Cincinnati Children's™
Research Foundation

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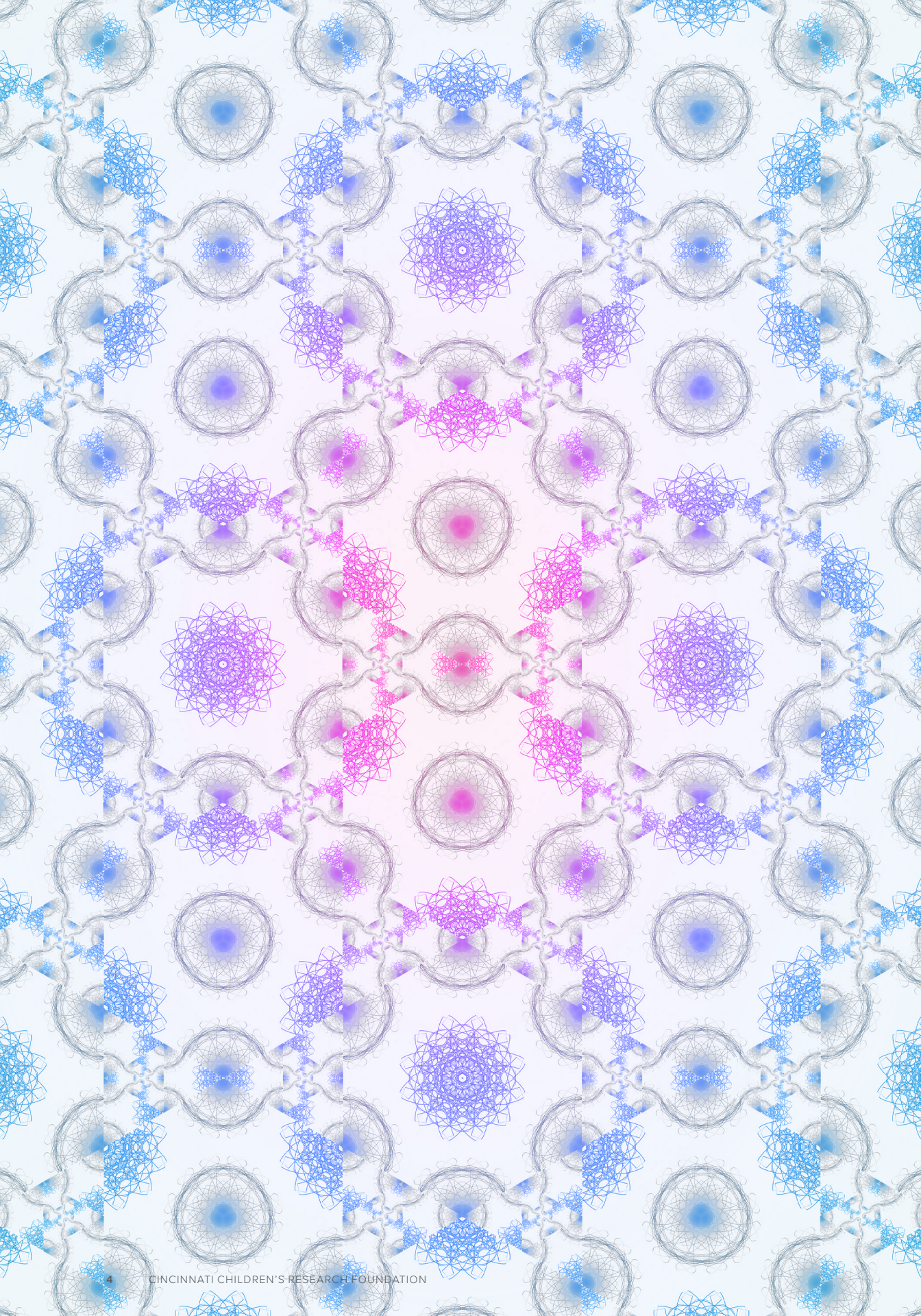
ABOUT THE COVER
With each turn of the kaleidoscope comes a unique vision of light, reflection, and wonderment. With each translational intersection of research and clinical medicine comes a unique vision of inspiration, innovation, and discovery.
by Reed DeWinter

2022

Division Summaries
Scientific Achievements

Indicates Top Breakthrough in 2022



Dear colleagues,

On behalf of the Cincinnati Children's Research Foundation, I am delighted to share our fiscal 2022 Research Annual Report—a celebration of our accomplishments as we chart our path for the future, not just for Cincinnati Children's but also for children.

We have much to be proud of from this past year. As one of the leading pediatric research institutions in the nation, our accomplishments in science, innovation and discovery continue to truly change outcomes for children. Health care providers, here and around the world, are using treatments, cures, medications and more that were created, tested, taught and proven at Cincinnati Children's.

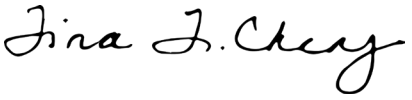
The six most significant achievements featured in this year's report reflect the wide spectrum of research performed here—from basic, preclinical, and clinical research to clinical implementation and public health. Investigators here collaborated to produce the most complex stomach organoid to date, worked with colleagues in Uganda to improve outcomes for children with rheumatic heart disease, revealed the untapped potential of antibodies produced during pregnancy, advanced our understanding of muscular dystrophy, uncovered a rapid immune reaction system that may transform allergy treatment for many, and demonstrated that adult cardiovascular risks can be detected—and potentially reduced—during childhood.

These discoveries and all the advances featured here reflect the dedication of our exceptionally talented faculty, lab teams and research collaborators, who actively push discoveries forward to improve child health, each and every day. Our people and our culture of collaboration are some of the greatest keys to our success.

As a result of our research performance, we consistently rank as one of the top three pediatric departments in the country for extramural support. This year, I am pleased to report that we have set a new all-time record, totaling more than $277 million dollars awarded from extramural grants and contracts.

This past year, we also finalized our new five-year strategic plan for research, which outlines how we will realize our shared vision of transforming child health through discovery, innovation and the translation of new knowledge into improved care. This plan serves as our research-specific blueprint for accelerating our work to prevent, cure or radically improve outcomes for individuals, populations and communities.

The work to implement this plan has already begun. This next year will be a time of action and execution, as we aspire to transform child health and well-being, accelerate discovery, and enrich the environment for research. I look forward to what we can achieve, together.



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

‘Super’ Antibody Discovery Opens Doors for New Vaccines, Therapies

PUBLISHED JUNE 2022
Nature

Scientists discovered years ago that newborn infants depend upon immune components transferred from their mothers to survive the onslaught of pathogens that begin invading their bodies as soon as they are born. Eventually, children develop their own immune systems, built through surviving natural exposures to viruses and bacteria, and augmented by a phalanx of well-established childhood vaccines. But in the meantime, it's one of a mother's most important gifts that keeps their babies safe: antibodies.

Now, a far-reaching study published June 8, 2022, in *Nature*, provides a surprising explanation of how those early days of mother-provided immunity actually work—and what that information could mean for preventing death and disability from a wide range of infectious diseases. The findings suggest that researchers may be able to mimic the amped-up antibodies that expecting mothers produce to create new drugs to treat diseases as well as improved vaccines to prevent them.

"For many years, scientists believed that antibodies cannot get inside cells. They don't have the necessary machinery. And so, infections caused by pathogens that live exclusively inside cells were thought to be invisible to antibody-based therapies," says Sing Sing Way, MD, PhD, Division of Infectious Diseases at Cincinnati Children's. "Our findings show that pregnancy changes the structure of certain sugars attached to the antibodies, which allows them to protect babies from infection by a much wider range of pathogens."

"The maternal-infant dyad is so special. It's the intimate connection between a mother and her baby," says John Erickson, MD, PhD, Division of Neonatology, and first author of the study. Both Way and Erickson are part of Cincinnati Children's Center for Inflammation and Tolerance and the Perinatal Institute, which strives to improve outcomes for all pregnant women and their newborns.

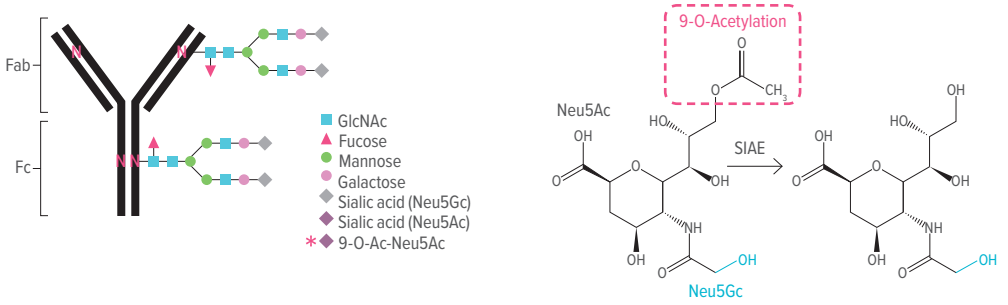
Erickson continues, "This special connection starts when babies are in the womb and continues after birth. I love seeing the closeness between mothers and their babies in our newborn care units. This discovery paves the way for pioneering new therapies that can specifically target infections in pregnant mothers and newborns babies. I believe these findings also will have far-reaching implications for antibody-based therapies in other fields."

STUDY ADDRESSES A 'SILENT EPIDEMIC'

While COVID-19 has reminded the world of the scale of a pandemic, infections from various pathogens combine to kill 2 to 3 million infants and mothers a year worldwide, Way says.

FROM LEFT Tzu-yu Jenny Shao, PhD, Hilary Miller-Handley, MD, Ashley Severance-Masello, PhD, Yuehong Wu, Research Asst., John Erickson, MD, PhD, (lead author), Sing Sing Way, MD, PhD (senior author), Jeanette Miller, PhD, Andrew Herr, PhD.

Making Super Antibodies



This schematic illustrates fetal acquisition of maternal antibodies. New research shows antibodies undergo protective conversion during pregnancy through deacetylation of sialic acid residues, which unmasks natural ligands for immune regulatory receptors, expanding the ways that antibodies protect against infection. These results will help scientists produce more powerful antibodies to treat a variety of conditions, according to a study from experts at Cincinnati Children's published June 8, 2022, in *Nature*.

This study explored, in mice, the interactions between antibodies and *Listeria monocytogenes*, a common bacterium that replicates primarily within cells. Pregnant women are 10 times more likely than women in general to become infected by *Listeria*. Severe infections can lead to miscarriages, stillbirths, preterm labor, and serious illness or death in newborns.

For years, scientists believed the bacteria was unreachable by antibodies. But the Cincinnati Children's team showed that during pregnancy, *Listeria* can be targeted by antibodies. Way says the scientific world tends to focus on non-pregnant states during pre-clinical studies, and generally avoids conducting clinical drug research involving pregnant women. This can mean that biological changes that affect the immune system during pregnancy also can be overlooked.

"If we had not approached this with the goal of understanding the maternal-fetal dyad, we would not have found this unique naturally occurring shift in antibody structure," Way says.

HOW MOTHERS MAKE SUPER ANTIBODIES

The new study identifies which specific sugar is changed during pregnancy, as well as how and when the change occurs. During pregnancy, the "acetylated" form of sialic acid (one of the sugars attached to antibodies) shifts to the "deacetylated" form. This very subtle molecular change allows immunoglobulin G (IgG)—the body's most common type of antibody—to take on an expanded protective role by stimulating immunity through receptors that respond specifically to deacetylated sugars.

"This change is the light switch that allows maternal antibodies to protect babies against infection inside cells," Way says.

"Mothers always seem to know best," Erickson adds. The findings impressed Louis Muglia, MD, PhD, former director of Human Genetics at Cincinnati Children's, now president and CEO of the Burroughs Wellcome Fund, which provided support for this study.

"The Burroughs Wellcome Fund prioritizes research funding in reproductive sciences that has the potential to transform our understanding of pregnancy health. Drs. Way and Erickson reveal novel immunological changes that occur during pregnancy that optimize antimicrobial host defense during these developmental windows of vulnerability," Muglia says.

REVVED-UP ANTIBODIES CAN BE PRODUCED IN THE LAB

Using advanced mass spectrometry techniques and other methods, the research team pinned down the key biochemical differences between antibodies in virgin mice compared to pregnant ones. They

also identified the enzyme naturally expressed during pregnancy responsible for driving this transformation.

Further, the team successfully restored lost immune protection by supplying lab-grown supplies of the antibodies from healthy pregnant mice to pups born to mothers that were gene-edited to lack the ability to remove acetylation from antibodies to enhance protection. Hundreds of monoclonal antibodies have been produced as potential treatments for various disorders including cancer, asthma, multiple sclerosis, as well as hard-to-shake viral and bacterial infections—including new treatments rapidly developed for COVID-19. Some are already FDA approved, many more are in clinical trials, and some have failed to show strong results.

Way says the molecular alteration of antibodies that naturally occurs during pregnancy can be replicated to change how antibodies stimulate the immune system to fine-tune their effects. This potentially could lead to improved treatments for infections caused by other intracellular pathogens including HIV, herpes, and respiratory syncytial virus (RSV), a common virus that poses serious risks to infants.

ANOTHER REASON TO ACCELERATE VACCINE DEVELOPMENT

Since the paper was published, the work has been presented at the 2022 Howard Hughes Medical Institute Microbes and Host Response Meeting and at the 2022 NIH & FDA Glycoscience Research Day, held June 13, 2022.

RESEARCH & TRAINING DETAILS	Division of Infectious Diseases	Division of Perinatal Institute
Faculty	21	61
Joint Appointment Faculty	0	1
Research Fellows & Post Docs	3	3
Research Graduate Students	13	12
Total Annual Grant Awards	$21.9M	$15.5M
Total Annual Industry Awards	$752,450	$1.3M

The research team is investigating how the findings may apply to immunity against other prenatal pathogens, and how acetylation controls immunity in a variety of other immunological contexts including transplantation, pregnancy, and autoimmunity. Ultimately, it may take 20 years of further research to follow the multiple trails opened by this discovery, Erickson says. But some potential impacts could be realized much sooner.

"We've known for years the many far-reaching benefits of breastfeeding," Erickson says. "One major factor is the transfer of antibodies in breastmilk."

The study shows that the molecular switch persists in nursing mothers so that antibodies with enhanced protective scope are also transferred to babies through breastmilk. Additionally, Way says the findings underscore the importance of receiving all available vaccines for women of reproductive age—as well as the need for researchers to develop even more vaccines against infections that are especially prominent in women during pregnancy or in newborn babies.

"The immunity needs to exist within the mother for it to be transferred to her child," Way says. "Without natural exposures or immunity primed by vaccination, when that light switch flips during pregnancy, there's no electricity behind it."

ABOUT THE STUDY A patent on antibody sialic acid modification has been filed by Cincinnati Children's with first author Erickson and senior author Way as inventors (PCT/US2022/018847). In addition to Erickson and Way, the study in *Nature* was co-authored by nine researchers at Cincinnati Children's and the University of Cincinnati: Alexander Yarawsky, BS, Jeanette Miller, PhD, Tzu-Yu Shao, BS, Ashley Severance, PhD, Hilary Miller-Handley, MD, Yuehong Wu, MS, Giang Pham, PhD, Yueh-Chiang Hu, PhD, and Andrew Herr, PhD. Contributors also included experts from the University of Georgia, the Ohio State University, Cornell University, and Roswell Park Comprehensive Cancer Center in Buffalo.

Erickson JJ, Archer-Hartmann S, Yarawsky AE, Miller JLC, Seveau S, Shao TY, Severance AL, Miller-Handley H, Wu Y, Pham G, Wasik BR, Parrish CR, Hu YC, Lau JTY, Azadi P, Herr AB, Way SS. Pregnancy enables antibody protection against intracellular infection. Nature. 2022 Jun;606(7915):769-775. doi: 10.1038/s41586-022-04816-9. Epub 2022 Jun 8. PMID: 35676476; PMCID: PMC9233044.

Novel Approach Generates Most Complex Stomach, Esophagus Organoids to Date

PUBLISHED JANUARY 2022
Cell Stem Cell

In a significant step forward in regenerative medicine, scientists at Cincinnati Children's report success at developing a stomach organoid so sophisticated that it has distinct glands and nerve cells that can control smooth muscle contractions.

The achievement demonstrates that separate layers and portions of complex organs can be grown from separate lines of human pluripotent stem cells (PSCs) and be combined for continued development. Importantly, the approach used to produce these multi-layered stomach organoids also can be used to make more-complex versions of other lab-grown organs.

"This advance in tissue engineering is important because we can now assemble complex organ tissues from separately derived components, similar to an assembly line approach," says corresponding author James Wells, PhD.

Co-authors from Cincinnati Children's include lead author Alexandra Eicher, PhD, Daniel Kechele, PhD, Nambirajan Sundaram, PhD, H. Matthew Berns, DO, Holly Poling, BS, Lauren Haines, BS, J. Guillermo Sanchez, BS, Mansa Krishnamurthy, MD, MSc, Lu Han, PhD, Michael Helmrath, MD, and Aaron Zorn, PhD. Keishi Kishimoto, PhD, from the RIKEN Center for Biosystems Dynamics Research in Japan also was a co-author.

"This advance in tissue engineering is important because we can now assemble complex organ tissues from separately derived components, similar to an assembly line approach."

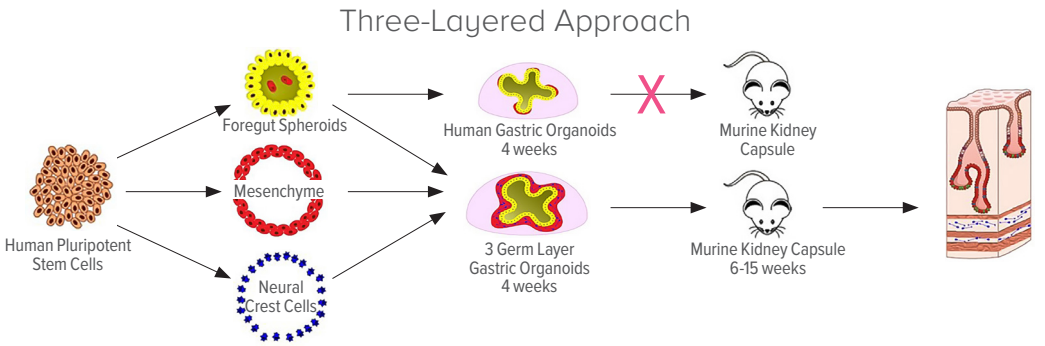
— James Wells, PhD

LAYER-BY-LAYER ASSEMBLY

Most organoids made so far can form 3D structures involving multiple cell types. In a lab dish, these tiny organs perform real functions that provide new opportunities to study diseases and develop cures. But they typically lack one or more cell types needed to produce a full-sized functional organ, such as nerve fibers, internal blood vessels, immune cells, and other critical ducts and glands. This new stomach organoid does not yet have every cell type it needs, but it represents a leap forward.

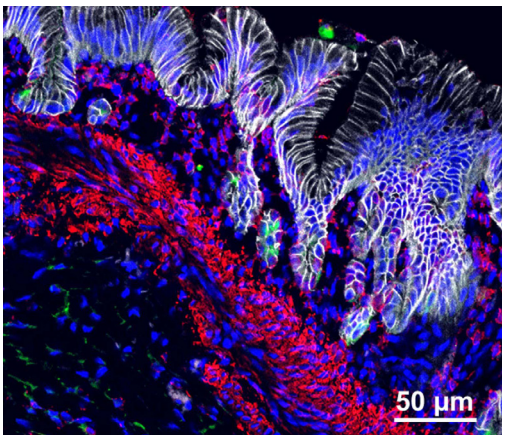
"We started with cells from the three primary germ layers—enteric neuroglial, mesenchymal, and epithelial precursors—all separately derived from PSCs," Eicher says. "From these we gen-

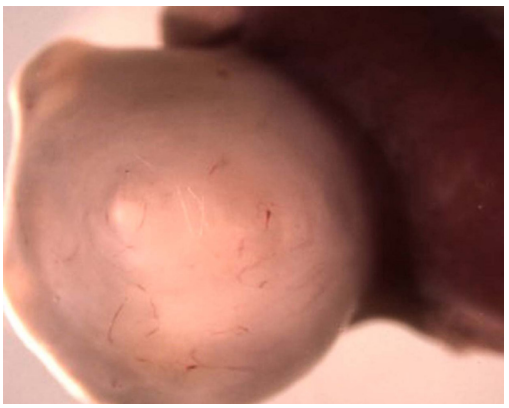
FROM LEFT Holly Poling, BS, Daniel Kechele, PhD, H. Matthew Berns, DO, J. Guillermo Sanchez, BS, Jim Wells, PhD, Aaron Zorn, PhD, Keishi Kishimoto, PhD, Nambirajan Sundaram, PhD, and Michael Helmrath, MD



erated stomach tissue that contained acid-producing glands, surrounded by layers of smooth muscle containing functional enteric neurons that controlled contractions of the engineered antral stomach tissue."

Importantly, the development of these mini human stomachs was not limited to a thin layer of medium in a lab dish. Once the organoids reached a critical stage (at about 30 days) the team performed microsurgery to transplant the organoids into a mouse, which provided the blood flow and biological space to allow much more growth.





The variety of colors in this confocal microscope image (top) illustrate the complexity of cell types in new stomach organoids. (Below) Instead of dot-sized spheres, implanting organoids in mice allowed 1,000x growth.

Instead of spheres of cells that look like dots in a dish, these organoids grew a thousand-fold in volume inside the mice to form tissues plainly visible to the naked eye. When viewed under a confocal microscope, with different cell types stained to glow in different colors, these organoids radiate a rainbow of complexity.

