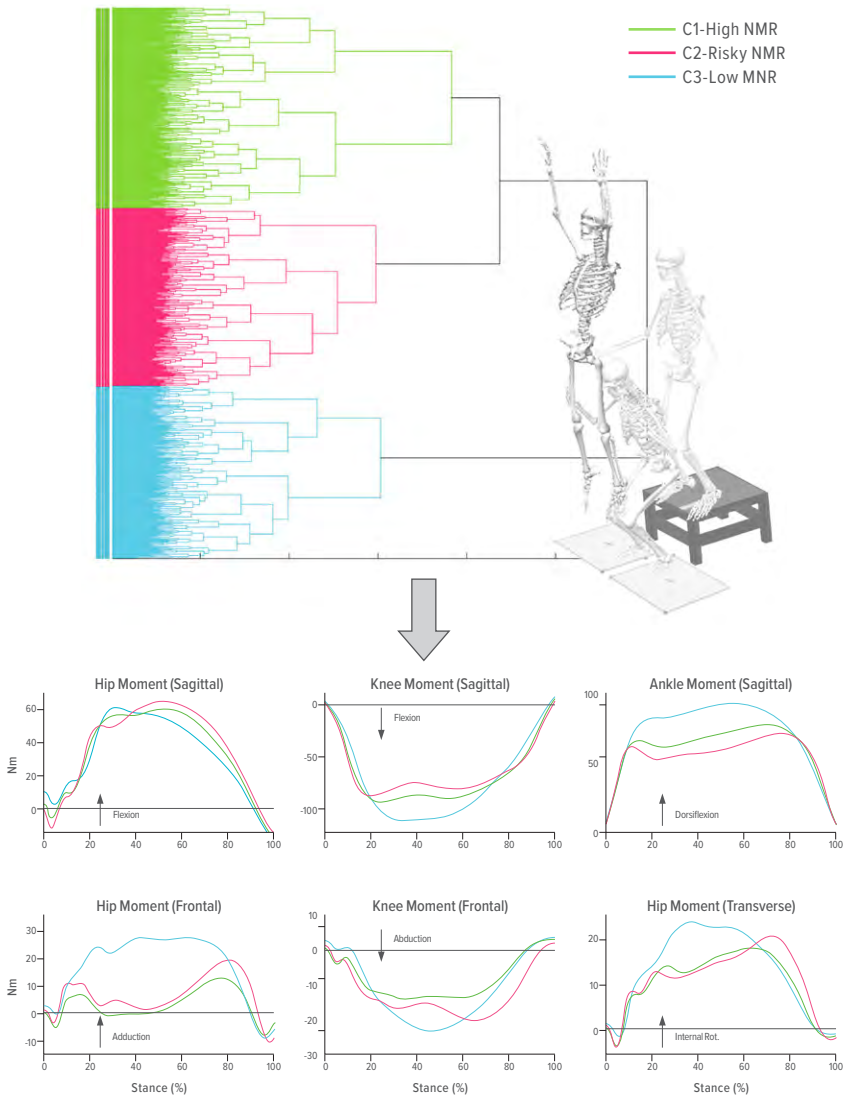
"Large-scale data science has not been as prevalent with the biomechanical/human movement science community," he says. "It was challenging to apply these techniques and interpret the results without points of reference in the current literature. The advanced analytic approach employed by Dr. DiCesare can help us identify and treat undesirable movement patterns in the future."

RESEARCH & TRAINING DETAILS

Faculty	7
Joint Appointment Faculty	1
Research Fellows & Post Docs	3
Total Annual Grant Awards	$1.3M
Total Annual Industry Awards	$220,250

Dicesare CA, Minai AA, Riley MA, Ford KR, Hewett TE, Myer GD. Distinct Coordination Strategies Associated with the Drop Vertical Jump Task. Med Sci Sports Exerc. 2020;52(5):1088-1098.

Profiling Sport-Relevant Movements



Clustering of biomechanical data exhibited by adolescent athletes produced three distinct, persistent biomechanical profiles, each with its own performance outcomes and injury risk stratification.