In fact, the lab-grown tissue closely resembles naturally grown human tissue at similar stages of development. This includes developing a Brunner's gland, which secretes an alkaline mucus that protects the duodenum from the acidity of stomach contents. The team also discovered that all these cell types and components are needed to generate true stomach tissue because each component helps guide the proper formation of the other components. For example, the authors found that if they did not add the nerves during the assembly process, the stomach glands and muscle tissue did not form properly. Beyond the stomach, the research team also demonstrated a similar approach for developing more sophisticated esophageal organoids.

IMMEDIATE AND LONG-TERM POTENTIAL

At a minimum, these more-complex organoids will serve as useful tools for studying genetic variations and other cell signaling dysfunctions that contribute to gastric diseases. They also will serve as improved platforms for evaluating potential treatments. But there may be even wider-scale impact from these findings.

"Given that this technology is broadly translatable to other organs, it is possible that engineered tissue might be a source of material for reconstructing elements of the upper GI tract that are damaged by congenital disorders or acute injuries," Wells says. While much works remains to develop organoid tissue that would be suitable for transplantation, much progress also has been made.

LEADER IN REGENERATIVE MEDICINE

Cincinnati Children's has played a leading role in organoid research since 2010 when Wells and colleagues published findings in *Nature* reporting their first success at developing functional intestinal tissue. In 2019, the medical center launched its Center for Stem Cell and Organoid Medicine (CuSTOM) to further accelerate the work. Over the years, the growing team has:

- Added nerves to intestinal organoid tissue
- Demonstrated how to mass-produce liver "buds"
- Produced liver organoids for specific disease states
- Grown both major portions of the stomach
- Developed functional esophagus tissue
- Grown a three-organoid system (liver, pancreas, bile ducts)

INVESTING IN CURES

The Helmrath lab at Cincinnati Children's is working with 35 other labs in 15 divisions at Cincinnati Children's to expand organoid development for use in human transplantation.

This line of research is funded in large part through a $10 million grant from Cincinnati Children's awarded as part of the medical center's Pursuing Our Potential Together initiative. Support also has come from the Farmer Family Foundation, which helped launch the CuSTOM Accelerator Lab.

More grants, gifts, and investments are needed because growing organoids for clinical purposes requires that the entire process meets Good Manufacturing Practice (GMP) regulations established by the U.S. Food and Drug Administration to assure consistency and safety. That means, for example, the research team needs to find and validate replacements for certain materials used to grow organoids because those materials do not fully meet GMP standards.

"Thanks to all the support we have received so far we have taken several steps needed to scale up production of therapeutic quality organoid tissues. We still have work to do," Wells says. "Our goal is to achieve transplantation into patients by the end of the decade."

ABOUT THE STUDY This research was supported by several grants from the NIH: U18 EB021780 (JMW, MAH), U19 AI116491 (JMW), P01 HD093363 (JMW), UG3 DK119982 (JMW), U01 DK103117 (MAH), 1F31DK118823-01 (AKE), NIEHS 5T32-ES007250-29 (DOK), the Shipley Foundation (JMW), and the Allen Foundation (JMW). This study also received support from the Digestive Disease Research Center (P30 DK078392).

RESEARCH & TRAINING DETAILS	Division of Developmental Biology	Division of Pediatric General & Thoracic Surgery	Division of Perinatal Institute
Faculty	24	21	61
Joint Appointment Faculty	25	4	1
Research Fellows & Post Docs	33	5	3
Research Graduate Students	19	--	12
Total Annual Grant Awards	$14.5M	$3.5M	$15.5M
Total Annual Industry Awards	--	$842,065	$1.3M

Eicher AK, Kechele DO, Sundaram N, Berns HM, Poling HM, Haines LE, Sanchez JG, Kishimoto K, Krishnamurthy M, Han L, Zorn AM, Helmrath MA, Wells JM. Functional human gastrointestinal organoids can be engineered from three primary germ layers derived separately from pluripotent stem cells. Cell Stem Cell. 2022 Jan 6;29(1):36-51.e6. doi: 10.1016/j.stem.2021.10.010. Epub 2021 Dec 1. PMID: 34856121; PMCID: PMC8741755.

In Uganda, Rheumatic Heart Disease Research Reaches its GOAL

PUBLISHED JANUARY 2022
New England Journal of Medicine

The study was dubbed "Gwoko Adunu pa Lutino" (GOAL), meaning "protect the heart of a child."

Its findings addressed a surprisingly common yet under-researched condition that poses serious long-term risks: rheumatic heart disease.

"The GOAL trial is a stunning example of global collaboration, including investigators from six continents working together to find innovative solutions to reduce the global burden of rheumatic heart disease," says principal investigator Andrea Beaton, MD.

Rheumatic heart disease is a chronic valvular heart disease caused by rheumatic fever, which develops after an untreated case of strep throat. More than 40.5 million people globally are estimated to be living with rheumatic heart disease, and approximately 306,000 deaths are attributed to it annually.


Andrea Beaton, MD

In the U.S., rheumatic fever and rheumatic heart disease were leading killers of children and young adults in the early 1900s. But widespread use of penicillin after World War II stopped the deaths, and now most cases of strep throat are treated long before serious complications arise.

But in low-resource settings, 85% of children with rheumatic heart disease are diagnosed only after the disease has become well-advanced. This makes medications ineffective and surgical intervention (typically heart valve replacement) less likely to succeed if available at all.

"Imagine people in their 20s coming into the hospital because they've had a stroke," says Emmy Okello, MD, chief of cardiology at the Uganda Heart Institute and co-principal investigator of the GOAL trial. "These cases start in childhood, but the sore throats and fevers get missed. The healthcare system is looking for malaria, tuberculosis and HIV."

Now, the public health system has evidence that a widely available and highly affordable treatment can change the life course for affected children: penicillin.

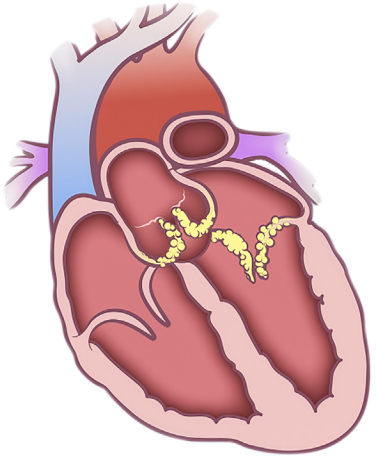
PREVENTION TRIAL SHOWS PROMISING RESULTS

The GOAL trial was conducted in Northern Uganda from July 2018 through October 2020 and involved 818 children ages 5-17 years with latent rheumatic heart disease. The participants either received penicillin injections every four weeks for two years, or no treatment. All participants underwent echocardiography screening at the start and end of the trial.

Detailed results were published Nov. 13, 2021, in the *New England Journal of Medicine*. Beaton and co-authors reported that just three participants (0.8%) who received penicillin experienced latent rheumatic heart disease progression after two years, compared to 33 (8.3%) who didn't receive the treatment. Prior to this study, it was unknown if antibiotics were effective at preventing the progression of latent rheumatic heart disease.

The prevention results are important because people across Uganda with latent rheumatic heart

Rheumatic Heart Disease



Top: Map showing GOAL study locations in Uganda. Middle: While children were treated near their homes, analyzing study data involved international collaboration. Bottom: How rheumatic fever can damage the heart.

disease who develop irreversible valve damage have little or no access to valve surgery, Okello says.

Importantly, unlike many other pathogens that have developed resistance to older antibiotics, penicillin remains effective against *Group A strep* bacteria.

GLOBAL COLLABORATION MAKES IMPACT

Beaton and Okello collaborated with scientists from more than a dozen institutions based in nations including the U.S., Uganda, Australia, India, Mozambique, France, South Africa, and Brazil to conduct the study.

"This was the first contemporary randomized controlled trial in rheumatic heart disease," Beaton says. "The results are incredibly important on their own, but also demonstrate that high-quality clinical trials are feasible to address this neglected cardiovascular disease."

NEXT CHALLENGE: BUILDING A SCREENING SYSTEM

While penicillin itself is low-cost, much more work is needed in Uganda and other low-resource nations to make echocardiogram screenings more accessible for children. Hurdles include setting up clinics, addressing transportation issues, and overcoming a limited public understanding of the disease.

However, establishing improved screening programs will likely be more affordable than the infrastructure required to provide heart valve replacement surgery, Beaton notes. While partners in Uganda work to find infrastructure funding, Beaton will lead a five-year follow-up study called "GOAL Post." It remains unclear how long monthly injections should continue, especially once a person's heart appears to return to normal.

"That study will look at the durability of prophylaxis in preventing adverse outcomes as well as determining whether it is safe for children to stop antibiotic prophylaxis once their heart returns to normal," Beaton says.

The team has received NIH funding for a related project called "ADUNU"—which means "heart" in Luo—that will support developing and

Ugandan children participating in the GOAL rheumatic fever study.

evaluating district-wide programs, including active case finding with echocardiography and registry-based care using a mobile platform developed at Cincinnati Children's. The team also has applied for funding for a study to evaluate the use of oral vs. injected penicillin, which may be more practical in low-resource settings.

While the research focused on Uganda, the findings have implications across sub-Saharan Africa and beyond. "Anywhere there's poverty, or fractured healthcare systems, or poor access to primary healthcare, you can find rheumatic heart disease," Beaton says.

ABOUT THE STUDY The inspiration for this research dates back more than a decade to when Beaton and Okello were cardiology fellows at Children's National Hospital in Washington, DC. "I was really lucky to get plugged into the Uganda Heart Institute team. Once I got to go over there, I saw first-hand the enormous need, so we worked together to develop this research program," Beaton says.

Funding sources for this study included the Thrasher Research Fund, Gift of Life International, Children's National Hospital Foundation, the Elias–Ginsburg Family, Wiley Rein, Philips Foundation, AT&T Foundation, Heart Healers International, the Karp Family Foundation, Huron Philanthropies, and the Cincinnati Children's Heart Institute Research Core.

Also contributing to the study were researchers from the University of Cincinnati College of Medicine; Makerere University, Uganda; Children's National Hospital, Washington, DC; The Royal Children's Hospital, Melbourne; Telethon Kids Institute, Western Australia; Virginia Tech Carilion School of Medicine; Université de Paris; Instituto Nacional de Saude, Mozambique; Universidade Federal de Minas Gerais, Brazil; Emory University School of Medicine, Atlanta; Starship Children's Hospital, Auckland; Geisel School of Medicine, New Hampshire; Red Cross Children's Hospital, South Africa; and the All-India Institute of Medical Sciences.

RESEARCH & TRAINING DETAILS	Division of Cardiology
Faculty	57
Joint Appointment Faculty	5
Total Annual Grant Awards	$5.1M
Total Annual Industry Awards	$1.2M

Beaton A, Okello E, Rwebembera J, Grobler A, Engelman D, Alepere J, Canales L, Carapetis J, DeWyer A, Lwabi P, Mirabel M, Mocumbi AO, Murali M, Nakitto M, Ndagire E, Nunes MCP, Omara IO, Sarnacki R, Scheel A, Wilson N, Zimmerman M, Zühlke L, Karthikeyan G, Sable CA, Steer AC. Secondary Antibiotic Prophylaxis for Latent Rheumatic Heart Disease. N Engl J Med. 2022 Jan 20;386(3):230-240. doi: 10.1056/NEJMoa2102074. Epub 2021 Nov 13. PMID: 34767321.

Two-Hit Model of Muscular Dystrophy May Redirect Hunt for Cures

PUBLISHED MAY 2022
Nature Communications

Scientists discovered in 1986 that common muscular dystrophies (MDs) could be traced to specific mutations of a single gene: *dystrophin (DMD)*. Dramatic breakthroughs in curative treatment seemed just around the corner.

Slow scroll forward three decades.

It took until 2016 for the first in a class of "exon-skipping" treatments of the *DMD* gene to win FDA approval (eteplirsen). Since then, three more similar-acting drugs have been approved (golodirsen, viltolarsen, and casimersen). The drugs are predicted to help slow disease progression for up to 30% of people with muscular dystrophies. They are not considered cures, according to CureDuchenne.org.

Now, a study led by experts at Cincinnati Children's sheds light on why the hunt for cures has been so sluggish. The findings were so surprising to peer reviewers that it took three years for the paper to move from preprint to final publication in *Nature Communications*.

"The MDs as a group are most typically associated with genetic mutations in genes that underlie some aspect of plasma membrane support, repair, or the activity of select channels and signaling components within the membrane," writes lead author Justin Boyer, PhD. "Our results suggest that these underlying genetic defects that comprise the MDs only represent the first 'hit' in a 'two-hit' model, with the second hit being that of additional destabilization associated with induction of the myogenic fetal gene program due to new satellite cell (muscle stem cells) activity and myoblast fusion."

In essence, the research team found yet another double-edged sword amid the workings of the human genome—this one involving the mechanisms of muscle tissue healing. The discovery came about in an unexpected fashion.

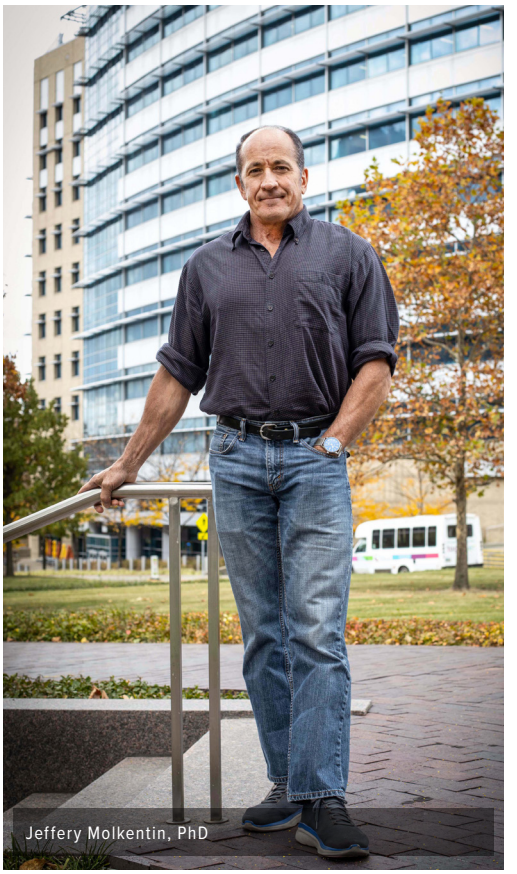
Initially, the team was examining the opposite hypothesis, mainly that greater induction of muscle stem cells would protect from MD by causing more regeneration. However, inducing greater stem cell activity and the attempts at repair further destabilized the myofiber plasma membrane, which synergized with the loss of dystrophin.

Attempts at repair further destabilized the myofiber plasma membrane, which synergized with the loss of dystrophin.

WHEN GOOD SATELLITE CELLS CAUSE HARM

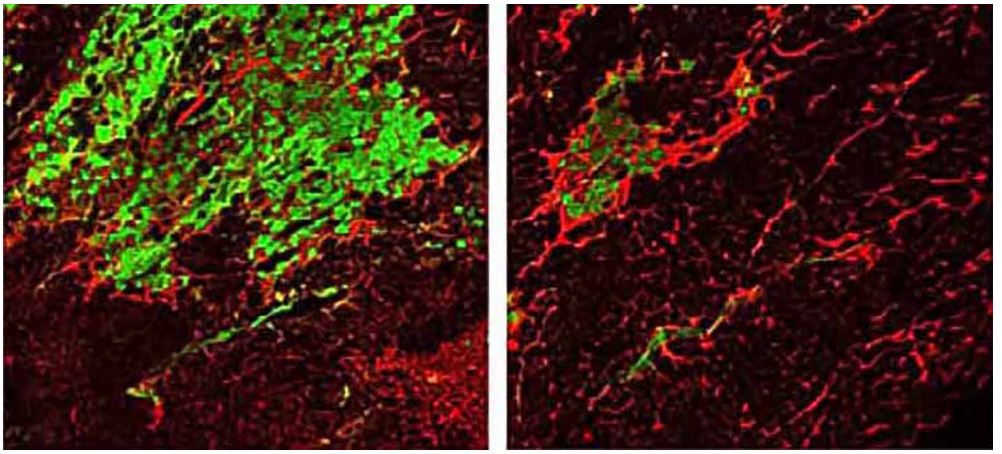
The MDs are genetic disorders that share progressive muscle deterioration and weakness as distinguishing symptoms.

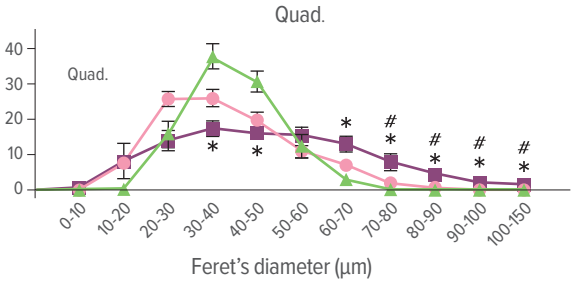
In general, the most common form of MD, Duchenne MD, is diagnosed between ages 3 and 5 and the deterioration worsens over time. This form of MD occurs in about one of every 3,600 male births worldwide. It affects males because the *dystrophin* gene is on the X chromosome.



Jeffery Molkentin, PhD

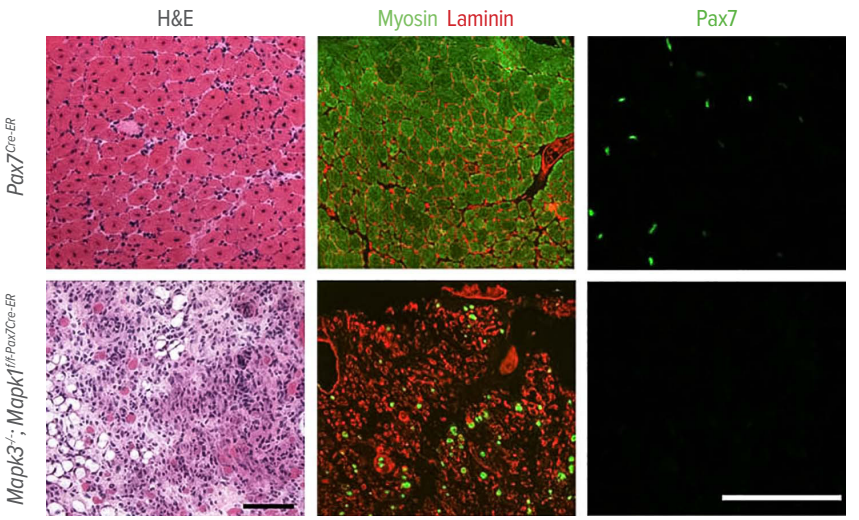
Turning Off an Unwanted Repair Process





Top: Quad muscle samples show immunoglobulin M (IgM) (green) and laminin (red) in mice of the indicated genotypes
Left: Tracking feret's diameter of muscle fibers shows that satellite cell ablation mitigates disease severity.

Erk1/2 Required for Satellite Cell Viability



TA muscle sections stained with H&E (left panels), anti-myosin antibody (MF-20, green) and anti-laminin antibody (red, middle panels) or with anti-Pax7 antibody (green, right panels) 10 days post-CTX injury. Scale bars= 100 μm

For most people, muscle injury healing is spurred along by muscle satellite cells that function to regenerate the tissue. But for people with MD, this study shows that satellite cells actually contribute to muscle wasting.

Boyer and colleagues determined that this natural repair program, whereby newly activated satellite cells fuse into existing damaged myofibers, requires weakening of the plasma membrane, which when coupled with the loss of dystrophin, causes MD. That's the two-hit hypothesis.

IN MICE, UNWANTED REPAIR PROCESS CAN BE TURNED OFF

"By depleting satellite cells and their induction of the MyoD-dependent fetal gene program in myofibers using either of two separate genetic approaches in two different mouse models of MD, we demonstrate an overwhelming effect on myofiber plasma membrane stability," the co-authors state.

The paper details how the team depleted satellite cell populations in mouse muscle tissue, and how that produced the initially unexpected result of slowing muscle wasting in mice with MD mutations.

"However, a therapeutic approach aimed at depleting satellite cells in MD patients would be ill-advised at this point in time," says senior author Jeffery Molkentin, PhD, director, Division of Molecular Cardiovascular Biology at Cincinnati Children's. "But this does not mean that a valuable future treatment is beyond imagination. First, more research is needed to define the most critical molecular effectors of these disease processes, such as new ways of preventing myofiber plasma membrane instability."

Molkentin presented data from the study in July 2021 at the New Directions in Biology and Disease of Skeletal Muscle Conference held in Charleston, SC. Since the findings were published in May 2022, the paper has been accessed online more than 4,700 times.

ABOUT THE STUDY In addition to Boyer and Molkentin, co-authors from Cincinnati Children's and the University of Cincinnati include graduate student Jiuzhou Huo, medical student Sarah Han, MD/PhD student Julian Havens, Vikram Prasad, PhD, Brian Lin, PhD, Taejeong Song, PhD, and Sakthivel Sadayappan, PhD, MBA. The study also included collaborators from Johns Hopkins, the University of Maryland, and Myologica LLC. Funding sources included grants from the National Institutes of Health and a Developmental Award from the Muscular Dystrophy Association.


Lead author Justin Boyer, PhD

RESEARCH & TRAINING DETAILS	Division of Molecular Cardiovascular Biology
Faculty	10
Research Fellows & Post Docs	12
Research Graduate Students	3
Total Annual Grant Awards	$9.0M
Total Annual Industry Awards	$11,574

Boyer JG, Huo J, Han S, Havens JR, Prasad V, Lin BL, Kass DA, Song T, Sadayappan S, Khairallah RJ, Ward CW, Molkentin JD. Depletion of skeletal muscle satellite cells attenuates pathology in muscular dystrophy. Nat Commun. 2022 May 26;13(1):2940. doi: 10.1038/s41467-022-30619-7. PMID: 35618700; PMCID: PMC9135721.

Targeting RipIL-33 Pathway Could Transform Allergy Treatment

PUBLISHED OCTOBER 2021
Nature Immunology

Despite many years of research and the development of a number of medications intended to help control common allergies, only some people find consistent relief from the sudden inflammation of airways, the itchy eyes and other symptoms when they encounter the allergens plaguing them.

Millions of people have allergies because so many aspects of our environment can trigger reactions, be it ragweed, mold, pet dander, insects, tree pollen and more. Yet medications that help one form of allergy often do not help against another, in large part because the precise molecular mechanisms that drive immune response to allergens have remained elusive.

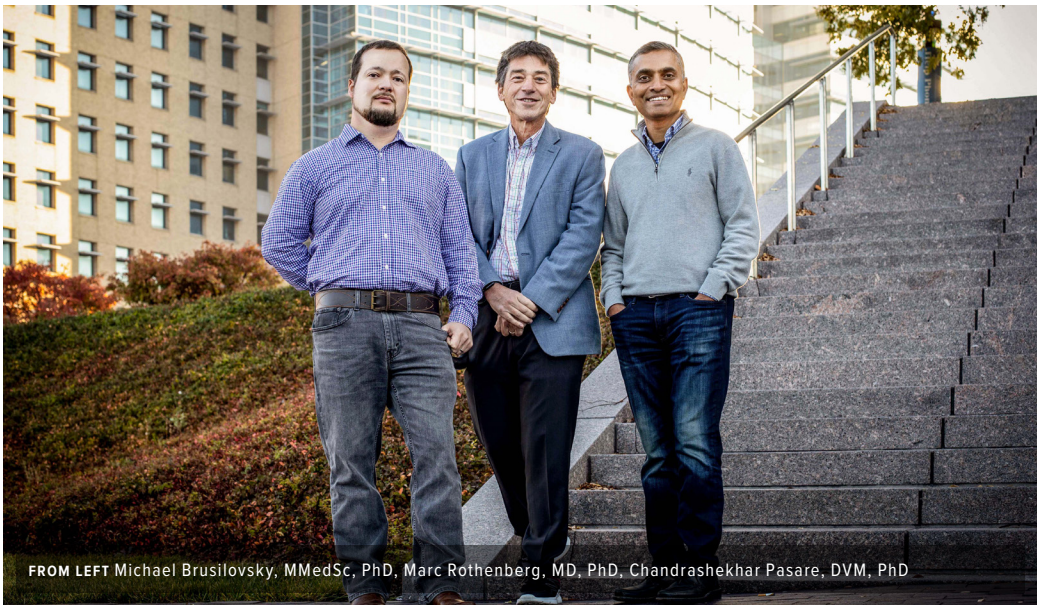
Now, the discovery of a built-in rapid reaction system that triggers inflammatory responses when people are exposed to a large set of common allergens may open the door to dramatically improved treatments. The findings focus on the responses to allergens from insects, mites and fungi, which turn out to differ significantly from allergic responses to plant pollens or food.

The study, led by Cincinnati Children's scientists Michael Brusilovsky, MMedSc, PhD, Chandrashekhar Pasare, DVM, PhD, and Marc Rothenberg, MD, PhD, reveals unexpected new details about how the type 2 innate immune response system works.

> "The discovery of this mechanism is the most important breakthrough in understanding how the innate immune system senses allergens— a question that has puzzled immunologists for a long time."
>
> — Chandrashekhar Pasare, DVM, PhD

Among the many experiments involved, the team compared responses at a molecular level to several types of allergy-inducing exposures. This work included exposing mice to substances including house dust mite, *A. fumigatus*, cat dander, canary feathers, cockroach, birch pollen, Bermuda grass, peanut, whole wheat, and cow milk extracts.

Ultimately, the team determined that a common biological response platform kicks in to rapidly release inflammation-causing IL-13 in response to allergens from cockroaches, mites and fungi—but not to food allergens or plant pollens.



FROM LEFT Michael Brusilovsky, MMedSc, PhD, Marc Rothenberg, MD, PhD, Chandrashekhar Pasare, DVM, PhD

Top: How common allergens activate the RipIL-33 response pathway. Bottom: Ribbon diagram demonstrates that IL-33 processed via the RipIL-33 pathway is biologically active and binds its cognate receptor ST2.

"Disrupting this allergen-sensing pathway could provide a unique opportunity to counteract type 2 immunity and alleviate allergic inflammation," Rothenberg says.

In theory, any new medication that proves capable of controlling this response pathway could benefit people suffering from a wide range of allergies.

FAR-REACHING IMPLICATIONS

The findings impressed other experts in immune response, who co-authored a commentary in *Cellular & Molecular Immunology* about the work.

"The authors elegantly describe how epithelial cells contribute to the onset of allergic airway inflammation by activating the ripoptosome, which subsequently drives the maturation and secretion of IL-33," states the editorial written by Jutta Horejs-Höck, PhD, University of Salzburg, and colleagues Theresa Neuper and Richard Weiss.

"First, the authors showed that allergens derived from a wide range of organisms, including fungi, cockroaches and mites, but not pollen or food allergens, induce intracellular maturation and subsequent secretion of IL-33 by epithelial cells," they continue. "This was a completely unexpected finding because maturation of IL-33 induced by allergens was believed to be an exclusively extracellular event mediated by allergen proteases."

Other Cincinnati Children's researchers on the study include Mark Rochman, PhD, Yrina Rochman, PhD, Julie Caldwell, PhD, Lydia Mack, MS, Jennifer Felton, PhD, Jeff Habel, PhD, and Alexey Porollo, PhD.

Previous research had established that multiple allergens can induce a similar IL-33 response upon breaching the epithelial layer of mucosal membranes. The Cincinnati Children's team pinned down the mechanisms at work in the process.

"This breakthrough was made possible by new insights into the role of ripoptosome signaling and caspases in allergic inflammation," says Brusilovsky.

Specifically, the allergens trigger activity among an interlocked set of cell death-inducing signals called the ripoptosome. This signaling "platform" includes numerous components, but for allergic inflammatory reactions, the key player

appears to be a molecular switch called caspase 8. The investigators named the pathway, "RipIL-33" because IL-33 is processed (ripped) by the ripoptosome.

Connecting the dots to common allergy response between the ripoptosome and IL-33 was especially important, the researchers say. This is because released IL-33 elicits innate type 2 responses and amplifies responses in both atopic and non-atopic forms of allergic inflammation.

In the last two decades, immunologists have discovered mechanisms by which bacteria and viruses are sensed by the innate immune system, but how allergens are sensed has remained a mystery.

"The discovery of this mechanism is the most important breakthrough in understanding how the innate immune system senses allergens—a question that has puzzled immunologists for a long time," says Pasare.

EARLY PROGRESS IN TREATMENT

The Cincinnati Children's team used its experience at treating a variety of allergies to look for a method to control the rapid-response sensing system. In mouse models they found that inhibiting the activity of caspase 8 reduced the IL-33 response to allergen exposure and limited bronchial inflammation in the lungs.

Importantly, the paper shows that a similar response pathway occurs in humans. "In the human allergic disease eosinophilic esophagitis, we found that ripoptosome activation markers and mature IL-33 levels dynamically correlated with the degree of esophageal eosinophilia and disease activity," the study states.

In the mouse studies, the most powerful effects were noted when using Q-VD-OPh, a broad-spectrum and irreversible "pan-inhibitor" of caspase 8. However, even though this inhibitor has been used for years in lab studies, it is not considered a safe candidate for human use.

SINCE PUBLICATION

Now, members of the research team are working to further confirm the mechanisms of the RipIL-33 pathway in human allergic reaction. They also are looking for existing drugs, or a new compound, that can safely disrupt the inflammation cycle.

Rothenberg, director of the Division of Allergy and Immunology, has an extensive research portfolio that includes numerous advances in the study and treatment of eosinophilic disorders.

In recognition of his contributions to the field, Rothenberg was honored in October 2022 with election to the National Academy of Medicine.

ABOUT THE STUDY Funding sources for this study included the National Institutes of Health (R37 AI045898, R01 AI123176, R01 AI113125 and R01 CA231303); the Campaign Urging Research for Eosinophilic Disease (CURED); and the Sunshine Charitable Foundation and its supporters, Denise and David Bunning.

RESEARCH & TRAINING DETAILS	Division of Allergy & Immunology
Faculty	14
Joint Appointment Faculty	4
Research Fellows & Post Docs	3
Total Annual Grant Awards	$4.5M
Total Annual Industry Awards	$1.6M

Brusilovsky M, Rochman M, Rochman Y, Caldwell JM, Mack LE, Felton JM, Habel JE, Porollo A, Pasare C, Rothenberg ME. Environmental allergens trigger type 2 inflammation through ripoptosome activation. Nat Immunol. 2021 Oct;22(10):1316-1326. doi: 10.1038/s41590-021-01011-2. Epub 2021 Sep 16. PMID: 34531562; PMCID: PMC8487942.

Five Childhood Risk Factors Predict Risk of Adult Cardiovascular Events

PUBLISHED MAY 2022
New England Journal of Medicine

Cardiologists, endocrinologists and others have suspected for years that soaring rates of childhood obesity, along with other unhealthy risk factors, posed bad news for the heart health of future adults. In fact, several studies led here at Cincinnati Children's have documented alarming signs of arterial stiffness, cholesterol build-up and other metabolic and epigenetic changes occurring far too early in far too many children.

Now, a long-term, large-scale study conducted by the International Childhood Cardiovascular Consortium (i3C) has confirmed a clear link between five childhood risk factors and the likelihood of adult cardiovascular events. Importantly, children did not have to be extremely obese to face elevated risks later in their lives.

Details were presented April 4, 2022, at the American College of Cardiology annual meeting and simultaneously published in the *New England Journal of Medicine (NEJM)*. Jessica Woo, MHSA, PhD, Division of Biostatistics and Epidemiology, served as corresponding author. Elaine Urbina, MD, MS, director of Preventive Cardiology at the Heart Institute at Cincinnati Children's, was a senior co-author.

The study involved 38,589 participants from Australia, Finland, and the US, who were followed from age 3-19 years for a period of 35-50 years. The team found that five risk factors, individually or in combination, present in childhood were predictors of fatal and non-fatal cardiovascular events. These risk factors were detected in over half the children studied—and for some, the risk was nine times higher than those with below-average risk factors.

Especially concerning, 75% of the strokes and heart attacks occurring in the higher-risk study participants people occurred before age 53. While most survived their initial events, more than 300 died.

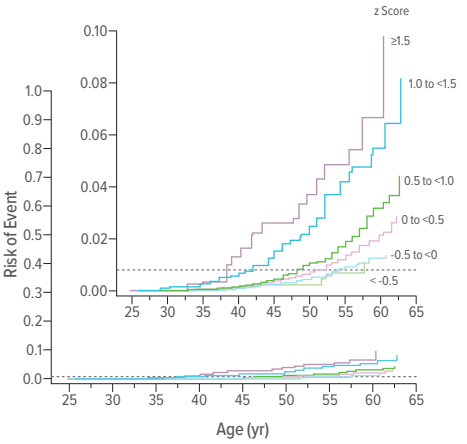
"These findings are remarkable in demonstrating that children with only mildly elevated body mass index, blood pressure or lipids, and youth who start smoking, may be at higher risk for adult cardiovascular disease," Woo says. "However, we also show that when these risk factors are lower in adulthood than in childhood, for example quitting smoking between childhood and adulthood, risk of suffering from adult cardiovascular disease was lower. This highlights the importance of ensuring that all children develop and maintain healthy habits into adulthood."

Massive longitudinal study links childhood risk factors such as body mass index, blood pressure, blood lipids, and cigarette smoking to strokes and heart attacks in adults—with 75% of events occurring before age 53.

FROM LEFT Jessica Woo, MHSA, PhD, Elaine Urbina, MD, MS

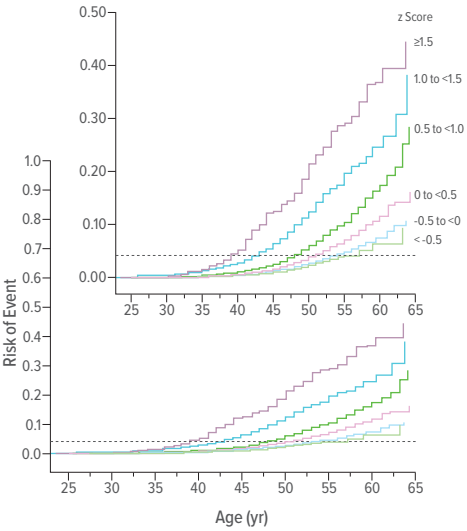
Cumulative Risk of Cardiovascular Events

FATAL CARDIOVASCULAR EVENT



z Score	No. at Risk								
≥1.5	399	399	365	336	286	188	144	100	48
1.0 to <1.5	1,628	1,625	1,594	1,474	1,317	909	582	330	125
0.5 to <1.0	6,497	6,492	6,390	6,113	5,577	3,862	2,314	1,373	446
0 to <0.5	14,579	14,566	14,320	13,771	12,702	9,080	5,399	3,001	816
-0.5 to <0	12,791	12,774	12,392	11,924	11,078	8,042	4,834	2,559	441
< -0.5	2,695	2,695	2,584	2,467	2,327	1,498	849	475	0
Total	38,589	38,551	37,645	36,085	33,287	23,579	14,122	7,838	1,876

FATAL OR NONFATAL CARDIOVASCULAR EVENT



z Score	No. at Risk								
≥1.5	399	399	391	331	277	196	122	73	23
1.0 to <1.5	1,628	1,621	1,593	1,464	1,287	851	474	283	73
0.5 to <1.0	6,497	6,492	6,405	6,083	5,544	3,708	1,997	1,128	303
0 to <0.5	14,579	14,575	14,375	13,736	12,581	8,788	4,900	2,649	602
-0.5 to <0	12,791	12,789	12,602	12,057	11,047	8,014	4,613	2,217	353
< -0.5	2,695	2,694	2,641	2,541	2,337	1,691	979	431	9
Total	38,589	38,570	38,007	36,212	33,073	23,248	13,085	6,781	1,363

FIVE PREDICTIVE RISK FACTORS

The study whittled a host of possible risk factors down to a combined "z score" based on five risk factors with statistically significant importance.

Overall, each 1-point increase in the z score measured during childhood was associated with a 2.71- to 3.54-fold higher likelihood of death from adult cardiovascular events:

- For total cholesterol: 1.30 (95% CI 1.14-1.47)
- For BMI: 1.44 (95% CI 1.33-1.57)
- For systolic blood pressure: 1.34 (95% CI 1.19-1.50)
- For triglycerides: 1.50 (95% CI 1.33-1.70)
- For smoking: 1.61 (95% CI 1.21-2.13)

"Much evidence suggests that the seeds of cardiovascular disease are in childhood, but the specific evidence linking childhood measurements to clinical disease was absent until our study," says co-first author David Jacobs, Jr., PhD, Division of Epidemiology and Community Health at the University of Minnesota Medical School. "This study is remarkable in that we now have that evidence and we found it by following participants from childhood to adulthood over many decades."

In an editorial published alongside the study, *NEJM* deputy editor Julie Ingelfinger, MD, of the Mass General Hospital for Children in Boston, wrote that the findings mark a "coming of age" for robust clinical cohorts that finally provided

The cumulative risk of cardiovascular events is shown as the estimated probability according to the combined-risk z score and age (Kaplan–Meier method). The horizontal dashed line in each panel indicates the overall risk of the event. Top panel shows the hazard ratios for fatal cardiovascular events, and bottom panel shows the hazard ratios for fatal or nonfatal cardiovascular events. All participants were included in these analyses; there were 319 fatal events and a mean of 1,563 fatal or nonfatal events across imputations. In each panel, the inset shows the same data on an enlarged y-axis.

once-elusive evidence connecting childhood risks to adult outcomes.

"If CV risk factors can be identified early in life, we as clinicians have opportunities to address health issues early and might uncouple risk from an inexorable march toward CVD and death," Ingelfinger wrote. "We have been waiting for hard data showing that risk factors seen in childhood forecast future disease, and now we have a good start concerning CVD."

"More than 126 million people worldwide are affected every year by cardiovascular disease. This is the leading cause of death in the United States and throughout the world," Urbina says. "Unfortunately, few maintain the ideal cardiovascular health that nearly all children have at birth."

NEXT STEPS: START PREVENTIVE MESSAGING EVEN EARLIER

Each of the five factors called out in the study can be enough by itself to drive cardiovascular risk, but frequently, these factors co-exist for individuals to build even higher combined, cumulative risk scores.

This suggests that programs to reduce risk should not wait until adulthood begins, although many do. Routine heart health testing may need to start at earlier ages than most families would expect. The sheer frequency of children already coping with one or more heart health risk factors suggests a need for wide-ranging public health preventive strategies. It may not be enough to encourage exercise and healthy eating on their own. It may not be effective to treat concerns about childhood smoking and vaping as a siloed issue.

"More research is needed to understand what preventive strategies can be scaled up enough to make an impact," says Urbina.

Meanwhile, research continues to develop tools to more precisely identify children at highest risk. These children may need interventions previously reserved for adults, including medications, bariatric surgery, cognitive behavior therapy or other interventions. For example, few cardiac medications have been studied for safety and efficacy in children. Long-term impacts of other treatments and interventions also remain under-studied.

"Our next step is to refine our risk score by adding genetic factors and social determinants of health," says Woo.

ABOUT THE STUDY In addition to researchers from Cincinnati Children's and the University of Cincinnati, this study involved collaborators from the University of Minnesota, the University of Colorado, Children's Hospital Colorado, the University of Turku and Turku University Hospital in Finland, Tampere University in Finland, the University of Tasmania in Australia, Tulane University, the University of Iowa, Wake Forest School of Medicine, Murdoch Children's Research Institute in Australia, and the University of Oxford in the United Kingdom.

RESEARCH & TRAINING DETAILS	Division of Biostatistics & Epidemiology
Faculty	22
Joint Appointment Faculty	3
Research Fellows & Post Docs	3
Research Graduate Students	12
Total Annual Grant Awards	$13.5M

Jacobs DR Jr, Woo JG, Sinaiko AR, Daniels SR, Ikonen J, Juonala M, Kartiosuo N, Lehtimäki T, Magnussen CG, Viikari JSA, Zhang N, Bazzano LA, Burns TL, Prineas RJ, Steinberger J, Urbina EM, Venn AJ, Raitakari OT, Dwyer T. Childhood Cardiovascular Risk Factors and Adult Cardiovascular Events. N Engl J Med. 2022 May 19;386(20):1877-1888. doi: 10.1056/NEJMoa2109191. Epub 2022 Apr 4. PMID: 35373933; PMCID: PMC9563825.

Science Takes on Health Inequities

Experts at Cincinnati Children's Dive Deep to Make Biomedical Research Matter to All

Living and championing diversity, equity and inclusion is fundamental to who we are at Cincinnati Children's and embedded in every aspect of our work. In fiscal 2022, our commitment to respecting everyone was expressed in numerous tangible ways in our research and discovery efforts.

We are proud to celebrate all the faculty members, lab teams and other staff at Cincinnati Children's who helped make these achievements in understanding and reducing the impact on children of our society's health inequities and social determinants of health.

Robert Kahn, MD, MPH

Andrew Beck, MD, MPH

Nana-Hawa Yayah Jones, MD

Andrea Maxwell, MD

Applying Research Skills to Long-Standing Issues

Reaching beyond the walls of our hospital to address housing concerns is just one of many ways that Cincinnati Children's devotes its research skills and experience to addressing issues involving systemic racism and social determinants of health. In fiscal 2022, ended June 30, investigators at Cincinnati Children's produced a wide body of work, including:

COLLABORATION WITH LEGAL AID SOCIETY HELPS FAMILIES, ATTRACTS INTEREST FROM WHITE HOUSE

Ever since a 2009 project to push a large landlord in Cincinnati to correct toxic housing conditions that were sending too many children to the hospital with asthma exacerbations, we have known that an ongoing partnership with the Legal Aid Society of Greater Cincinnati was making real improvement in child health outcomes.

In a study published March 7, 2022, in *Health Affairs*, researchers at Cincinnati Children's assembled the data to prove it.

By examining thousands of cases involving referrals to our Child HeLP program and comparing them in a novel way to a pool of similar cases that did not involve intervention from the program, a research team led by Andy Beck, MD, MPH, and Rob Kahn, MD, MPH, demonstrated a 38% reduction in the hospitalization rate among kids who got Child Help assistance from 2012 through 2017.

"If this were a pill that demonstrated a 38% reduction across so many kids in terms of hospitalization, every pharmaceutical company in the country would be going after it, and every healthcare payer would be figuring out how to cover it," says Kahn, who was recently named a vice president at Cincinnati Children's and director of the new Michael Fisher Child Health Equity Center.

The *Health Affairs* study has attracted interest from the Social Interventions Research and Evaluation Network (SIREN) in California as well as many of the 450 members of the National Center for Medical-Legal Partnership. Then, in September 2022, Beck was invited to meet with White House officials as art of an event dubbed "Communities in Action: Building a Better Ohio." Among those attending: HUD Secretary Marcia Fudge.

"I had a conversation with her about how important and influential housing quality is for the health of a child," Beck said. "I mentioned the medical-legal partnership, and Secretary Fudge suggested that all children should have access to legal representation. I handed Secretary Fudge a copy of our recent *Health Affairs* study highlighting the benefit of such legal advocacy on health outcomes."