Multi-Center Study Explores Long-Term Outcomes for Classic Bladder Exstrophy

Andrew Strine, MD

PUBLISHED DECEMBER 2019
The Journal of Urology

Parents of children born with bladder exstrophy, an abnormality in which the bladder and penis are open and exposed on the outside of the abdomen at birth, face many questions about long-term impact on kidney function, urinary continence, sexual function, fertility, quality of life, and transitional care to adulthood.

A multi-center study of 216 patients born with exstrophy between 1980-2016 provides insights into the long-term management of the bladder after its initial closure. Many patients require timed voiding, pelvic floor muscle retraining, medications, and/or clean intermittent catheterization to empty the bladder at regular intervals throughout the day to achieve urinary continence. Some patients ultimately require additional surgery, such as bladder augmentation or diversion. Augmentation uses the patient's own gastrointestinal tissues to increase the size of the bladder; diversion re-routes urine into a reservoir or an ostomy bag.

"This was the first study to assess the long-term outcomes for a large cohort of patients with classic bladder exstrophy, and it demonstrated the importance and feasibility of multi-center collaboration on rare diseases," says Andrew Strine, MD, Co-Director of the Comprehensive Fertility Care and Preservation Program at Cincinnati Children's. "These findings are particularly useful in counseling patients and families."

The probability of bladder augmentation or diversion after closure was 14.9% by age 5 years, 50.7% by 10 years and 70.1% by 18 years. Among all patients, 67.4% performed intermittent catheterization at last follow-up.

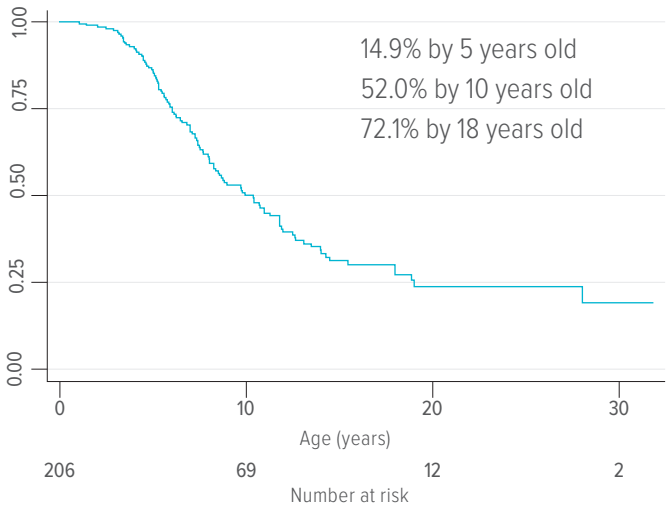
The study was chosen as the best clinical abstract at the 2017 Pediatric Urology Fall Conference in Montreal. Data also were presented at the 2018 International Exstrophy Conference. Now the team is working on a follow-up study to describe the prevalence of chronic kidney disease and renal failure in patients with classic bladder exstrophy.

RESEARCH & TRAINING DETAILS

Faculty	6
Joint Appointment Faculty	1
Research Fellows & Post Docs	1
Total Annual Grant Awards	$602,343

Szymanski KM, Fuchs M, McLeod D, Rosoklija I, Strine AC, VanderBrink B, Whittam B, Yerkes E, Gargollo PC, Pediatric Urology Midwest A. Probability of Bladder Augmentation, Diversion and Clean Intermittent Catheterization in Classic Bladder Exstrophy: A 36-Year, Multi-Institutional, Retrospective Cohort Study. J Urol. 2019;202(6):1256-1262.