NEIGHBORHOOD POVERTY, PUBLIC INSURANCE STATUS OUTWEIGH RACE FOR RISK OF DIABETES-RELATED HOSPITALIZATION

Research led by Andrea Maxwell, MD, and Nana-Hawa Yayah Jones, MD, published August 18, 2021, in the *Journal of Hospital Medicine*, found that children living in high-poverty areas or on public insurance are significantly more likely to be admitted to the hospital for diabetic ketoacidosis (DKA). To understand and respond to these equity

Pamela Williams-Arya, MD

Tanya Froehlich, MD, MS

Tesfaye Mersha, PhD

Sarah Beal, PhD

gaps, researchers in endocrinology at Cincinnati Children's are working with patients, community members, case workers, social workers, and diabetes educators.

DRIVING REAL-WORLD CHANGE FOR CINCINNATI FAMILIES EXPERIENCING HOMELESSNESS

Faculty members Pamela Williams-Arya, MD, and Tanya Froehlich, MD, MS, used a focus group methodology called Group-Level Assessment (GLA) to gather perspectives from 53 parents who were living in Cincinnati homeless shelters. Recommendations from the project led to a number of policy and practice enhancements in these shelters, and a paper published in *Family & Community Health*. (see page 62.)

SYSTEMIC RACISM EXPLAINS MOST DIFFERENCES IN ASTHMA RE-ADMISSION RATES

Research led by Tesfaye Mersha, PhD, and Robert Kahn, MD, MPH, published online July 1, 2021, in the *Journal of Allergy and Clinical Immunology*, reports that differences between Black and White children in asthma-related hospital readmissions is more about structural racism built into the health system than it is about genetic differences.

NEW TECHNOLOGY TO IMPROVE WELL-BEING OF KIDS IN FOSTER CARE

Nearly 500,000 U.S. children are in foster care. Too often, their health records get lost in a maze of storage systems. Now improved data sharing is possible thanks to the IDENTITY software system developed by Sarah Beal, PhD, Judith Dexheimer, PhD, and Mary Greiner, MD, MS. In September 2021, Cordata Healthcare Innovations licensed the technology to expand its use. (see related study page 42.)

"Advancing technology comes with increased responsibility."

– Victor Dzau, MD
National Academy of Medicine President

SOCIOECONOMIC FACTORS TIED TO CHILDHOOD ASTHMA INCIDENCE

Data from a long-running birth cohort study shows that children from poorer or more densely populated neighborhoods were more likely to develop asthma, as were Black and Hispanic children—even in more affluent neighborhoods—compared to White children. The study, led by Antonella Zanobetti, PhD, Harvard T.H Chan School of Public Health, Department of Environmental Health, and by Patrick Ryan, PhD, MS, Cincinnati Children's, was published online May 23, 2022, in *JAMA Pediatrics*. Patrick Ryan, PhD, MS, also will provide scientific support for an air monitoring program in Lower Price Hill, recently funded through a $75,000 grant from the EPA to Groundwork Ohio River Valley. Compared to the rest of Cincinnati, residents of Lower Price Hill suffer from disproportionately higher rates of cancer and asthma, upper respiratory ailments, seizures, learning disabilities, lead poisoning, and other health outcomes.


Judith Dexheimer, PhD


Mary Greiner, MD, MS


Patrick Ryan, PhD, MS


Michael Fisher

Providing Thought Leadership to Reduce Health Inequities

Research leaders here are working to assure that the groundbreaking science happening every day at Cincinnati Children's serves to help all children thrive. Here's how we are demonstrating that commitment.

COALITION FOR PEDIATRIC MEDICAL RESEARCH LAYS OUT PRIORITIES

Research Foundation Director Tina Cheng, MD, MPH, and diversity liason Conrad Cole, MD, MPH, led a national policy-setting convening in May 2022 in Washington, DC, to encourage diversity in pediatric research. The coalition's recommendations include:

- Support and expand the Pediatricians Accelerate Childhood Therapies (PACT) Act of 2021
- Support loan repayment for child and adolescent health researchers
- Fund a cross-institutional cohort for child and adolescent health researchers from underrepresented groups
- Invest substantially in career pathways for diverse child and adolescent health researchers

"There is great momentum to make change," Cheng says. "The convening and activity around the policy brief led to an action plan related to legislative priorities. We welcome your participation."

MICHAEL FISHER'S PARTING GIFT

Cincinnati Children's selected Robert Kahn, MD, MPH, to oversee the new Michael Fisher Child Health Equity Center, which was established to address social, environmental and health care factors that influence child health so that all kids can reach their full potential and thrive. The goal: To eliminate disparities by race and ensure that a child's ZIP code is no longer a predictor for health outcome.

"This is an honor I will cherish for the rest of my life," Fisher says. "I love Cincinnati Children's, I love this community, and I love all kids. I am forever grateful to the enormously talented and passionate employees who are devoting their lives and careers to education, research, clinical care, and working with families to help every child pursue their potential."

WITH CARE, MEDICINE'S BRAVE NEW WORLD CAN BE BRIGHT

"We as scientists, clinicians, and socially conscious individuals, we know that advancing technology comes with increased responsibility. No longer can scientists and physicians just do their science without considering the social implications of their work," says National Academy of Medicine President Victor Dzau, MD. The need to guide the dissemination of discovery so that all people share in the benefits, not just the rich, was the central theme when Dzau spoke to a virtual audience Aug. 18, 2021, as part the Cincinnati Children's Research Foundation's "Envisioning Our Future For Children" speaker series.

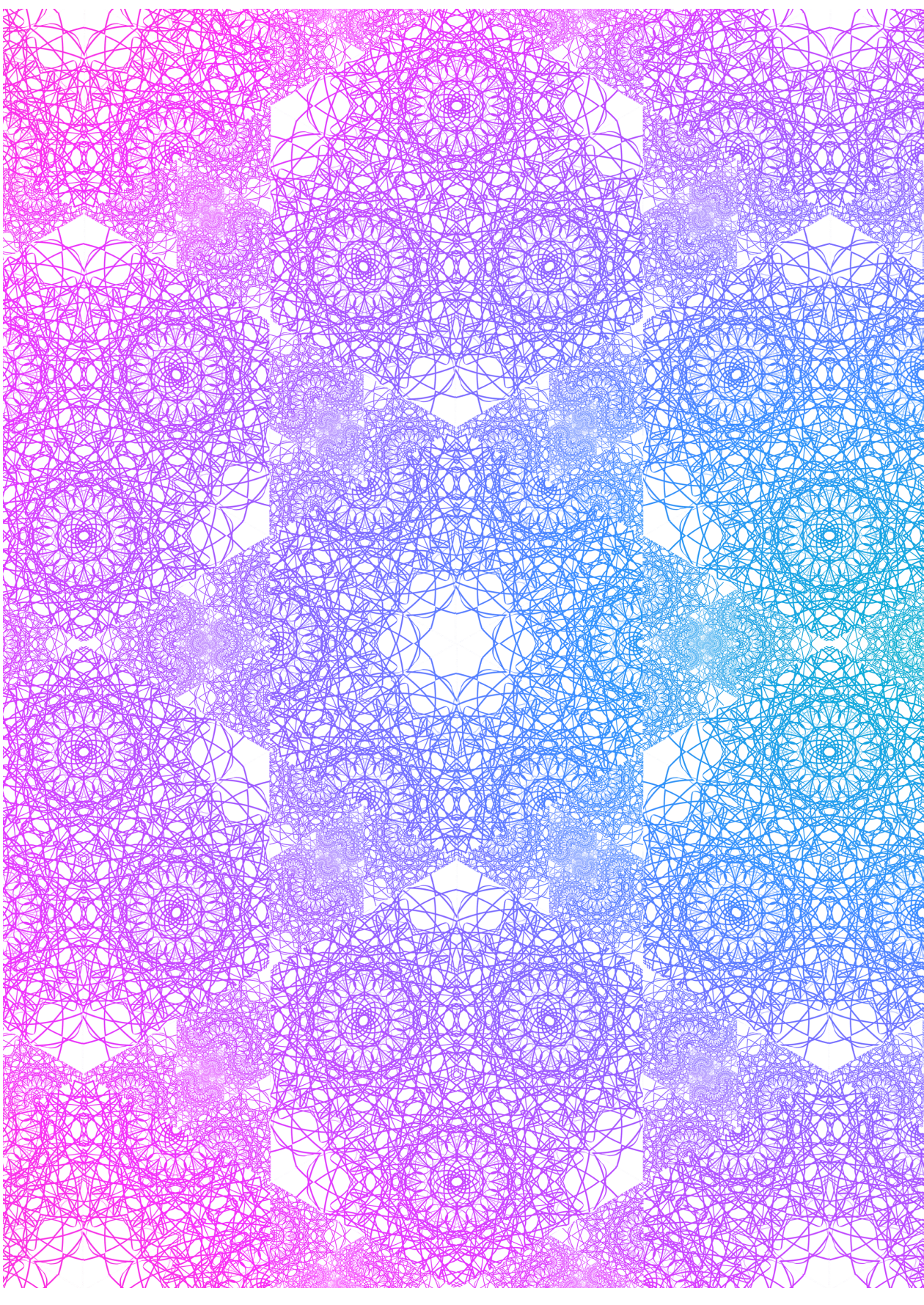
"You in Cincinnati, you are an anchor institution in your community. You hire people. You provide research. You provide care. You provide resources," Dzau says. "And you need to think as a leader in society about ethical and social issues."

Tina Cheng, MD, MPH

Conrad Cole, MD, MPH

Read More

about our research to address health inequities at our Science Blog.



2022 Scientific Achievements

Investigators here produced more than 2,400 peer-reviewed journal articles, book chapters, and other publications in FY2022. The following pages feature the most significant publication from each of our research divisions.

How Virtual Reality Can Improve HPV Vaccine Initiation

Joe Real, MD, MEd

Brittany Rosen, PhD, MEd

PUBLISHED JUNE 2022

American Journal of Preventive Medicine

Research led by Joe Real, MD, MEd, Brittany Rosen, PhD, MEd, and colleagues has identified a novel way to use virtual reality (VR) technology to improve the uptake of vaccinations, particularly for the three-part HPV series.

The research involved engaging providers in Virtual Immersive Communication Training on Recommending Immunizations (VICTORI). VICTORI gives physicians a safe virtual space to practice providing vaccine communication to families. The platform also gives feedback to physicians. Providers who used VICTORI showed an 18% increase in HPV vaccine initiation rates among their patients.

Vaccinations remain one of the safest and most effective ways to prevent disease. The HPV vaccine is an important one for children to receive early. HPV causes almost all cervical cancers and most vulvar, vaginal, anal, penile, and oropharyngeal cancer cases in the U.S.

Even with the benefits of a safe and effective vaccine, only 75% of children aged 13–17 years have received an initial dose. Even more are not current with the full series.

Families often rely on physicians to provide vaccine recommendations for their children. Unfortunately, many physicians feel they lack the resources to advise vaccine-hesitant families. This study demonstrated that training through VR can help lower the barriers to counseling and increase uptake among families.

Moreover, the success of this trial has the potential to help increase vaccination against other diseases.

"In addition to the success achieved with HPV vaccination, there was a spillover effect to other adolescent vaccines, including those for tetanus, diphtheria, and pertussis (Tdap) and meningococcal infection (MCV4)," Real says. "Now we are creating a COVID-19 vaccine curriculum that similarly uses virtual reality simulations to allow providers to practice vaccine counseling behaviors."

RESEARCH & TRAINING DETAILS

Faculty	14
Joint Appointment Faculty	2
Total Annual Grant Awards	$1.9M

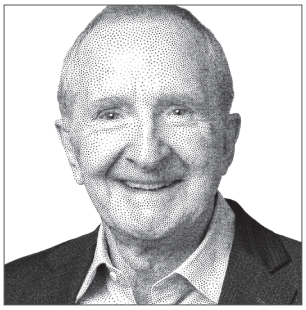
Real, FJ, Rosen BL. Impact of a Virtual Reality Curriculum on Human Papillomavirus Vaccination: A Pilot Trial. Am J Prev Med. 2022 Jun 28:S0749-3797(22)00293-8. doi: 10.1016/j.amepre.2022.05.003. Epub ahead of print. PMID: 35778065.

Virtual Immersive Communication Training on Recommending Immunizations (VICTORI)

An approach using virtual reality to train physicians in vaccine counseling has improved HPV vaccination rates with possible implications for vaccination against other diseases.

Propofol Infusion: The Anesthetic of Choice for Auditory Brainstem Response Testing

Ali Kandil, DO, MPH



John McAuliffe III, MD, MBA

PUBLISHED APRIL 2022
Anesthesia and Analgesia

When testing children for auditory brainstem response, using the anesthetic propofol is less likely to produce false positives for hearing loss compared to another commonly-used drug, sevoflurane.

That's the key finding of a study analyzing the impact of general anesthesia on children who need auditory testing. The comparison was led by first author Ali Kandil, DO, MPH, senior author John McAuliffe III, MD, MBA, and colleagues.

Five audiologists reviewed 1,259 records involving patients tested in at least four intensities in each ear.

"False-positive ABR tests, produced by certain anesthetic agents, can have significant life-long impact and negative psychosocial and developmental implications," McAuliffe says. "Sevoflurane produced more false positives for hearing loss and suggested more severe hearing loss than propofol."

Since publication, this data was presented at the American Academy of Audiology conference in St. Louis. The paper also was chosen as the Pediatric Anesthesia Article of the Day by Myron Yaster, MD, a major figure in pediatric anesthesia.

"I often thought that any anesthesia for ABRs that produced immobility would work," Yaster wrote. "So, when I initially saw this article about the best way to provide anesthesia for ABRs, I thought, 'Really?' Well, today's PAAD presents convincing evidence that there really is a better way to do it."

Word about the preferred agent is spreading. "Several colleagues have reached out from other institutions across the country asking for our data and inquiring about our experience," Kandil says. "Several have informed me they are changing their practice based on our experience at Cincinnati Children's and our paper."

RESEARCH & TRAINING DETAILS

Faculty	73
Joint Appointment Faculty	12
Research Fellows & Post Docs	4
Research Graduate Students	5
Total Annual Grant Awards	$2.9M

Kandil AI, Ok MS, Baroch KA, Subramanyam R, Mahmoud MA, McAuliffe JJ 3rd. Why a Propofol Infusion Should Be the Anesthetic of Choice for Auditory Brainstem Response Testing in Children. Anesth Analg. 2022 Apr 1;134(4):802-809. doi: 10.1213/ANE.0000000000005693. PMID: 35113042.

Comparing Anesthetics

Classifier Modeling of ABR Data Acquired Under Propofol Anesthesia

Classifier		Loss	Normal	True-positive rate	False-negative rate
True	Loss	16 (89%)	2 (11%)	89%	11%
Class	Normal	3 (2%)	134 (98%)	98%	2%

Classifier Modeling of ABR Data Acquired Under Propofol Anesthesia

Classifier		Loss	Normal	True-positive rate	False-negative rate
True	Loss	17 (94%)	1 (6%)	94%	6%
Class	Normal	3 (2%)	134 (98%)	98%	2%

Application of Classifier Models Fit to ABR Data Acquired Under Propofol Anesthesia to ABR Data Acquired Under Sevoflurane Anesthesia

Classifier		Loss	Normal	True-positive rate	False-negative rate
True	Loss	17 (89%)	1 (11%)	94%	6%
Class	Normal	31 (29%)	106 (71%)	71%	29%

Results from this study in *Anesthesia and Analgesia* have prompted practice changes at several institutions.

‘Atopic March’ Can Vary Along Racial Lines

Jocelyn Biagini, PhD

Gurjit Khurana Hershey, MD, PhD

RESEARCH & TRAINING DETAILS

Faculty	5
Joint Appointment Faculty	1
Research Fellows & Post Docs	9
Research Graduate Students	3
Total Annual Grant Awards	$5.9M

Biagini JM, Kroner JW, Baatyrbek Kyzy A, Gonzales A, He H, Stevens M, Grashel B, Spagna D, Paul S, Patel R, Bucci A, Sherenian MG, Murrison LB, Martin LJ, Khurana Hershey GK. Longitudinal atopic dermatitis endotypes: An atopic march paradigm that includes Black children. J Allergy Clin Immunol. 2022 May;149(5):1702-1710.e4. doi: 10.1016/j.jaci.2021.09.036. Epub 2021 Oct 18. PMID: 34673050; PMCID: PMC9275099.

PUBLISHED MAY 2022
Journal of Allergy and Clinical Immunology

When it comes to the ‘atopic march,’ a classic pattern of eczema earlier in life leading to allergies and asthma later in life, Black and White children often follow the beats of different drummers.

In one of the few studies to carefully examine how race can influence asthma risk, a research team led by Jocelyn Biagini, PhD, and Gurjit K. Khurana Hershey, MD, PhD, found clear differences between the allergic trajectories of Black and White children who were among 600 participants in the Mechanisms of Progression of Atopic Dermatitis to Asthma in Children (MPAACH) cohort.

White children were more likely to be sensitized to aero and food allergens and more than three times more likely to develop food allergy and/or allergic rhinitis without asthma risk. In contrast, Black children were over six times more likely to proceed to high asthma risk, without developing food allergies or allergic rhinitis.

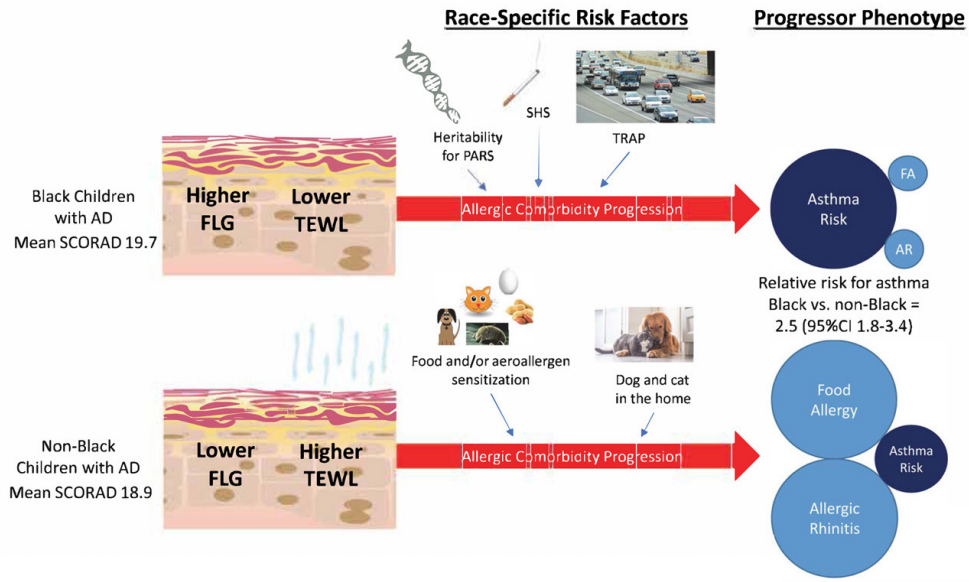
“Black and White children with atopic dermatitis have distinct allergic trajectories defined by different longitudinal endotypes,” Biagini says. “These observed racial differences are likely due in part to increased genetic heritability for asthma risk and increased exposures to harmful air pollutants affecting Black children. Black children also had higher skin barrier quality, leading to less sensitization.”

White children are more likely to have decreased skin barrier quality promoting sensitization, but also have higher exposures to pets in the home, which may protect against asthma development.

Until now, nearly all data about the “atopic march” has been based on studies of White children. Finding racial disparities in risk factors will help improve decision-support tools that many clinicians use to decide when intervention is needed.

“Collectively, our findings provide a new paradigm for an atopic march that is inclusive of Black children,” Biagini says.

Atopic March Progression in Children Participating in the Mechanisms of Progression of Atopic Dermatitis to Asthma in Children (MPAACH)



Longitudinal Cohort (n=601) Differs by Race

AD: atopic dermatitis, AR: allergic rhinitis, FA: food allergy, FLG: filaggrin, PARS: Pediatric Asthma Risk Score, SCORAD: scoring for atopic dermatitis, SHS: secondhand smoke, TEWL: trans-epidermal water loss, TRAP: traffic-related air pollution

Foster Care Does Not Cause Higher Service Utilization, Risky Behaviors Do

Sarah Beal, PhD

Mary Greiner, MD, MS

PUBLISHED APRIL 2022
Academic Pediatrics

Compared to others their age, children living in foster care and other forms of protective custody do tend to utilize more healthcare services. However, once adjusted to compare children in foster care to peers who also face mental health and substance abuse challenges, new research indicates that being placed in protective custody does not drive up healthcare utilization.

If anything, children in foster care are less likely than children not in protective custody to miss appointments and receive less routine primary care services, according to the study led by Sarah Beal, PhD, and Mary Greiner, MD, MS.

"We were surprised that health risk behaviors explained so much of the variability in emergency and inpatient healthcare use," Beal says.

The findings were based on data from 2,787 youth in protective custody compared to 2,787 demographically matched peers encountered by Cincinnati Children's.

"The gap in primary and specialty care, where youth in foster care are using less services once we control for health risk behaviors, could explain why our healthcare system is failing to address health risks in this population. Healthcare delivery changes customized for the needs of children in foster care could lead to improvements in primary care, more prevention of health risks, and declines in emergency and inpatient care," Beal says.

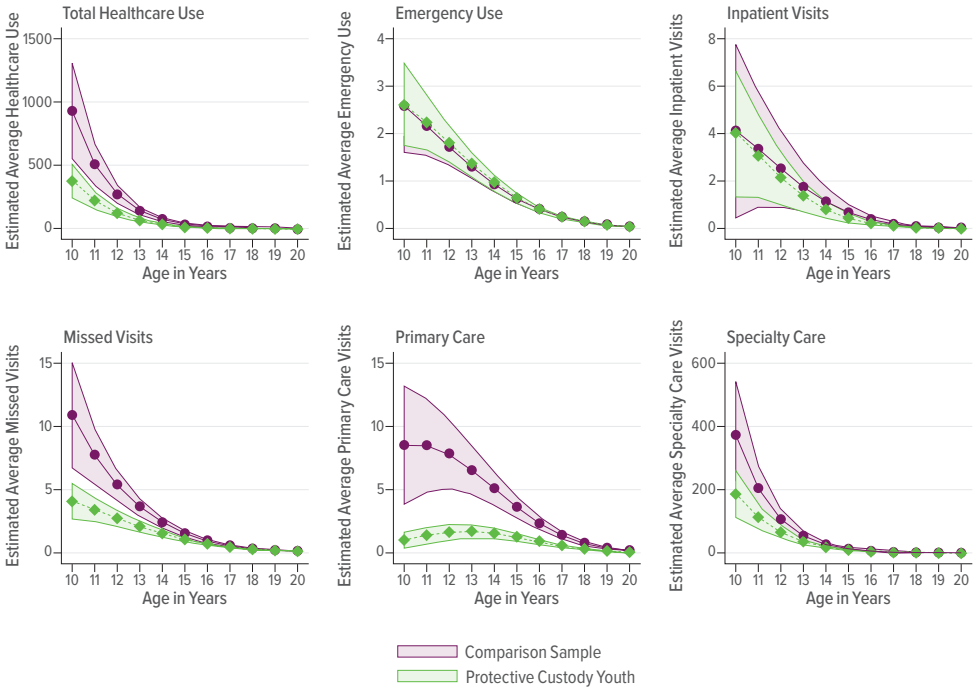
These findings and related substance use research have led to a 5-year grant from the Substance Abuse and Mental Health Services Administration (SAMHSA) to incorporate standardized screening, brief intervention, and referral to treatment to address substance use among young people in foster care. The CHECK (Comprehensive Health Evaluations for Cincinnati's Kids) Foster Care Center now screens all children aged 10 and older for substance use and provides intervention. Similar screening practices are being rolled out hospital-wide.

RESEARCH & TRAINING DETAILS

Faculty	73
Research Fellows & Post Docs	14
Research Graduate Students	3
Total Annual Grant Support	$11.8M
Total Annual Industry Support	$129,727

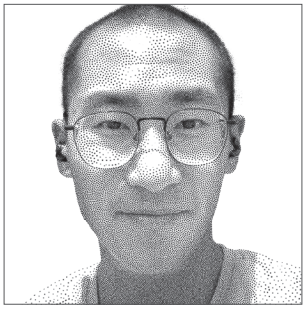
Beal SJ, Mara CA, Nause K, Ammerman RT, Seltzer R, Jonson-Reid M, Greiner MV. Effects of Child Protective Custody Status and Health Risk Behaviors on Health Care Use Among Adolescents. Acad Pediatr. 2022 Apr;22(3):387-395. doi: 10.1016/j.acap.2021.05.016. Epub 2021 May 21. PMID: 34023491; PMCID: PMC8606009.

Protective Custody and Healthcare Use



Differences in healthcare utilization for youth in protective custody and comparison youth across ages 10-20, adjusting for duration of representation in the study data, demographic characteristics, health characteristics, and health risk behaviors.

DeepImmuno Tunes into CNN to Predict T-Cell Immune Response



Guangyuan Li, PhD

Nathan Salomonis, PhD

PUBLISHED NOVEMBER 2021
Briefings in Bioinformatics

The DeepImmuno artificial intelligence platform developed by experts at Cincinnati Children's provides superior results when employing the convolutional neural network (CNN) model to predict how T-cells will recognize constantly mutating cancer cells and ever-evolving invasive pathogens. A study led by Guangyuan Li, PhD, Nathan Salomonis, PhD, and colleagues, benchmarked DeepImmuno's performance using five traditional machine learning models (ElasticNet, K-nearest neighbors, support vector machine, Random Forest and AdaBoost) and three deep learning models (CNN, Residual Net and graph neural network).

They found that the DeepImmuno-CNN model was the best at simulating how non-native peptides would interact with specific immune system genes that activate T-cell responses. Rather than attempting to sift through all potential interactions between peptides and major histocompatibility complex (MHC) genes, this tool predicts the immunogenicity of MHC-peptide pairs.

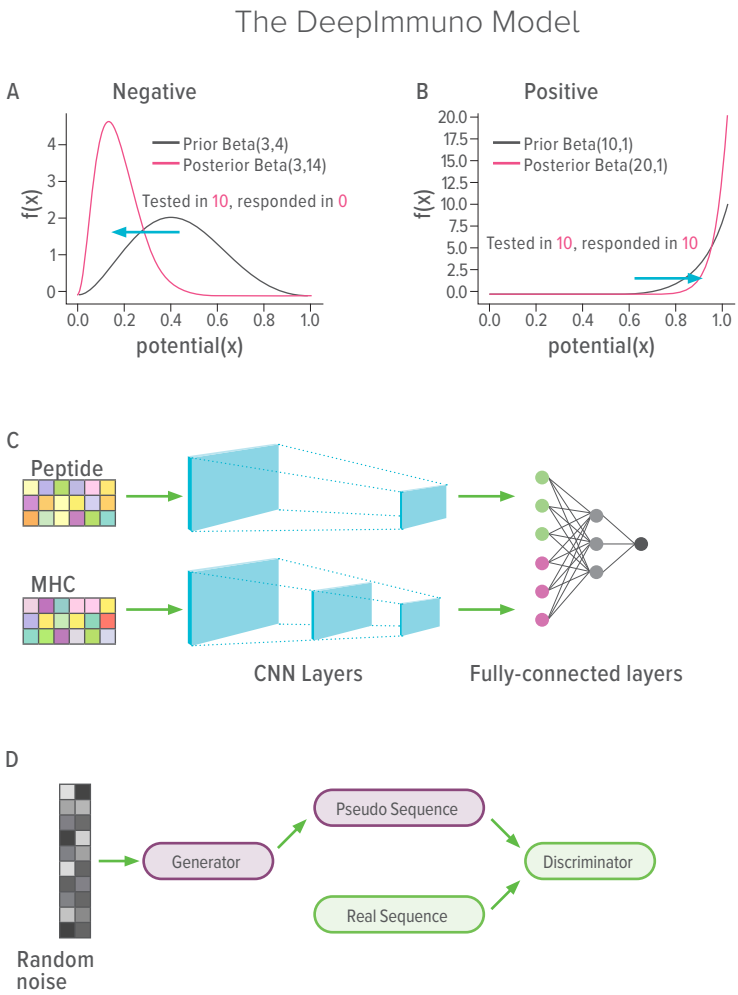
"In addition to outperforming two highly used immunogenicity prediction algorithms, DeepImmuno-CNN correctly predicts which residues are most important for T-cell antigen recognition and predicts novel impacts of SARS-CoV-2 variants," says Li, corresponding author for the study.

The published work updates information about DeepImmuno that had been shared as a preprint in 2020 during the early days of the COVID-19 pandemic. This tool is useful for researchers seeking to stay a step ahead of emerging mutations of the SARS-CoV-2 virus. It also can assist scientists working to develop cancer immunotherapies, which requires accurately predicting which cancer-specific neo-peptides are most likely to elicit an immune response. An artificial intelligence tool is needed for this work because thousands of potential disease-associated antigens can be presented in innate or foreign cells. Tools like DeepImmuno-CNN can help prioritize which candidates are most likely to induce a T-cell response prior to experimental validation.

RESEARCH & TRAINING DETAILS

Faculty	14
Joint Appointment Faculty	16
Research Fellows & Post Docs	3
Research Graduate Students	22
Total Annual Grant Awards	$5M
Total Annual Industry Awards	$94,254

Li G, Iyer B, Prasath VBS, Ni Y, Salomonis N. DeepImmuno: deep learning-empowered prediction and generation of immunogenic peptides for T-cell immunity. Brief Bioinform. 2021 Nov 5;22(6):bbab160. doi: 10.1093/bib/bbab160. PMID: 34009266; PMCID: PMC8135853.



To assess the probability that a given antigen is immunogenic, DeepImmuno computes variable peptide immunogenic potential by sampling from a posterior beta distribution of well-defined true-positive and true-negative immunogenic antigens to produce a continuous immunogenic score.

DeepImmuno Python3 code is available at github.com/frankligy/DeepImmuno.
The DeepImmuno web portal is available from deepimmuno.research.cchmc.org.

Gene Study Reveals Which Patients with Shwachman-Diamond Syndrome are at High Risk for Leukemia

Kasiani Myers, MD

PUBLISHED FEBRUARY 2021
Nature Communications

A recent translational study provides insight into the genetic underpinnings of leukemic development in Shwachman-Diamond Syndrome (SDS). Investigators anticipate that their findings could lead to better screening strategies, new diagnostic tests, and targeted therapies.

SDS is a rare, inherited disease predominantly caused by biallelic germline mutations in the *SBDS* gene. In SDS, ribosomes do not assemble correctly, leading to co-morbidities including bone marrow failure, pancreatic insufficiency, and other issues. About 40% of people with SDS develop myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), usually in early adulthood.

"Survival of people with SDS who develop blood cancers is poor because, if the disease is that advanced, even a bone marrow transplant may not be curative," says Kasiani Myers, MD, a pediatric hematologist and researcher with the Division of Bone Marrow Transplantation and Immune Deficiency at Cincinnati Children's. "If we knew a child with SDS had developed higher-risk features concerning for MDS or AML development, we could do an early allogeneic stem cell transplant and potentially save their life."

Samples from 110 SDS patients tested in the study came from the North American Shwachman-Diamond Syndrome Registry, which Myers co-directs with Akiko Shimamura, MD, PhD, at Boston Children's.

Researchers observed longitudinal changes in somatic mutations that lead to leukemic development—in some cases, changes that occur over 10 years. The most commonly and independently mutated genes were *EIF6* and *TP53*. The team also found that the presence of *TP53* mutations in both alleles is strongly associated with leukemic development.

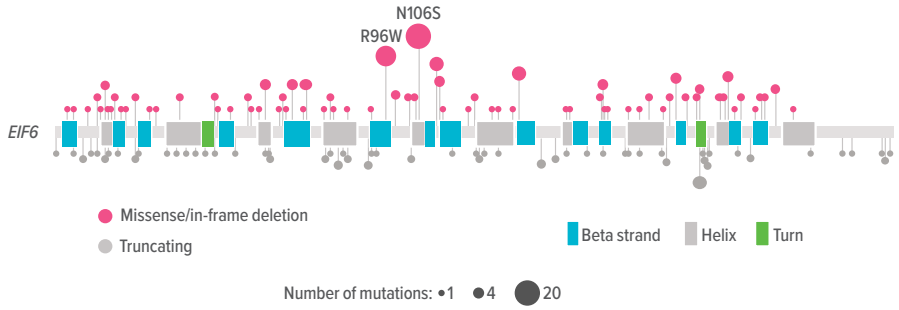
Clinical laboratories do not test for the biallelic *TP53* gene mutation. Myers and colleagues hope to develop a clinical test based on next-generation sequencing that would allow physicians to track changes in the mutated genes.

RESEARCH & TRAINING DETAILS

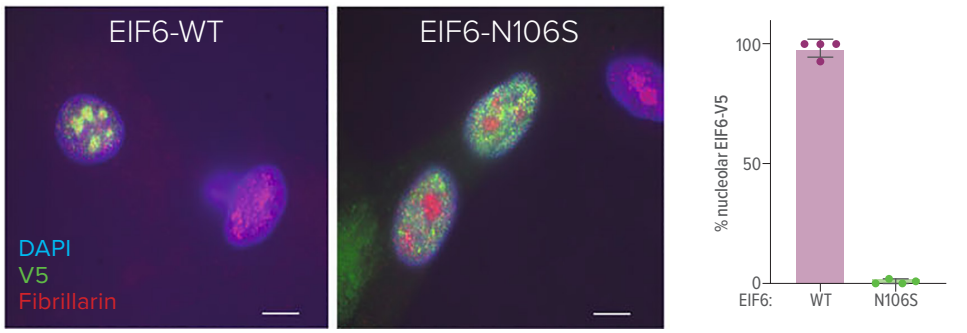
Faculty	19
Joint Appointment Faculty	2
Research Fellows & Post Docs	1
Total Annual Grant Awards	$6.4M
Total Annual Industry Awards	$1.4M

Kennedy AL, Myers KC, Bowman J, Gibson CJ, Camarda ND, Furutani E, Muscato GM, Klein RH, Ballotti K, Liu S. Distinct genetic pathways define pre-malignant versus compensatory clonal hematopoiesis in Shwachman-Diamond syndrome. Nat Commun. 2021 Feb 26. 12(1):1334. doi: 10.1038/s41467-021-21588-4. PMID: 33637765; PMCID: PMC7910481.

EIF6 Somatic Missense Mutations Alter EIF6 Protein Stability or Function to Improve Cell Fitness



Number and location of *EIF6* mutations according to variant type.



Immunofluorescence of V5-EIF-WT or V5-N106S-EIF6 protein in SDS patient-derived fibroblasts, V5 (green), fibrillarin (red), and DAPI (blue). Right panel: quantification of V5 nucleolar signal from four independent experiments. Error bars represent the mean ± standard deviation. Scale bar = 10 µm

Seminal Study Reveals a Hidden Culprit in the Development of Adult Blood Cancers

Timothy Chlon, PhD

Daniel Starczynowski, PhD

RESEARCH & TRAINING DETAILS

Faculty	26
Joint Appointment Faculty	12
Research Fellows & Post Docs	12
Research Graduate Students	17
Total Annual Grant Awards	$18.3M
Total Annual Industry Awards	$1.7M

Chlon TM, Stepanchick E, Hershberger CE, Daniels NJ, Hueneman KM, Davis AK, Choi Kwangmin, Zheng Y, Gurnari C, Haferlach T, Padgett RA, Maciejewski JP, Starczynowski DT. Germline DDX41 mutations cause ineffective hematopoiesis and myelodysplasia. Cell Stem Cell 2021 Nov 4; 28(11): 1966-1981.e6. doi: 10.1016/j.stem.2021.08.004. Epub 2021 Sep 1. PMID: 34473945. PMCID: PMC8571055.

PUBLISHED NOVEMBER 2021
Cell Stem Cell

Cancer researchers discovered in 2015 that inherited mutations in the *DDX41* gene cause predisposition to the development of adult blood cancers. A seminal study led by Timothy Chlon, PhD, goes a long way toward answering the question, "why?"

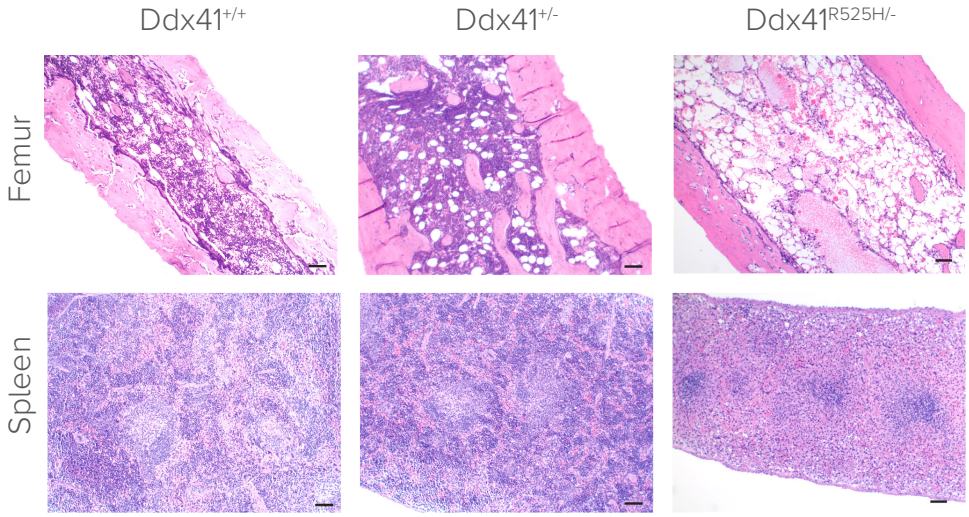
The *DDX41* mutation is present in a cohort of patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Despite possessing the mutated gene in all of their cells from birth, these individuals do not develop the disease until their 60s and 70s. Five-year survival rates of patients with these diseases are poor—about 30% overall. Chlon wanted to understand how the *DDX41* mutations contribute to the poor outcomes.

"We hypothesized that the *DDX41* defect drove the predisposition by dysregulating inflammatory and innate immune signaling pathways," Chlon says. "But instead, we found that an obvious defect in ribosome biology was responsible for the pathogenesis."

Chlon's team modeled the disease by generating a series of mouse models with mutations in *DDX41* similar to those seen in human patients. "One interesting aspect of these diseases is that in over 70% of MDS and AML patients with an inherited *DDX41* mutation, a second *DDX41* mutation is observed in a small proportion of their diseased bone marrow cells," he says.

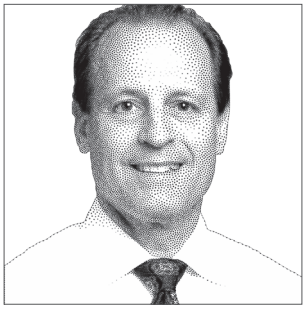
By generating mice with both the inherited and acquired *DDX41* mutations, the researchers found that the combination disrupts production of ribosomes, the cellular machines for making new proteins. The lack of ribosomes caused a defect in the production of new blood cells, creating an environment for leukemia to develop.

"We are in the early stages of understanding this complex disease," Chlon says. "If we can determine why these patients' cells are defective, that would go a long way towards developing treatment or prevention strategies."



Biallelic *DDX41* mutations cause cell death of blood progenitor cells, leading to bone marrow failure and atrophy of the spleen in genetic mouse models. Tissue samples taken 15 days after bone marrow transplant show healthy progenitor cell development in non-mutated *DDX41* (left) compared to an inherited mutation (center) and a second somatic mutation (right).

Jamaica EXTEND Study Demonstrates Value of Hydroxyurea for Children with Sickle Cell Disease



Russell Ware, MD, PhD

PUBLISHED NOVEMBER 2021
British Journal of Haematology

One in every 150 babies born in Jamaica has sickle cell anemia (SCA) and one in 10 carries the trait. In spite of recent developments, for many affected people, standard-of-care treatments for this life-threatening genetic condition remain difficult to access.

"Resource-constrained countries like Jamaica are dealing with everything from poverty and an aging health infrastructure to non-endemic mosquito-borne diseases like dengue," says Russell Ware, MD, PhD, director of the Division of Hematology at Cincinnati Children's. "Everything seems like a priority, and it can be challenging for public health leaders to know where to focus."

Ware and others at Cincinnati Children's have been working with clinicians in multiple nations to document the burden of SCA and expand use of effective, low-cost hydroxyurea treatments. In this study, Ware's team joined forces with the University of the West Indies in Kingston.

The team stratified 43 children into three risk categories: Group One had no stroke history and some exposure to hydroxyurea; Group Two had no stroke history and no exposure to hydroxyurea; Group Three had experienced one or more strokes and had no exposure to hydroxyurea.

Participants were escalated to the maximum tolerated dose of hydroxyurea and assessed for their stroke risk at baseline and after 18 months of treatment. As expected, hydroxyurea was more successful in preventing stroke for the first two groups.

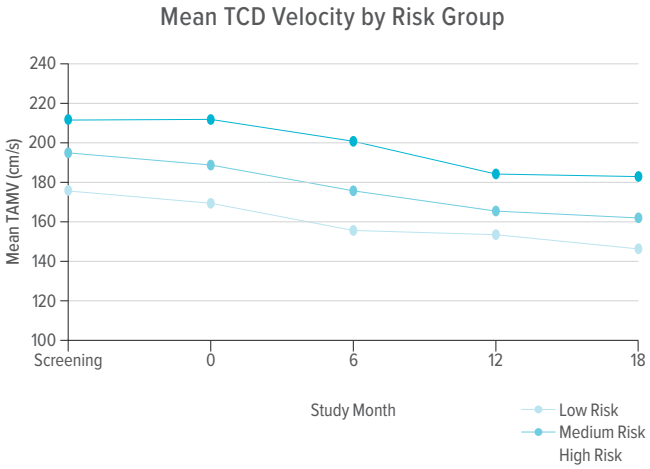
"Now, this study will increase the knowledge of physicians on screening techniques, effective dosing, safety monitoring, drug compliance and adherence for prescribing hydroxyurea," Ware says. "This capacity-building will improve the overall quality of care for children with SCA in Jamaica and help them experience much better health outcomes."

Research & Training Details	
Faculty	12
Joint Appointment Faculty	2
Research Fellows & Post Docs	2
Research Graduate Students	2
Total Annual Grant Awards	$4.8M
Total Annual Industry Awards	$5.6M

Rankine-Mullings A, Reid M, Soares D, Taylor-Bryan C, Wisdom-Phipps M, Aldred K, Latham T, Schultz WH, Knight-Madden J, Badaloo A, Lane A, Adams RJ, Ware RE. Hydroxycarbamide treatment reduces transcranial Doppler velocity in the absence of transfusion support in children with sickle cell anaemia, elevated transcranial Doppler velocity, and cerebral vasculopathy: the EXTEND trial. British Journal of Haematology 2021 Nov. 195(4):612-620. doi: 10.1111/bjh.17698. Epub 2021 Jul 22. PMID: 34291449.

Improving Sickle Cell Care

Researchers at Cincinnati Children's worked with healthcare providers in Jamaica to use transcranial doppler testing to monitor stroke risk.



Transcranial Doppler (TCD) velocity, a key risk marker for stroke in people with sickle cell anemia, declined among study participants as hydroxyurea (aka hydroxycarbamide) dosing was escalated to maximum tolerated dose (MTD).