Need for Additional Surgery in Bladder Extrophy



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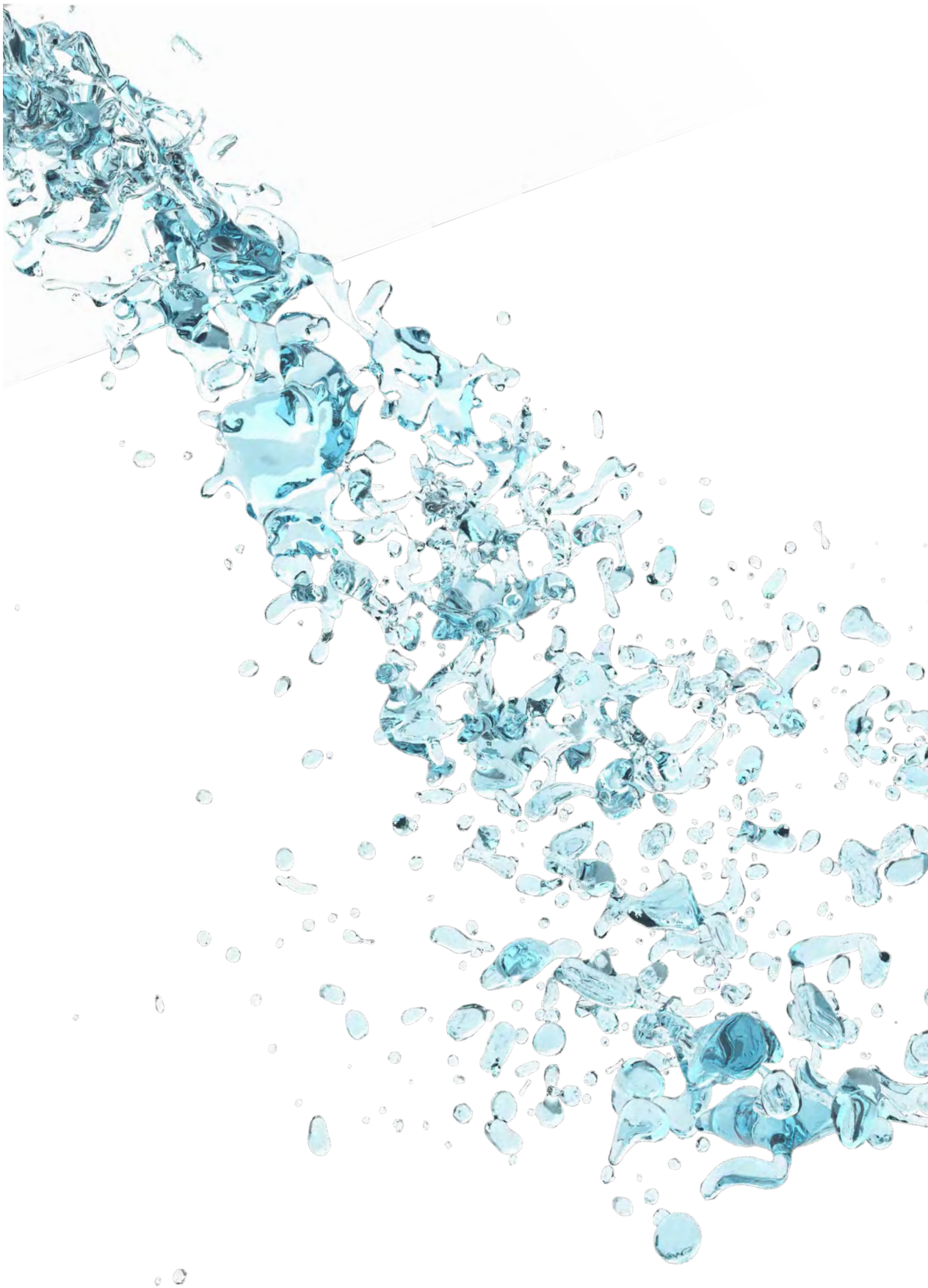
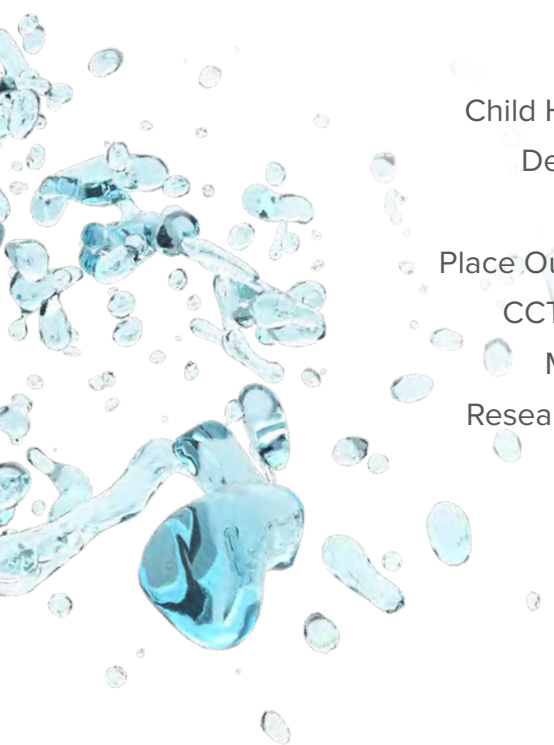


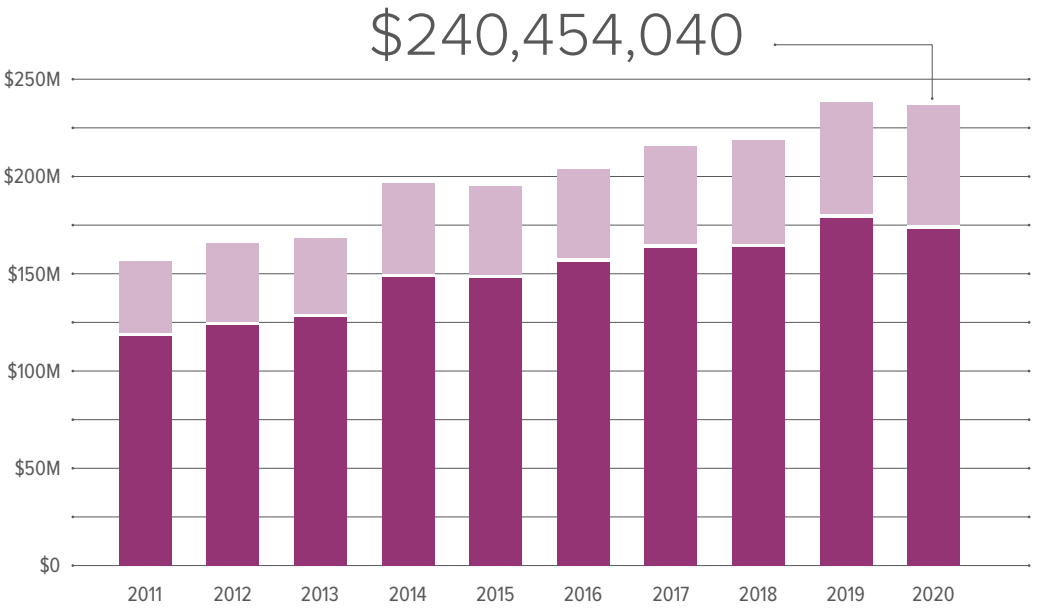
By the Numbers

EXTERNAL AND INTERNAL FUNDING & AWARDS
FACULTY, FELLOWS, AND STAFF

Sponsored Program Awards
National Institutes of Health Awards
Sources of External Funding
Sources of Federal Funding
State & Other Funding Sources
Philanthropic Gifts for Research
Trustee Awards
Fifth Third/Charlotte R. Schmidlapp
Woman Scholars
Procter Scholars
Child Health Research Career
Development Awards
Strauss Fellows
Place Outcome Research Awards
CCTST Program Awards
Medical Residents
Research Graduate Programs