Inotuzumab Leads to Remission in 58% of Children with Relapsed/Refractory B-ALL

Maureen O'Brien, MD, MS

PUBLISHED MARCH 2022
Journal of Clinical Oncology

A recently published phase II clinical trial demonstrated that inotuzumab ozogamicin (InO) is safe and effective as a single-agent therapy in treating children and adolescents with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL).

The study's principal investigator, Maureen O'Brien, MD, MS, director of the Leukemia/Lymphoma Program at Cincinnati Children's, also is co-principal investigator for a second study that will evaluate InO's safety and effectiveness when combined with chemotherapy in treating newly diagnosed high-risk B-ALL. Both studies are sponsored by Children's Oncology Group.

InO is a CD22-targeting antibody-drug conjugate approved by the U.S. Food and Drug Administration to treat adults with relapsed or refractory B-ALL. CD22 is a surface protein expressed on leukemic blasts in about 95% of B-ALL cases.

The phase II study of single-agent InO in relapse included 48 heavily pretreated patients ages 1 to 21 years with CD22-positive relapsed/refractory B-ALL.

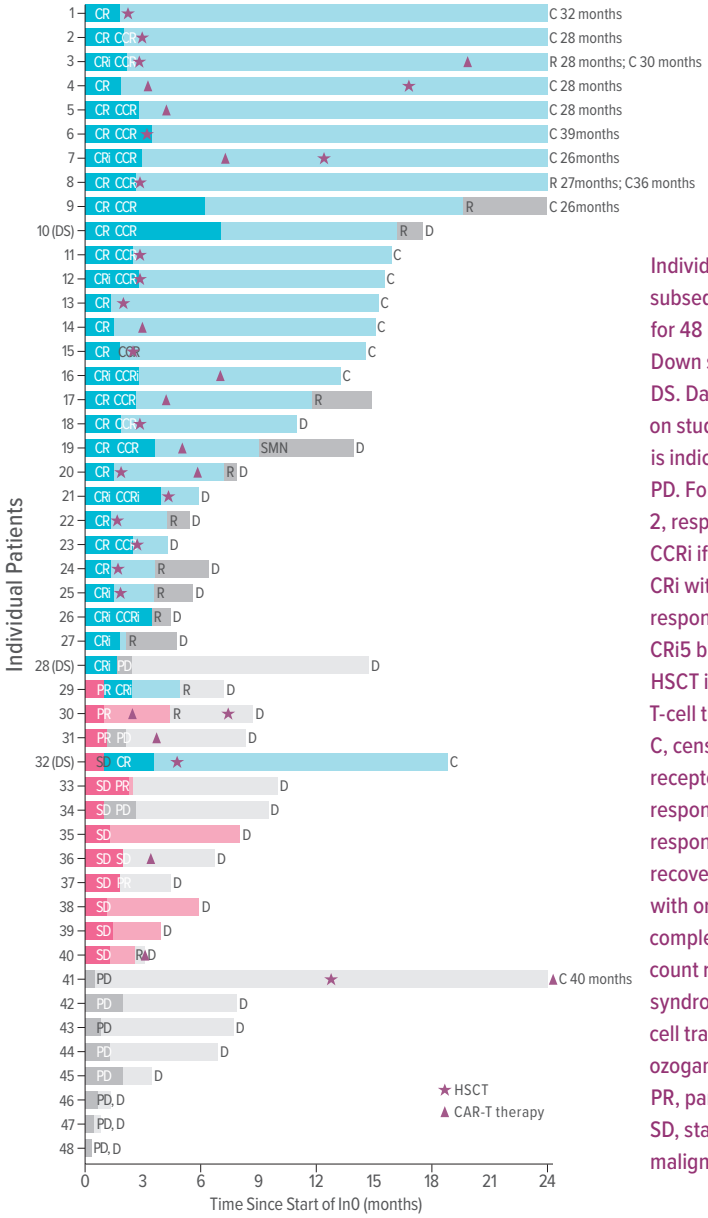
"The patients who participated in this trial had few available treatment options; many had received multiple intensive chemotherapy regimens and/or immunotherapies and had subsequently relapsed or did not respond," says O'Brien. "InO as a single agent led to remission in 28 patients (58.3%), many of whom went on to receive subsequent curative therapy—either hematopoietic stem-cell transplantation (HSCT) or CAR-T (chimeric antigen receptor T cell) therapy."

The phase II trial is enrolling a second cohort of patients with relapse who are receiving InO in combination with chemotherapy. The phase III study for newly diagnosed patients will enroll about 3,700 patients ages 1 to 25 years at 213 cancer centers in the US, Canada, Australia and New Zealand over the next four years.

RESEARCH & TRAINING DETAILS

Faculty	27
Joint Appointment Faculty	12
Research Fellows & Post Docs	1
Research Graduate Students	4
Total Annual Grant Awards	$6.4M
Total Annual Industry Awards	$2.5M

O'Brien MM, Ji L, Shah NN, Rheingold SR, Bhojwani D, Yuan CM, Xu X, Yi JS, Harris AC, Brown PA, Borowitz MJ, Militano O, Kairalla J, Devidas M, Raetz EA, Gore L, Loh ML. Phase II Trial of Inotuzumab Ozogamicin in Children and Adolescents With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia: Children's Oncology Group Protocol AALL1621. J Clin Oncol. 2022 Mar 20;40(9):956-967. doi: 10.1200/JCO.21.01693. Epub 2022 Jan 10. PMID: 35007127; PMCID: PMC8937013.



Individual patient response, subsequent therapy, and outcomes for 48 patients. Patients with Down syndrome are denoted as DS. Dark bars indicate InO given on study. Initial response to cycle 1 is indicated by CR, CRi, PR, SD, or PD. For patients who received cycle 2, response is indicated as CCR or CCRi if previously achieved CR or CRi with cycle 1. Duration of initial response is indicated by color (CR or CRi5 blue; PR or SD5 red, PD5 gray). HSCT is indicated by star, and CAR T-cell therapy is indicated by triangle. C, censored; CAR, chimeric antigen receptor; CCR, continuous complete response; CCRi, continuous complete response with incomplete count recovery; CR, complete response with or without count recovery; CRi, complete response with incomplete count recovery; D, death; DS, Down syndrome; HSCT, hematopoietic stem-cell transplantation; InO, inotuzumab ozogamicin; PD, progressive disease; PR, partial response; R, relapse; SD, stable disease; SMN, second malignant neoplasm.

Cannabis Use Disrupts SSRIs for Anxiety, Depression

Samuel Vaughn, MD, PhD

Laura Ramsey, PhD

PUBLISHED JULY ISSUE 2021
Journal of Personalized Medicine

Clinicians regularly prescribe selective serotonin reuptake inhibitors (SSRIs) to treat children and teens with anxiety and depression disorders. Meanwhile, many youths use cannabis recreationally while growing up.

The combination is not healthy, according to a study led by first author Samuel Vaughn, MD, PhD, and senior author Laura Ramsey, PhD, which shows that cannabis use can interfere with the benefits of SSRIs while increasing adverse events such as cough, fatigue, diarrhea, and dizziness.

The study presents a specific example of a 15-year-old female being treated for generalized anxiety disorder with panic attacks and recurrent depression. Her symptoms went into remission while treated with 10 mg a day of the SSRI escitalopram. However, over time, the panic attacks began increasing. As her physician increased the drug dosage to 15 mg and then 20 mg per day, the symptoms continued along with worsening nausea, headaches, and abdominal pain.

Unbeknownst to her clinician or parents, the patient had started consuming CBD/THC edibles. Once the usage was disclosed, and reduced, the girl began achieving improved symptom control with a reduced dose of escitalopram.

The study provides detail about how this drug-drug interaction affects the ability of the CYP2C19 enzyme to metabolize SSRIs in the liver, leading to excessive concentrations of the medication. This study did not evaluate SSRIs that rely on other metabolic enzymes.

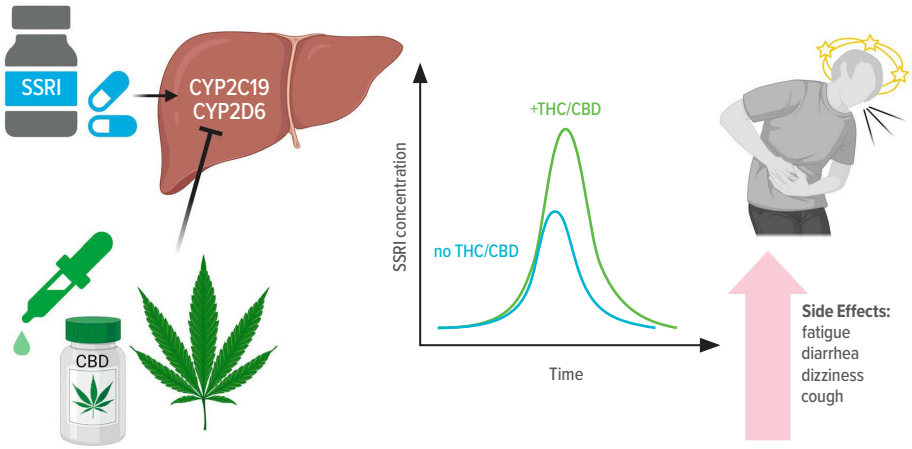
The key takeaway, the co-authors say, is that more clinicians should inquire about CBD and THC usage to allow for better-informed dosing. To date, only a few clinicians who prescribe SSRIs to children also monitor SSRI plasma drug levels on a regular basis. The co-authors say a larger-scale study is needed to better understand the nuances of these emerging drug-drug interactions.

RESEARCH & TRAINING DETAILS

Faculty	24
Joint Appointment Faculty	2
Research Fellows & Post Docs	1
Total Annual Grant Awards	$4.3M
Total Annual Industry Awards	$206,569

Vaughn SE, Strawn JR, Poweleit EA, Sarangdhar M, Ramsey LB. The Impact of Marijuana on Antidepressant Treatment in Adolescents: Clinical and Pharmacologic Considerations. J Pers Med. 2021 Jun 29;11(7):615. doi: 10.3390/jpm11070615. PMID: 34209709; PMCID: PMC8307883.

Cannabis and SSRIs Don't Mix



This graphical abstract outlines how cannabis use can disrupt how the liver metabolizes SSRIs used for treating anxiety and depression.

Optimizing Alemtuzumab Dosing Prior to Stem Cell Transplantation

Min Dong, PhD

Alexander Vinks, PharmD, PhD

PUBLISHED JANUARY 2022
British Journal of Clinical Pharmacology

While adults consistently benefit from receiving the anti-rejection drug alemtuzumab prior to receiving donor cells in hematopoietic stem-cell transplantation (HCT), wide variation in dosing strategies has led to wide variation in outcomes for children and young adults.

In fact, starting doses based only on a child's weight can result in excessively high doses in up to 40% of cases, because drug clearance rates for children of different weights do not match weight-based drug clearance patterns shown in adults. Many of these inaccuracies can be eliminated by following a pharmacokinetic/pharmacodynamic model detailed in a study led by Min Dong, PhD, Alexander Vinks, PharmD, PhD, and colleagues at Cincinnati Children's. The model allows clinicians to customize dosing for patients and receive automated feedback when drug levels fall outside therapeutic parameters.

"The currently used per-kg dosing was found to cause uneven alemtuzumab exposure across different age and weight cohorts," Dong says. "A body surface area-based starting dosing regimen in combination with individualized Bayesian pharmacokinetic estimation using concentration feedback provides optimized results."

The study used data from 29 young patients who received HCT to evaluate the target achievement with an established alemtuzumab concentration target of 0.15 to 0.6 μg/mL on the day of transplantation. Comparing models based on weight vs. body surface area revealed that clinicians can effectively use lower initial doses in many cases.

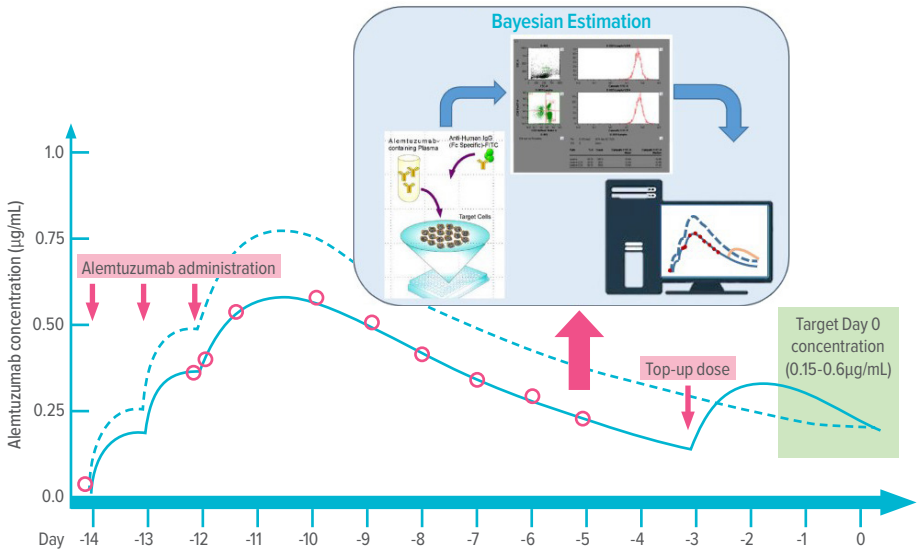
In 56% of simulated cases, sharply lower doses of medication could be administered without any need for top-up dosing on the day of transplant. For those that did need top-up dosing, the new predictive model developed at Cincinnati Children's accurately predicted the need. A clinical trial, led by Rebecca Marsh, MD, Division of Bone Marrow Transplantation and Immune Deficiency, was recently funded by the NIH to evaluate this new dosing scheme.

RESEARCH & TRAINING DETAILS

Faculty	5
Joint Appointment Faculty	3
Research Fellows & Post Docs	3
Research Graduate Students	3
Total Annual Grant Awards	$169,997

Dong M, Emoto C, Fukuda T, Arnold DE, Mehta PA, Marsh RA, Vinks AA. Model-informed precision dosing for alemtuzumab in paediatric and young adult patients undergoing allogeneic haematopoietic cell transplantation. Br J Clin Pharmacol. 2022 Jan;88(1):248-259. doi: 10.1111/bcp.14955. Epub 2021 Jul 18. PMID: 34182590.

Proposed Alemtuzumab Precision Dosing Strategy



This 14-day chart represents the predicted pharmacokinetic model for alemtuzumab dosing prior to a donor stem cell transplant. Dashed line reflects predicted model for a typical subject. Solid line represents an individualized profile, with red circles representing measured concentrations. Without a top-up, this patient would have lacked the proper dosing of this drug for rejection prevention.

Candidate Biomarkers for Sepsis-Associated Acute Kidney Injury Mechanistic Studies

James Odum, MD, MEd

Hector Wong, PhD

PUBLISHED MAY 2022
Shock

Sepsis and sepsis-associated acute kidney injury (SA-AKI) are common complications in hospitalized and critically ill patients, which increase the risk of developing multiple chronic diseases and often lead to death. Currently, doctors use a medical model published by Stanski *et al.* that predicts if a child will develop severe and persistent SA-AKI at day three of hospital admission using a sepsis biomarker panel generated by Wong *et al.*

Recently a team led by James Odum, MD, MEd, a former fellow at Cincinnati Children's now at Children's of Alabama, developed a mouse model to explore the biological mechanisms behind Stanski's model. They found that mice with a combination of two biomarkers, keratinocyte-derived chemokine (KC) and C-C chemokine ligand 3 (CCL3), predicted SA-AKI development in the mice after one day. This significant improvement over the current three-day prediction model can give doctors more time to anticipate and treat infections.

Now researchers are working to determine where these biomarkers are made within the kidney. They also are testing whether neutralizing KC with antibodies decreases SA-AKI rates in mice.

This initial study was presented by Odum at the 2021 Annual Conference on Shock (Virtual), where he was a New Investigator Award Finalist. He also presented this data at the 2022 AKI & CRRT Conference in San Diego.

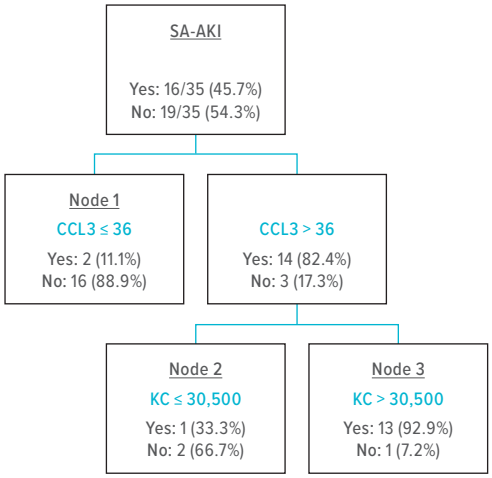
Odum wanted to make sure that he gave credit where it was due. He said, "The principal investigator for this work is the late Dr. Hector Wong, and the success of this research program is a testimony to his ability to develop young physician-scientists and form an innovative, collaborative team."

RESEARCH & TRAINING DETAILS

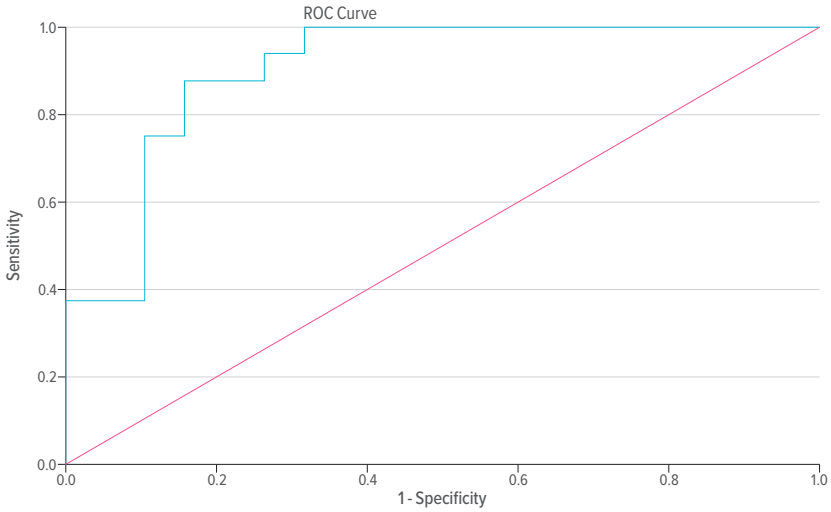
Faculty	16
Joint Appointment Faculty	1
Research Fellows & Post Docs	15
Total Annual Grant Awards	$3.0M
Total Annual Industry Awards	$4,000

Odum JD, Standage S, Alder M, Zingarelli B, Devarajan P, Wong HR. Candidate Biomarkers for Sepsis-Associated Acute Kidney Injury Mechanistic Studies. Shock. 2022 May 1;57(5):687-693. doi: 10.1097/SHK.0000000000001916. Epub 2022 Feb 28. PMID: 35234208; PMCID: PMC9117431.

Two Markers for Predicting Sepsis



The combination of two biomarkers, CCL3 and KC, predicts SA-AKI after 24 hours in mice with sepsis. This research will help doctors better understand how and when sepsis and sepsis-associated acute kidney injury develops in hospitalized patients.



Creating Guidelines for Retinoid Treatment for Ichthyosis

Anne Lucky, MD

PUBLISHED JANUARY 2022

Journal of the American Academy of Dermatology

Ichthyosis disorders are genetic disorders of the skin that can be painful and require long-term treatment to keep symptoms at bay. Retinoids, both topical and systemic, have been a common treatment for these conditions, but their use for different types of ichthyosis and recommended dosage had not previously been codified in guidelines.

These guidelines are especially crucial for treating children, who will likely be using these types of treatments over a long period, according to research conducted by Anne Lucky, MD, medical director, Epidermolysis Bullosa Center, and her colleagues, who developed consensus guidelines for the use of retinoids to treat these conditions.

Lucky and colleagues from more than a dozen research institutions formed the Pediatric Dermatology Research Alliance (PeDRA) Use of Retinoids in Ichthyosis Work Group. Experts from the group come from pediatric dermatology, general dermatology, pediatric cardiology, obstetrics-gynecology, bone development and ophthalmology.

Specifically, the working group evaluated the numerous clinical concerns around long-term retinoid use, including:

- Side effects impacting the bones and eyes
- Psychiatric effects
- Cardiovascular effects
- Contraceptive concerns
- Drug effects between hormonal birth control and long-term retinoid use

"Currently, there are no guidelines for which types of ichthyosis to treat with retinoids and at what doses," Lucky says. "This working group was a good example of collaboration between investigators and experienced clinicians at different institutions to help fill that unmet need."

RESEARCH & TRAINING DETAILS

Faculty	3
Total Annual Grant Awards	$86.592
Total Annual Industry Awards	$234,572

Lucky AW, PeDRA Use of Retinoids in Ichthyosis Work Group. Executive summary: Consensus recommendations for the use of retinoids in ichthyosis and other disorders of cornification in children and adolescents. J Am Acad Dermatol. 2022 Jan;86(1):158-161. doi: 10.1016/j.jaad.2021.08.047. Epub 2021 Sep 6. PMID: 34499997.