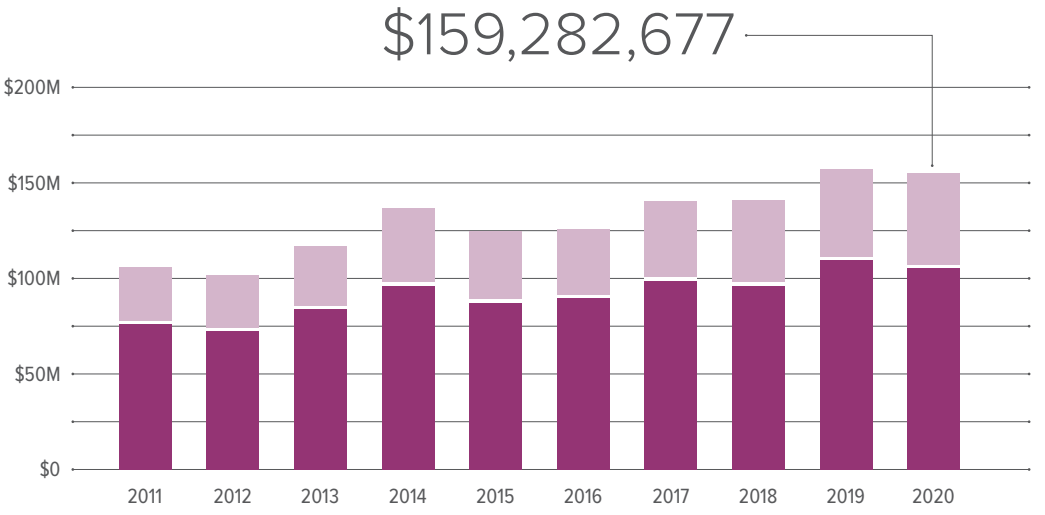


Sponsored Program Awards



Sponsored program award figures include funding awarded for direct and indirect costs, but exclude fee-for-service contracts.

National Institutes of Health Awards

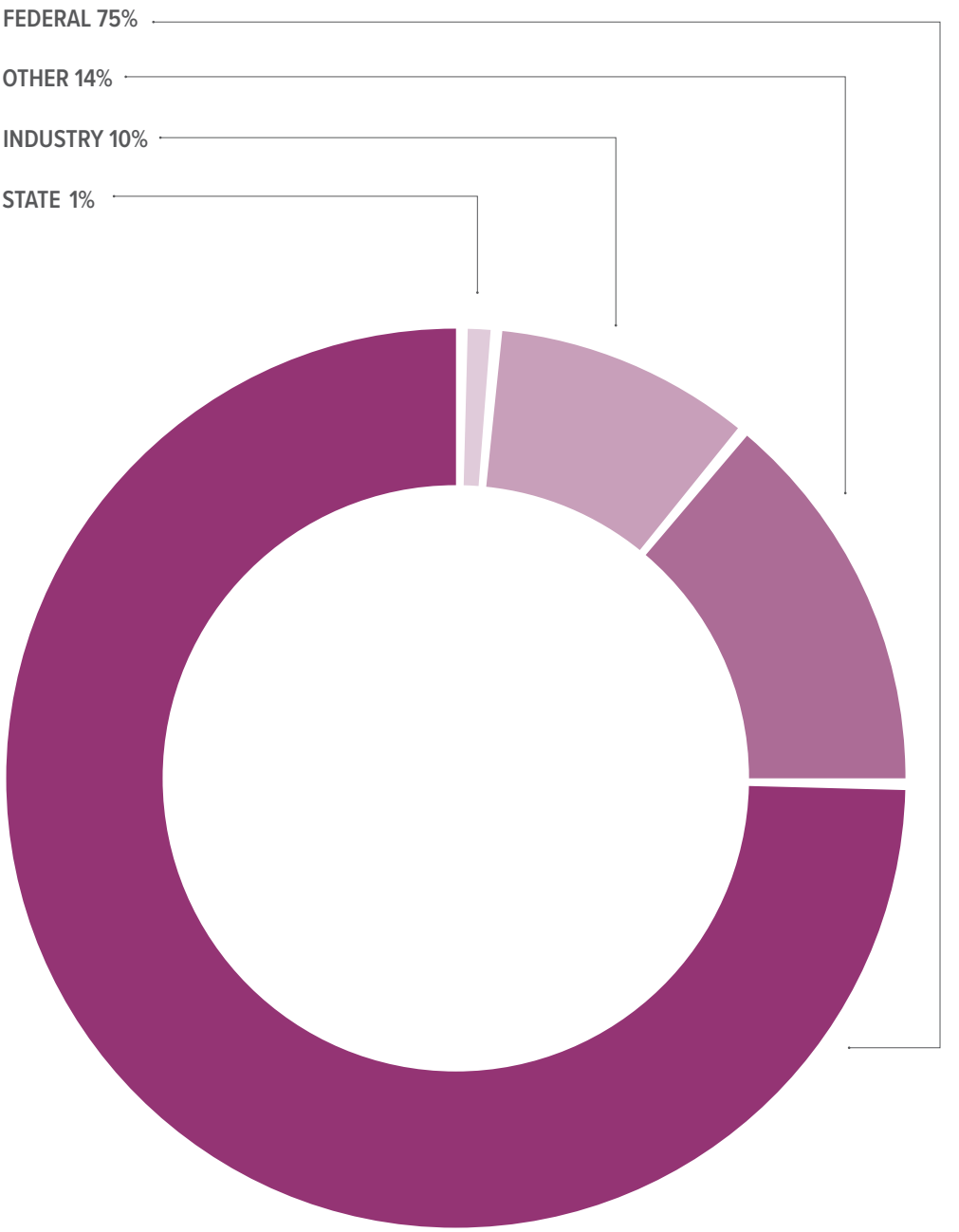


Indirect Funds

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



Sources of Federal Funding

National Institutes of Health (NIH)	$159,282,677
Center for Disease Control and Prevention	$4,457,745
Health Resources & Services Admin	$4,071,330
Department of Defense	$2,547,268
Agency for Healthcare Research and Quality	$1,613,526
Center for Medicare/Medicaid Services	$1,426,053
Administration for Community Living	$1,305,543
Department of Justice	$1,134,997
US Department of Education	$901,147
Department of Health and Human Services	$763,625
Federal Communications Commission	$719,098
Food and Drug Administration	$690,988
Department of Defense Army	$669,803
Department of Veteran Affairs	$319,652
National Science Foundation	$303,558
US Department of Energy	$185,200
Substance Abuse & Mental Hlth Svc Admin	$50,000
US Department of Agriculture	$45,607
Maternal & Child Health Bureau	$40,000
US Depart of Housing & Urban Development	$33,919
TOTAL	**$180,561,736**

State & Other Funding Sources

Patient-Centered Outcome Research Institute
$7,248,239

Cystic Fibrosis Foundation
$5,585,659

The Cure Starts Now Foundation
$2,139,492

ImproveCareNow, Inc.
$1,602,243

American Heart Association - National
$1,538,797

Ohio Department of Health
$1,402,905

PATH Vaccine Solutions
$1,025,025

March of Dimes National
$1,000,000

The Leona M & Harry B Helmsley Charitable Trust
$980,948

Stand Up to Cancer
$886,941

Other State and Non-Profit Organizations
$10,976,421

TOTAL
$34,386,670

Philanthropic Gifts for Research

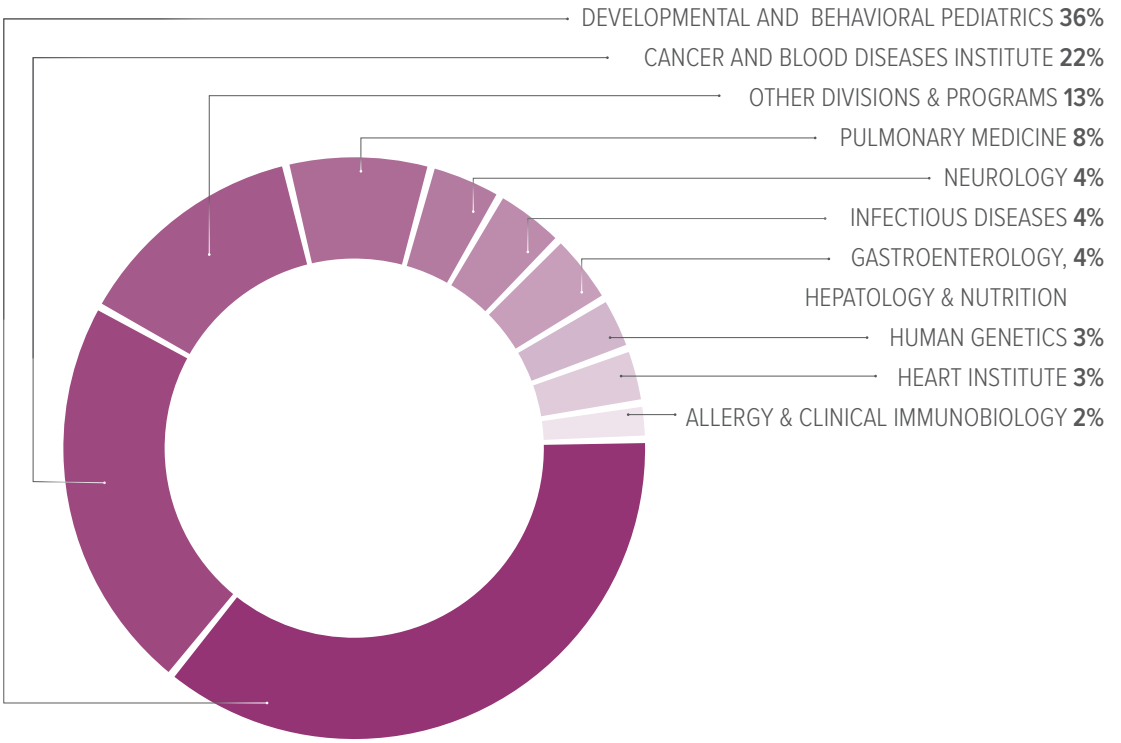
Our commitment to improving care for children through the application of research discovery is the backbone of Cincinnati Children's. And as a nonprofit hospital and research center, private donors play an important role in this work.