Consensus Statements on Use of Retinoids in Ichthyosis and Other Disorders of Cornification in Children and Adolescents

Retinoid Effects on the Skin	SORT
Both topical and systemic retinoids can improve scaling in patients with select forms of ichthyosis.	II, B
Utilization of retinoids in some disorders with skin fragility, peeling skin, atopic diathesis, or excessive desquamation (eg, Netherton syndrome) may exacerbate disease and should be used with caution.	II, B
Both adults and children with moderate-to-severe disorders of keratinization with significant functional or psychological impairment should be offered the opportunity to make a benefit/risk assessment of treatment with a systemic.	III, C
Retinoid Dosing	
When choosing a systemic retinoid for treatment of disorders of cornification, isotretinoin should be considered first line for patients of reproductive potential.	I, A
Because of the prolonged half life of acitretin (up to 3 years), clinicians should consider transitioning patients of childbearing potential from acitretin to isotretinoin before puberty if at risk of pregnancy.	III, C
The optimal dose of a systemic retinoid is the lowest dose that will achieve and maintain the desired therapeutic effect with acceptable mucocutaneous and systemic toxicities.	I, A
Systemic retinoid treatment of the disorders of cornification is often long term. Therefore, the clinician must counsel patients about potential long-term toxicities.	I, A
Retinoid Effects on Bone	
Long-term use of systemic retinoids in ichthyosis/DOC is associated with skeletal concerns.	I, A
The toxic effects of systemic retinoid use on bone are strongly dependent on dose and duration.	I, A
Potential bone toxicity should not preclude long-term systemic retinoid use in patients with ichthyosis if there is a clear clinical benefit.	III, C

Retinoid Effects on Bone (con't)	SORT
Genetic risk and modifiable factors that affect bone health, such as diet and physical activity, may impact susceptibility to systemic retinoid bone toxicity and should be discussed with the patient.	II, C
Systemic Retinoid Effects on the Eye	
Systemic retinoid therapy can cause retinal dysfunction, night blindness, and dry eyes. Use may exacerbate existing eye symptoms related to underlying ichthyosis.	I, A
For patients who are on long-term systemic retinoid therapy, evaluation by ophthalmology is recommended 4-6 mos. after initiation of systemic retinoid therapy, routine follow up every 6-12 mos.	III, C
Systemic Retinoid Effects on Lipids & the Liver	
Severe lipid abnormalities and hepatotoxicity with the use of systemic retinoids are very rare.	II, B
Serum lipid panels and liver function tests should be performed at baseline and, if in an acceptable range, repeated in 1-2 mos. after starting treatment. If the levels remain within the acceptable range, subsequent testing can be done every 6-12 mos.	II, B
Patients on long-term systemic retinoids with persistent, abnormal, clinically significant elevations in serum lipids may continue retinoid treatment with effective lipid management.	II, C
Psychiatric Effects of Systemic rRetinoid Therapy	
All patients, regardless of history, should be monitored for the development of psychiatric symptoms when they are taking systemic retinoids.	I, A
The Impact of iPLEDGE	
The iPLEDGE program was not designed for long-term use of isotretinoin in patients with ichthyosis and imposes a significant burden on this patient population.	III, C

DOC (disorders of cornification)
SORT (strength of recommendation taxonomy)

Parent Collaboration Leads to Homeless Shelter Improvements

Pamela Williams-Arya, MD

Tanya Froehlich, MD, MS

PUBLISHED OCTOBER 2021
Family & Community Health

Many scientists and clinicians understand that homelessness often has lasting negative impacts for child health, behavior, and development. However, few have worked as directly with parents experiencing homelessness as this team of researchers led by experts at Cincinnati Children's.

In a project led by Pamela Williams-Arya, MD, and Tanya Froehlich, MD, MS, the team gathered 53 parents from three homeless shelters to conduct a Group-Level Assessment (GLA). This community-based research methodology engages stakeholders to develop participant-driven results and relevant action plans. Participants were asked to respond to 20 open-ended questions about their child's medical, developmental, learning, social, and behavioral needs.

Responses coalesced around four themes: job and housing stability, education and skill development, emotional support, and improving shelter life. Sharing the findings with shelter and community leaders led to a number of policy and practice enhancements.

Improvements included enhanced child development programming at all the shelters. More staff were hired to coordinate services and activities for children, and a Play & Learn parenting support program was piloted. One local shelter also began providing childcare on-site, which made it easier for parents to attend and focus on their job and housing interviews.

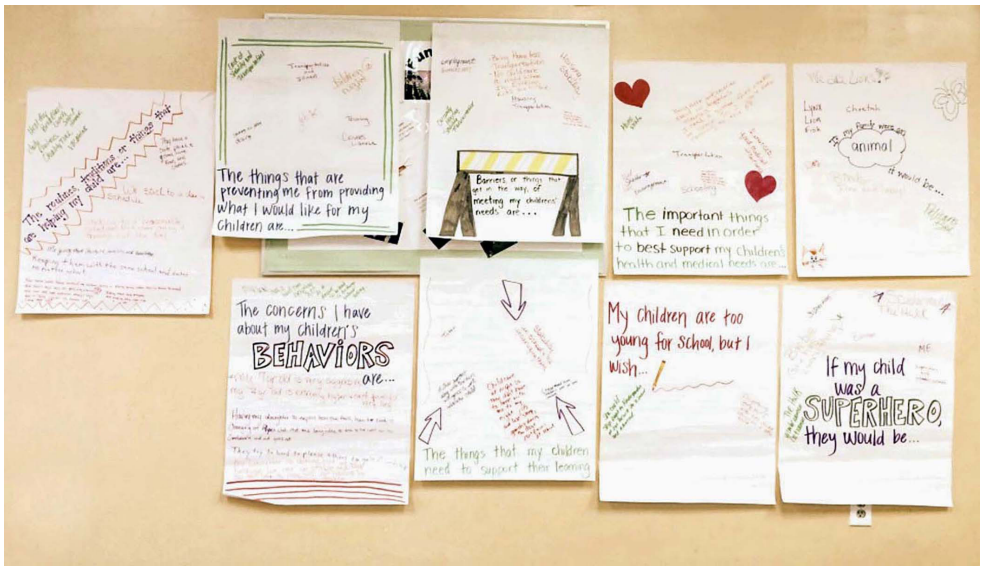
"GLA provides a valid, lived-experience way to uncover local needs and priorities and thus can be utilized in a wide range of settings," says Tanya Froehlich, MD, MS, director of research in the Division of Developmental and Behavioral Pediatrics and the study's senior author. "This research approach is also exciting because it can amplify diverse stakeholder voices, including those from historically marginalized groups, such as racial and ethnic minorities."

RESEARCH & TRAINING DETAILS

Faculty	22
Joint Appointment Faculty	1
Research Fellows & Post Docs	1
Total Annual Grant Awards	$3.7M

Williams-Arya P, Vaughn L, Nidey N, Sawyer M, Porter, Kayla BA, Froehlich T. Striving for Structure and Stability in Cincinnati's Family Homeless Shelters: A Community-Based Participatory Research Approach. Fam Community Health: October/December 2021 - Volume 44 - Issue 4 - p 282-291 doi: 10.1097/FCH.0000000000000305

Group-Level Assessment



Participants responded to up to 20 open-ended questions about their child's medical, developmental, learning, social, and behavioral needs.

Knowing Limits, Seeking Help Are Major Factors in Entrustment Decisions

Daniel Schumacher, MD, PhD, MEd

PUBLISHED MARCH 2022
Medical Education

One of the most important factors in deciding what we trust trainees to do in the future is the trainee's ability to know their own limits and seek help, but evaluation committees often lack robust data confirming those attributes, according to research by Daniel Schumacher, MD, PhD, MEd, and colleagues.

Entrustment committees (in undergraduate medical education) and clinical competency committees (in graduate medical education) understandably look at past performance as a predictor of future performance. This study explored what else is needed to make decisions about what a trainee would be allowed to do in future, unknown situations.

The team undertook a constructivist grounded theory study with 23 faculty participants from clinical competency and entrustment committees in the United States between October 2020 and March 2021.

"What we heard quite clearly and consistently is that ability to know limits and seek help is very important to decisions about what study participants would entrust someone to do in the future. We need to collect more data focusing on these areas," Schumacher says. "The other finding that stood out for me is that these committees often lack the data they need to make robust decisions and instead put trainees on default pathways of advancement unless red flags arise. As an assessment researcher for the past few decades, this is not a surprising finding to me. However, it is the first study to actually capture this sentiment from study participants. This has important implications for ensuring safe, effective patient care."

RESEARCH & TRAINING DETAILS

Faculty	47
Joint Appointment Faculty	3
Research Graduate Students	1
Total Annual Grant Awards	$3.9M

Schumacher DJ, Michelson C, Winn AS, Turner DA, Elshoff E, Kinnear B. Making prospective entrustment decisions: Knowing limits, seeking help and defaulting. Med Educ. 2022 Sep;56(9):892-900. doi: 10.1111/medu.14797. Epub 2022 Mar 16. PMID: 33465313.

Emergency Medicine

Type Matters: Children with T2 Diabetes Have More Heart Structure Changes than Children with T1 Diabetes

Elaine Urbina, MD, MS

Amy Shah, MD, MS

RESEARCH & TRAINING DETAILS

Faculty	21
Joint Appointment Faculty	2
Research Fellows & Post Docs	2
Total Annual Grant Awards	$3.7M
Total Annual Industry Awards	$852,613

Shah AS, Isom S, Dabelea D, D'Agostino R Jr, Dolan LM, Wagenknecht L, Imperatore G, Saydah S, Liese AD, Lawrence JM, Pihoker C, Urbina EM; SEARCH for Diabetes in Youth Study Group. A cross sectional study to compare cardiac structure and diastolic function in adolescents and young adults with youth-onset type 1 and type 2 diabetes: The SEARCH for Diabetes in Youth Study. Cardiovasc Diabetol. 2021 Jul 7;20(1):136. doi: 10.1186/s12933-021-01328-0. PMID: 34233679; PMCID: PMC8265135.

PUBLISHED JULY 2021
Cardiovascular Diabetology

A cross-sectional analysis spearheaded by Cincinnati Children's finds that children and young adults with youth-onset type 2 diabetes have worse left ventricle structural changes and diastolic function than those with type 1 diabetes.

Researchers from multiple institutions used data from the SEARCH for Diabetes in Youth Study. Led by Amy Shah, MD, MS, Lawrence Dolan, MD, and Elaine Urbina, MD, MS, investigators compared left ventricular structure and diastolic function from two-dimensional echocardiogram studies for patients in the SEARCH study group.

The team used linear models to examine the risk factors associated with worse diastolic function. The analysis showed abnormal diastolic function in both groups compared to published values from age-similar healthy controls.

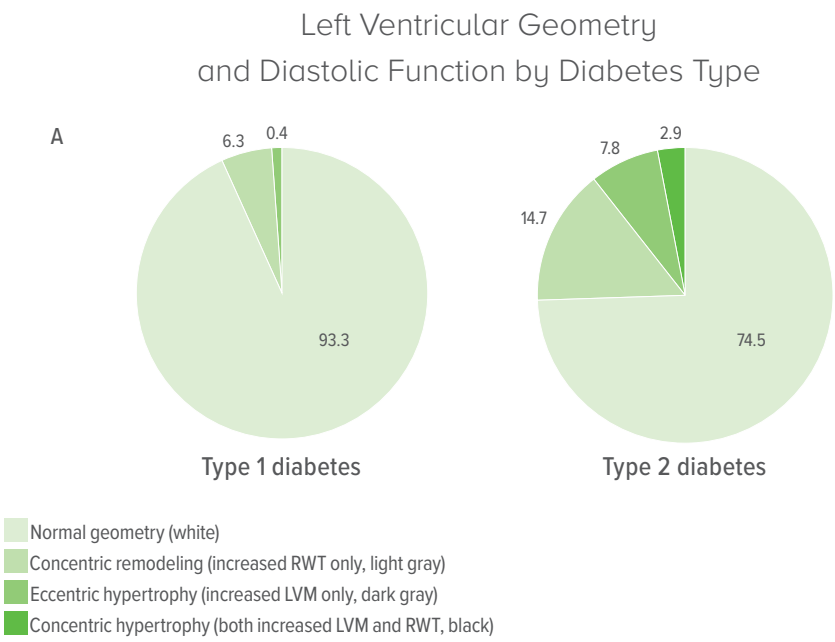
One challenge posed by the study was that echocardiograms are not routinely obtained in patients with diabetes unless high blood pressure is present, says Shah. Echocardiograms are available at most health centers, but the test can be expensive. It's also important to have standardized protocols for acquiring images and interpreting them.

"Until now we didn't know whether there was thickening of the left ventricle or changes in diastolic function in this population or that there was a difference by diabetes type," Shah says.

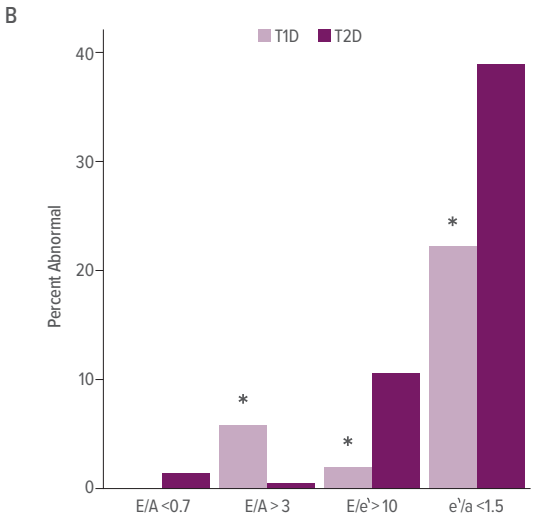
After 20 years of funding from the National Institutes of Health and the Centers for Disease Control and Prevention, the SEARCH study has ended.

Shah says it will be important to follow the young adults from the study as they age. Doing so will help explain the true meaning of these findings.

"We were just hitting a time in these youth and young adult lives where we were seeing early heart complications," Shah says.

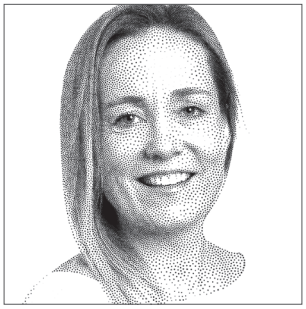


A. Distribution of Left Ventricular Geometry by Diabetes Type. Participants with type 1 and type 2 diabetes were stratified into four groups according to the left ventricle mass (LVM) cutoff > 51 g/m2.7 and relative wall thickness (RWT) cutoff of > 0.41: The p value difference between groups was < 0.0001.



B. Prevalence of Abnormal Diastolic Function by Diabetes Type. Diastolic function was compared to data from age-similar healthy controls to assess the percent of abnormal diastolic function in participants with type 1 diabetes (T1D) and type 2 diabetes (T2D).

DNA Methylation May Serve as Biomarker for Maternal Stress Passed to Children



Katherine Bowers, PhD, MPH

Alonzo "Ted" Folger, PhD, MS

PUBLISHED OCTOBER 2021
BMC Pediatrics

Developmental delays affect more than 10% of school-age children in the United States and are increasing in prevalence. Children from socioeconomically disadvantaged families have an even higher risk for impaired cognitive and social-emotional development.

Experts often attribute the gap to adversity factors such as violence, relocation, food insecurity, or maternal depression. More recently, research indicates that some factors, such as maternal stress, can cause epigenetic changes that affect brain development. To further measure this potential intergenerational effect, the PRegnancy and Infant DEvelopment (PRIDE) pilot study included more than 50 mothers and their infants who were already participating in Every Child Succeeds—a home-visiting intervention program for at-risk families. The team found that maternal depression, perceived stress, and overall distress during pregnancy were associated with child internalizing and externalizing behaviors at 24 and 36 months.

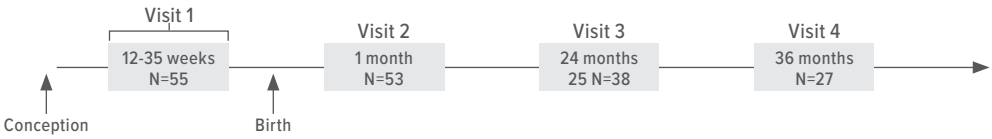
The team, led by Katherine Bowers, PhD, MPH, Division of Biostatistics and Epidemiology, and Alonzo "Ted" Folger, PhD, MS, director of evaluation and epidemiologic research for Every Child Succeeds, also collected cheek swabs to conduct DNA methylation analyses, which may serve as a biomarker of stress-related developmental delay risk. DNA methylation results were not specified in this paper.

Now researchers plan to follow up the pilot study with a 400-family longitudinal cohort study funded by the National Institute on Minority Health and Health Disparities. This larger study will collect data from pregnant women and their infants at 1, 4, 12, and 18 months.

"If we can identify the type and timing by which adversity (and protective factors) affect development, services can be targeted to best support families," Bowers says. "Through our partnership with Every Child Succeeds, we are uniquely positioned to translate findings from this research through precision home visiting and additional strategies."

Bowers, K., Ding, L., Yolton, K. et al. Pregnancy and Infant Development (PRIDE)—a preliminary observational study of maternal adversity and infant development. BMC Pediatr 21, 452 (2021). https://doi.org/10.1186/s12887-021-02801-1

Overview of PRIDE-Cincy Study Visits and Data Collection



- Sociodemographic, including addresses for community-level indicators
- Edinburgh Postnatal Depression Scale
- Adverse Childhood Experiences
- Brief Symptom Index-18
- Interpersonal Support Evaluation List
- Hair Cortisol

- Repeated Measures of Maternal Adversity and Resilience
- NICU Network Neurobehavioral Scale
- DNA/RNA

- Repeated Measures of Maternal Adversity and Resilience
- Child Behavior Checklist
- Ages and Stages Questionnaire-Social-Emotional-2
- DNA/RNA

- Repeated Measures of Maternal Adversity and Resilience
- Child Behavior Checklist
- Ages and Stages Questionnaire-Social-Emotional-2
- DNA/RNA

ABCC12 Gene Mutations Tied to Idiopathic Chronic Cholestasis

Chunyue Yin, PhD

Alexander Miethke, MD

RESEARCH & TRAINING DETAILS

Faculty	48
Joint Appointment Faculty	1
Research Fellows & Post Docs	13
Research Graduate Students	1
Total Annual Grant Awards	$13.6M
Total Annual Industry Awards	$654,679

Pham DH, Kudira R, Xu L, Valencia CA, Ellis JL, Shi T, Evason KJ, Osuji I, Matuschek N, Pfuhler L, Mullen M, Mohanty SK, Husami A, Bull LN, Zhang K, Wali S, Yin C, Miethke A. Deleterious Variants in ABCC12 are Detected in Idiopathic Chronic Cholestasis and Cause Intrahepatic Bile Duct Loss in Model Organisms. Gastroenterology. 2021 Jul;161(1):287-300.e16. doi: 10.1053/j.gastro.2021.03.026. Epub 2021 Mar 23. PMID: 33771553; PMCID: PMC8238842.

PUBLISHED JULY 2021
Gastroenterology

Research led by Chunyue Yin, PhD, and Alexander Miethke, MD, uncovered a novel candidate gene for inherited chronic cholestasis and a potential therapeutic target for progressive intrahepatic bile duct loss. Cohorts of children with idiopathic chronic cholestasis were surveyed with whole exome and candidate gene sequencing.

Researchers collaborated with the Molecular Genetics Laboratory at Cincinnati Children's and with the multicenter, NIH-funded consortium ChiLDReN. They found a homozygous deleterious variant in the gene *ABCC12* — in just one patient. This gene encodes multidrug resistance-associated protein 9 (MRP9) that belongs to the adenosine 5′-triphosphate-binding cassette transporter C family with unknown function and no previous implication in liver disease.

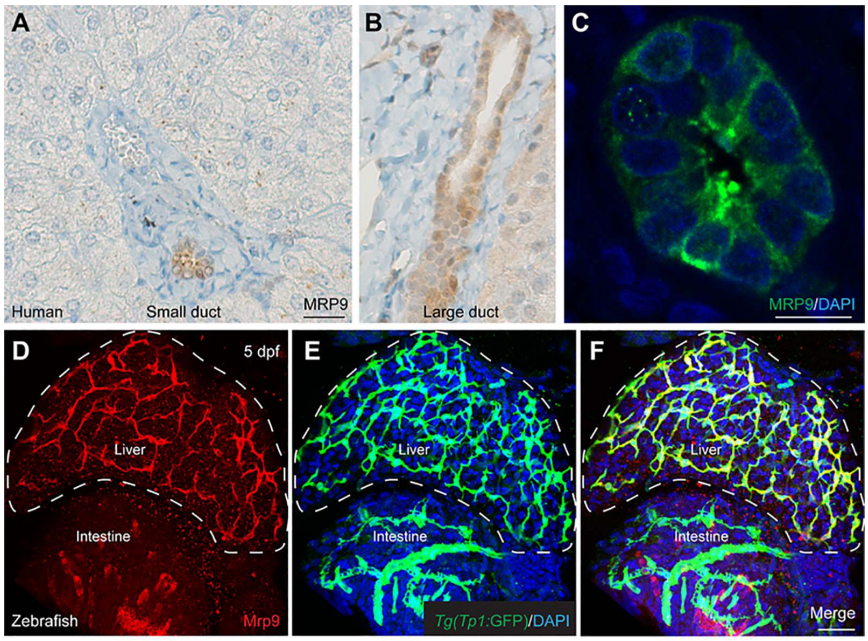
"Variants in *ABCC12* had never been connected to cholestasis," Yin says. "Nothing was known about the function of this gene and its protein product."

With little previous study on *ABCC12*, researchers developed two animal models to validate the causality of *ABCC12* variants in cholestasis. They created zebrafish and mouse *ABCC12* mutants in-house, plus assays, reagents and tools to study *ABCC12*.