OF THE $85.8 MILLION RAISED THROUGH PHILANTHROPY IN 2020, 31% 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.

$26,315,524 million

DONATED TO RESEARCH IN 2020



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.

Paritha Arumugam, PhD
Neonatology & Pulmonary Biology

Yueh-Chiang Hu, PhD
Developmental Biology

Yizhao Ni, PhD
BMI

Rachelle Ramsey, PhD
Behavioral Medicine & Clinical Psychology

Lili He, PhD
Neonatology & Pulmonary Biology

Massashi Yamaji, PhD
Reproductive Sciences

Marina Lopez Sola, PhD
Anesthesiology

Natoshia Cunningham, PhD
Behavioral Medicine & Clinical Psychology

Alonzo Folger, PhD
Division of Epidemiology and Biostatistics

Makiko Iwafuchi, PhD
Developmental Biology

Yaping Lu, PhD
Human Genetics

Laura Walkup, PhD
Pulmonary Medicine

Juan Sanchez Gurmaches, PhD
Endocrinology

Hee Woong Lim, PhD
BMI

Kelli VanDussen, PhD
Gastroenterology

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.

Vidya Chidambaran, MD
Anesthesia

Elisa Boscolo, PhD
Experimental Hematology and Cancer Biology

Procter Scholars

This program supports faculty members from the Departments of Pediatrics, Surgery, Radiology, Patient Services, and Anesthesia who are pursuing academic research careers

Akihiro Asai, MD, PhD
Gastroenterology

Nathan Evanson, MD, PhD
Anesthesia

Elizabeth Kramer, MD, PhD
Pulmonary Medicine

Ravindra Arya, MD, DM
Neurology

Nicole Weaver, MD
Human Genetics

Daniel Swarr, MD
Neonatology/Pulmonary Bio

Matthew Alder, MD, PhD
Critical Care

Francis Real, MD, Med
Gen Peds

Omar Niss, MD
CBDI/Hematology

Child Health Research Career Development Awards

This program provides $93,000 grants to support training physician-scientists to stimulate pediatric research across a variety of disciplines.

Michael Sherenian, MD
Asthma Research

Anna Peters, Instructor
Gastroenterology, Hepatology & Nutrition

Meredith Schuh, MD
Nephrology and Hypertension

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.

Nicholas Szugye, MD
Cardiology

Allison Ta, MD
Gastroenterology, Hepatology & Nutrition

Timothy Wang, MD
Neonatology & Pulmonary Biology

Daniel Peck, MD
Cardiology

Kristina Prus, MD
Hematology/Oncology

Liang Hu, PhD
EHCB/CBDI

Yuting Tang, PhD
Cancer Pathology

Nicole Edwards, PhD
Developmental Biology

Sandra Schrenk, PhD
EHCB/CBDI

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 FY2019 are:

Meera Kotagal, MD, MPH
General and Community Pediatrics

Patrick Brady, MD, MSc
Hospital Medicine and Anderson Center

Sarah Corathers, MD
Endocrinology

Mark Paterno, PT, PhD, MBA, SCS, ATC
Sports Medicine

Ellen Lipstein, MD, MPH
Anderson Center

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). These faculty 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.

Matthew Alder MD, PhD
Critical Care

Sheila Angeles-Han, MD, MSc
Rheumatology

Fukun Guo, PhD
Experimental Hematology, Cancer Biology

Kotagiri Nalinikanth, MD, PhD
Pharmacy

Xiaoting Zhang, PhD
Cancer Biology

Ming Tan, PhD
Infectious Diseases

Nicolas Nassar, PhD
Cancer & Blood Diseases Institute

Takahisa Nakamura, PhD
Endocrinology

Christina Gross, PhD
Neurology

Xiaoyang Qi, PhD
Hematology Oncology

Eric Hall, PhD
Biomedical Informatics

Sarah Beal, PhD
Behavioral Medicine and Clinical Psychology

Bin Huang, PhD
Biostatistics and Epidemiology

Tzu-Yu (Danny) Wu, PhD, MSI
Biomedical Informatics

Dylan Steen, MD, MS
Cardiovascular Health and Disease

David Fleck, PhD, MA, BA
Psychiatry and Behavioral Neuroscience

Brett Harnett, MS
Biomedical Informatics

Todd Kelley, MD
Orthopedic Surgery

Cole Brokamp, PhD
Biostatistics and Epidemiology

Maya Dewan, MD, MPH
Critical Care

Karen Burkett, PhD
Patient Services - Nursing

RESIDENTS **267**

Research Graduate Programs

Biomedical Informatics	Immunology Program	MSTP Program	BRT Graduate Program - MS	MDB Graduate Program - PhD
45 Students (21 PhD/24 GC)	45 Students (33 PhD/12 MS)	70 Students	14 Students	57 Students

Our Faculty

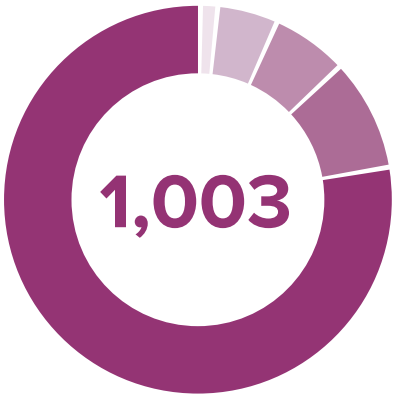
PEDIATRICS
785 total [735 full time / 50 part time]

SURGERY
95 total [86 full time / 9 part time]

ANESTHESIA
63 total [44 full time / 19 part time]

RADIOLOGY
50 total [41 Full time / 9 part time]

PATIENT SERVICES
10 total [8 Full time / 2 part time]



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Science News

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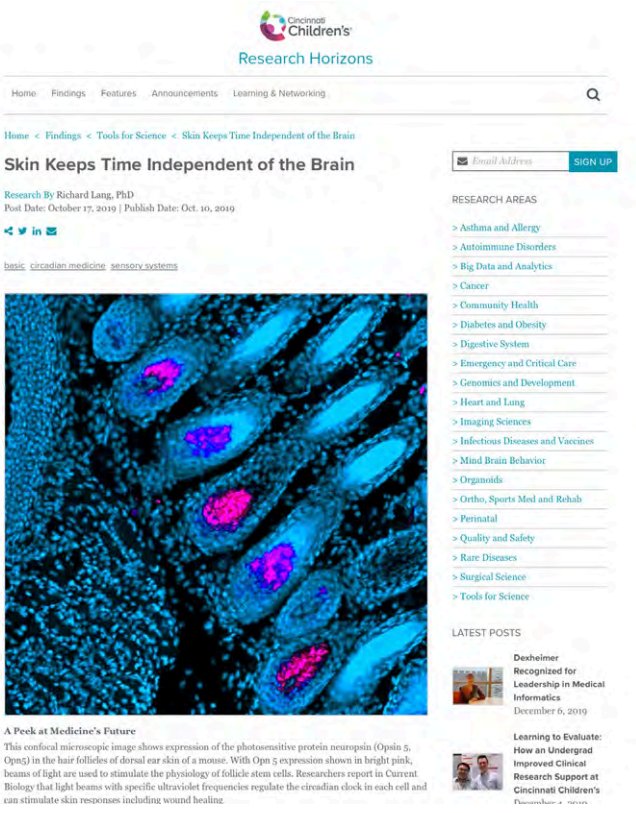

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