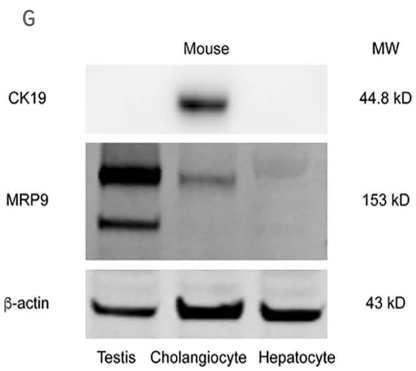
There were many trials and failures, Yin says. What's now known is that MRP9 deficiency renders cholangiocytes susceptible to bile acid-induced death in zebrafish and mouse models. Yin and Miethke have submitted an R01 grant proposal to investigate how loss of *ABCC12* causes cholangiocyte death and cholestasis. Understanding that mechanism could help develop personalized treatments.

A retrospective analysis for rare variants in *ABCC12* from more than 770 next generation sequencing (NGS) cases with cholestasis also is underway, in collaboration with the Cincinnati Children's Division of Human Genetics.

MRP9 Protein Was Expressed in Cholangiocytes in Human, Zebrafish and Mouse



(A-B) Chromogenic detection of MRP9 protein in the control liver of a child without known liver disease. (C) Confocal single plane image showing expression of MRP9 protein (green) in the intrahepatic bile duct in the control human liver. (D-F) Confocal three-dimensional projections showing MRP9 protein expression (image D) and Tg(Tp1:GFP) transgene expression (image E) in the intrahepatic bile ducts in WT zebrafish at 5 days post fertilization (dpf). Image F shows the merged image of D and E. (G) Immunoblotting of protein lysates from mouse testis (positive control), purified primary intrahepatic cholangiocytes, and hepatocytes with antibodies against CK19, MRP9, and loading control β-actin. Molecular weights (MW) are listed. Scale bars: (A) 20 µm; (B) 10 µm; (C-E) 30 µm.



Mechanical Support Before Transplantation Improves Survival for Pediatric Heart Failure Patients

Karthik Thangappan, MD

David Morales, MD

PUBLISHED APRIL 2022
ASAIO Journal

Data from children with end-stage heart failure shows that pediatric ventricular assist devices (VADs) make many patients better transplant candidates, improves their end-organ function at transplantation and significantly improves post-transplant survival. The study, based on the first 1,200 children to receive VADs as bridges to transplantation, was led by Cincinnati Children's cardiothoracic surgery research fellow Karthik Thangappan, MD, and David Morales, MD. Without mechanical circulatory support (MCS), pediatric patients often do not survive their time on organ waiting lists.

"This was the largest ever report of pediatric VAD patients from the U.S.," Morales says. "In 2004, only four VADs had been placed in the U.S. This shows what our field has achieved together, with cooperation."

Researchers identified pediatric MCS patients from the vast United Network for Organ Sharing database, then divided the data into three eras: first (2005-2009), second (2010-2014) and third (2015-2019). Findings include:

- More MCS patients were successfully bridged to transplantation in the third era (28%) compared to the first era (16%) and second era (24%).
- The proportion of patients discharged on VAD healthy enough to wait at home for a possible transplant increased from 3% to 22%.
- One-year survival post-transplant reached 96% in the third era and three-year survival reached 89%, both improvements compared to the previous eras.

Renal dysfunction, ventilator dependence, inotrope use and functional status all improved for patients on MCS while waiting for transplantation. Now with a large database, researchers plan to focus future studies on more specific questions and larger goals.

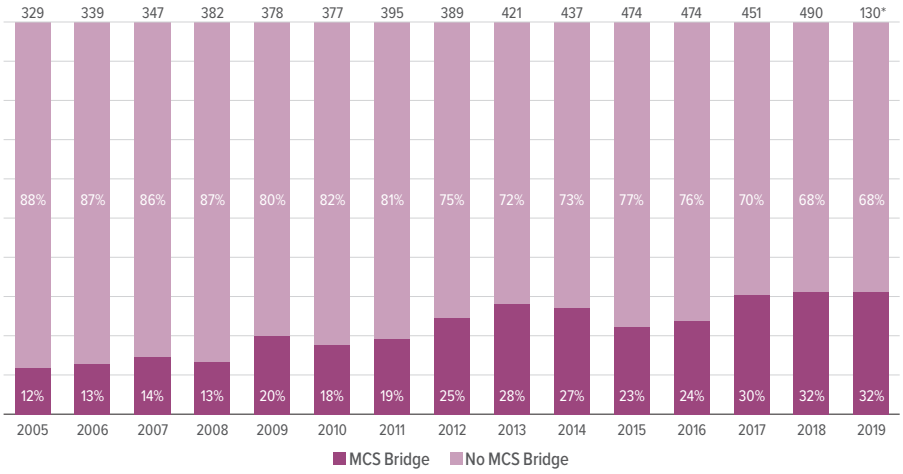
"This is the first step toward our ultimate goal of creating a predictive tool on an AI platform to inform clinicians and families about the outcomes they can expect after VAD implantation," Morales says.

RESEARCH & TRAINING DETAILS

Faculty	7
Total Annual Grant Awards	$1.1M
Total Annual Industry Awards	$981,420

Thangappan K, Zafar F, Lorts A, Adachi I, Rosenthal D, Rossano J, Maeda K, Morales DLS. MILESTONE: More Than 1,200 Children Bridged to Heart Transplantation with Mechanical Circulatory Support. ASAIO J. 2022 Apr 1;68(4):577-583. doi: 10.1097/MAT.0000000000001635. PMID: 35349524.

More than 1,200 Children BTT with MCS
MCS Bridge vs. No-MCS Bridge to Transplant



The proportion of pediatric heart transplant recipients bridged to transplant over the years. Stacked bar plot denoted the yearly proportion of pediatric heart transplants using and not using mechanical circulatory support to bridge to transplantation (BTT) over the 15-year study period.

Numbers on top of bars denote the total number of pediatric heart transplantations in the given year.

*The 2019 total reflects only the first three months of the year. Censored events are standard for Kaplan-Meier analysis: only account for any lack of post-transplant follow-up survival data.

Deprivation Disrupts Clinic Visits, Does Not Increase Hospital Utilization

Joanna Thomson, MD, MPH

Andrew Beck, MD, MPH

PUBLISHED APRIL 2022
Pediatrics

Children with medical complexity (CMC) living in areas of greater socioeconomic deprivation have higher odds of missing outpatient visits, but such deprivation is not associated with more hospitalizations nor emergency department utilization.

That's the conclusion of a cross-sectional study led by Joanna Thomson, MD, MPH, Andrew Beck, MD, MPH, and colleagues that involved 512 children with complex conditions receiving care in a Cincinnati Children's patient-centered medical home. The study found a 13% relative increase in the missed clinic visit rate for every 0.1 unit increase in the Deprivation Index but found no association between area-level deprivation and emergency department visits, hospitalizations, or inpatient bed-days.

The co-authors suggest that the patient-centered concept followed by the Complex Care Center at Cincinnati Children's may blunt expected increases in hospital utilization caused by poverty and related factors. However, families with children who require complex care still experience barriers to preventive, follow-up appointments.

"To ensure equitable care and outcomes for all children with medical complexity, health systems and providers should seek to understand and address any barriers to care arising from the socioeconomic context in which they live," Thomson says.

The Cincinnati Children's community health initiative has been working closely with families and community partners to identify strategies to help children receive the right care at the right time and place, and in the right way.

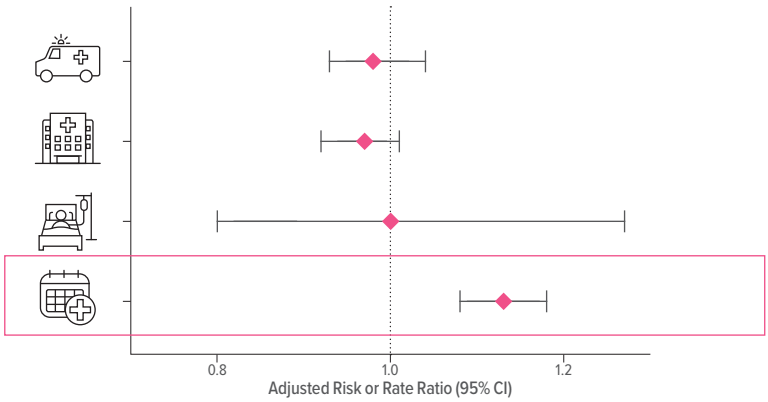
Watch a video abstract of the findings:

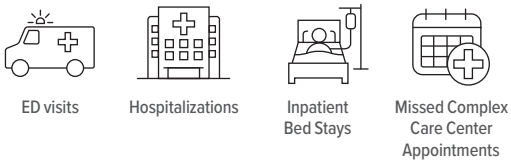
RESEARCH & TRAINING DETAILS

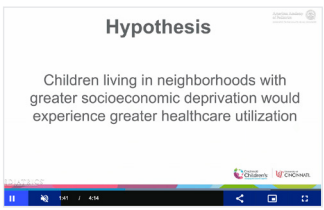
Faculty	62
Joint Appointment Faculty	9
Total Annual Grant Awards	$965,795

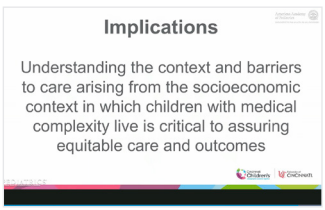
Thomson J, Butts B, Camara S, Rasnick E, Brokamp C, Heyd C, Steuart R, Callahan S, Taylor S, Beck AF. Neighborhood Socioeconomic Deprivation and Health Care Utilization of Medically Complex Children. Pediatrics. 2022 Apr 1;149(4): e2021052592. doi: 10.1542/peds.2021-052592. PMID: 35253047.

How Socioeconomics Affects Adherence





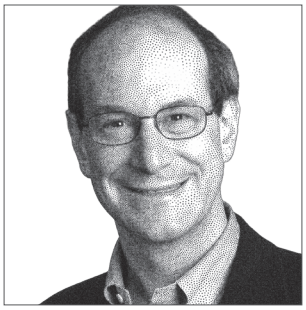




A child's socioeconomic context is associated with their adherence to primary care medical home (PCMH) visits. Our PCMH for CMC includes children living in neighborhoods with a range of socioeconomic deprivation and may blunt effects from harmful social determinants. Incorporating knowledge of the socioeconomic context of where CMC and their families live is crucial to ensure equitable health outcomes.

14-Center Study Finds Key Genes Linked to Different Forms of Pediatric Cardiomyopathy

Lisa Martin, PhD



Bruce Aronow, PhD

RESEARCH & TRAINING DETAILS

Faculty	37
Joint Appointment Faculty	5
Research Fellows & Post Docs	31
Research Graduate Students	15
Total Annual Grant Awards	$11.7M
Total Annual Industry Awards	$1.2M

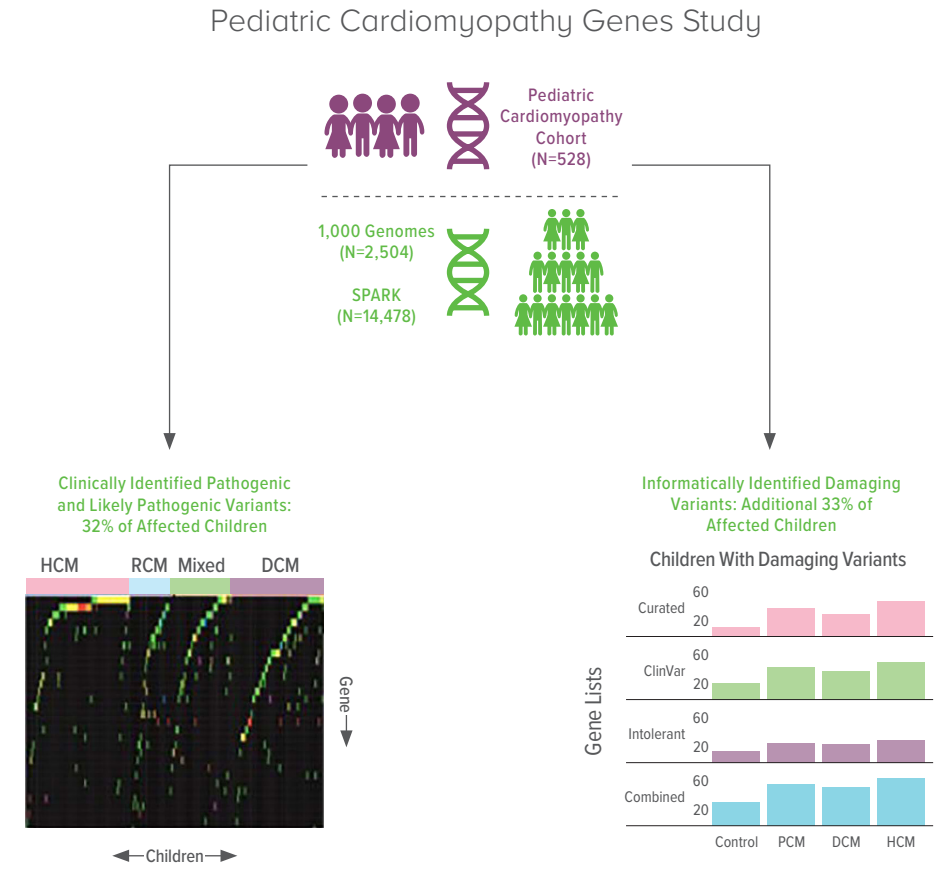
Ware SM, Bhatnagar S, Dexheimer PJ, Wilkinson JD, Sridhar A, Fan X, Shen Y, Tariq M, Schubert JA, Colan SD, Shi L, Canter CE, Hsu DT, Bansal N, Webber SA, Everitt MD, Kantor PF, Rossano JW, Pahl E, Rusconi P, Lee TM, Towbin JA, Lal AK, Chung WK, Miller EM, Aronow B, Martin LJ, Lipshultz SE, Pediatric Cardiomyopathy Registry Study Group. The genetic architecture of pediatric cardiomyopathy. Am J Hum Genet. 2022 Feb 3;109(2):282-298. doi: 10.1016/j.ajhg.2021.12.006. Epub 2022 Jan 12. PMID: 35026164; PMCID: PMC8874151.

PUBLISHED FEBRUARY 2022

American Journal of Human Genetics

While both children and adults can develop cardiomyopathy, until now, most knowledge about risk genes causing the condition have been derived from adult studies. That landscape has changed since the Pediatric Cardiomyopathy Registry Study Group conducted a 14-center exome sequencing project involving 528 children suffering from distinct forms of cardiomyopathy and at high risk of needing a heart transplant. Data analyses were led by Surbhi Bhatnagar, PhD student, as a co-first author, and by Lisa Martin, PhD, Division of Human Genetics, and Bruce Aronow, PhD, co-director, Computational Medicine Center, as co-senior authors. When comparing affected genes among these children to an existing list of known genes linked to cardiomyopathy, only 32% of the cohort displayed risk variants. However, comparing the children to a wider set of candidate genes—compiled using a gene, protein, cell, and multi-population human gene variation network analysis approach—revealed that 56% of the cohort carried potentially causal genes and damaging variants.

"These results suggest that while current clinical genetic testing is warranted, more research on the genes of cardiomyopathy is needed. Future studies should include wider diversity. Further, larger sample sizes will enable us to evaluate the impact of harboring multiple damaging variants," says Martin. The yield of risk genes detected varied by ancestry, type of cardiomyopathy, and age. For example, patients with European ancestry and hypertrophic cardiomyopathy showed higher yields. The most commonly found variants involved the genes *MYH7* and *MYBPC3*. However, no *MYBPC3* variants were found in children of African descent. Other Cincinnati Children's co-authors included Erin Miller, MS, CGC, Phillip Dexheimer, PhD student, and Jeffrey Towbin, MD (now with Le Bonheur Children's Hospital). All exome sequencing was performed at Cincinnati Children's. The team also used the ToppGene suite, developed at Cincinnati Children's, to analyze candidate genes.



Differential gene burden per phenotype and ancestry

Novel Treatment May Help Manage Cytokine Storms, Reduce CAR-T Risks

Chandrashekhar Pasare, DVM, PhD

PUBLISHED JANUARY 2022
Science Immunology

Whether it's children coping with rare autoimmune diseases or cancer patients receiving promising new immune therapies, many clinicians and scientists have been working to reduce the risks of patients experiencing a potentially deadly cytokine storm. Now, a team from Cincinnati Children's reports early-stage success at taming these immune system over-reactions by disrupting signals emanating from activated T cells.

The team developed a mouse model that mimics the cytokine storm that can be triggered by chimeric antigen receptor T cell (CAR-T) therapy. The model helped them identify a critical signaling node used by effector memory T cells (T_{EM}) to mobilize a broad proinflammatory program in the innate immune system.

The findings show that these signals can be disrupted, both through gene editing and with small molecule compounds. Without treatment, 100% of mice induced to experience a cytokine storm died within five days. But 80% of mice treated with antibodies to block T_{EM} signals survived at least seven days.

"This discovery is important because we have shown, in mice, that the systemic inflammatory pathways involved in this type of T cell-driven cytokine storm can be mitigated," says corresponding author Chandrashekhar Pasare, DVM, PhD, co-director of the Center for Inflammation and Tolerance at Cincinnati Children's. "More work will be needed to confirm that the approach we used in mice can also be safe and effective for humans. But now we have a clear target to pursue."

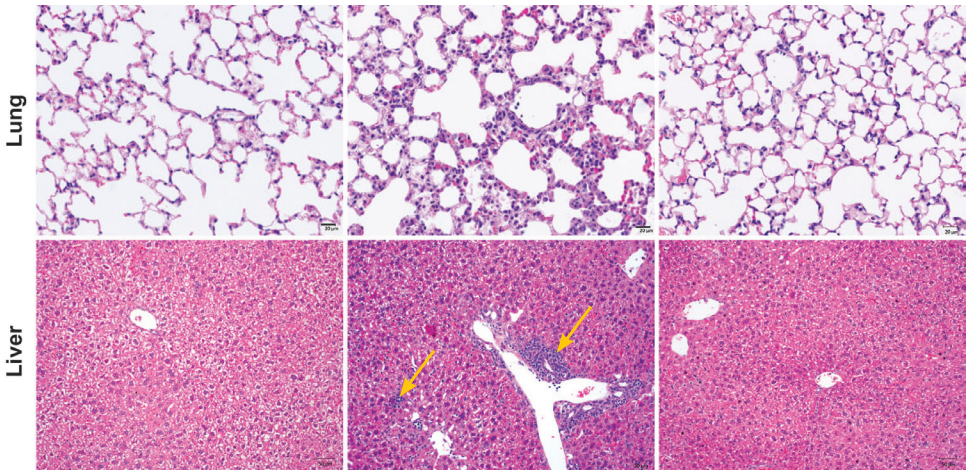
While people with SARS-CoV-2 also have suffered cytokine storms, this "sterile" form of runaway inflammation differs significantly from systemic inflammation triggered by a viral infection, Pasare says.

In addition to Pasare, the study included three lead authors: Margaret McDaniel, Aakanksha Jain, and Amanpreet Singh Chawla, PhD, all formerly with Cincinnati Children's.

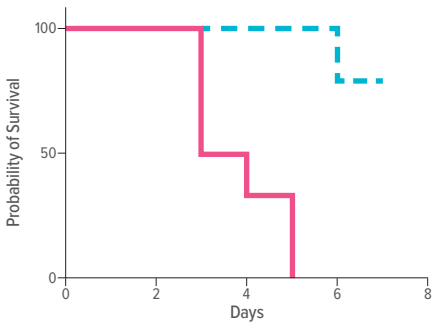
RESEARCH & TRAINING DETAILS

Faculty	13
Joint Appointment Faculty	3
Research Fellows & Post Docs	14
Research Graduate Students	29
Total Annual Grant Support	$10.3M
Total Annual Industry Support	$40,258

McDaniel MM, Chawla AS, Jain A, Meibers HE, Saha I, Gao Y, Jain V, Roskin K, Way SS, Pasare C. Effector memory CD4+ T cells induce damaging innate inflammation and autoimmune pathology by engaging CD40 and TNFR on myeloid cells. Sci Immunol. 2022 Jan 21;7(67):eabk0182. doi: 10.1126/sciimmunol.abk0182. Epub 2022 Jan 21. PMID: 35061504; PMCID: PMC9036191.



These microscope images of mouse lung tissue (top) and liver tissue (bottom) compare immune cell infiltration between healthy control mice (left), untreated mice experiencing auto-immune cytokine storm (middle) and mice receiving antibody treatment to block T cell-induced activation of inflammatory cytokines. Arrows indicate periportal and lobular infiltrates in the liver.



Survival rates in mice experiencing a T cell-induced cytokine storm. Untreated mice died within 5 days. Mice pretreated with neutralizing antibodies against TNF and CD40 for 12 hours before induction showed significantly improved survival.

Families Praise "Enhanced Pre-Consent Discussions" Before Entering Clinical Trials

Ellen Lipstein, MD, MPH

William Brinkman, MD, MEd, MSc

PUBLISHED JULY 2021
Patient Education and Counseling

The good news is that families participating in a large clinical trial of a medication to treat Crohn's disease generally liked it when clinicians used an "enhanced pre-consent discussion" technique during the enrollment process.

The challenging news is that the measures used to evaluate the technique were not sensitive enough to demonstrate much impact. And that has the study leaders, Ellen Lipstein, MD, MPH, and William Brinkman, MD, MEd, MSc, planning further research.

This project started from the idea that if people better understood that clinical trials are conducted when doctors do not know the best way to treat a condition, they may be more willing to participate. The team's hypothesis: improved decision-support interventions could lead to higher enrollment rates.

To test this, the team developed a more conversational approach to describing the aims of a clinical trial, with the specific goal of engaging participants in shared decision-making. Increasing understanding would, in theory, improve willingness to join. The technique was introduced to 241 participants in the multi-center COMBINE clinical trial, which evaluated low-dose methotrexate as a therapy for pediatric Crohn's disease.

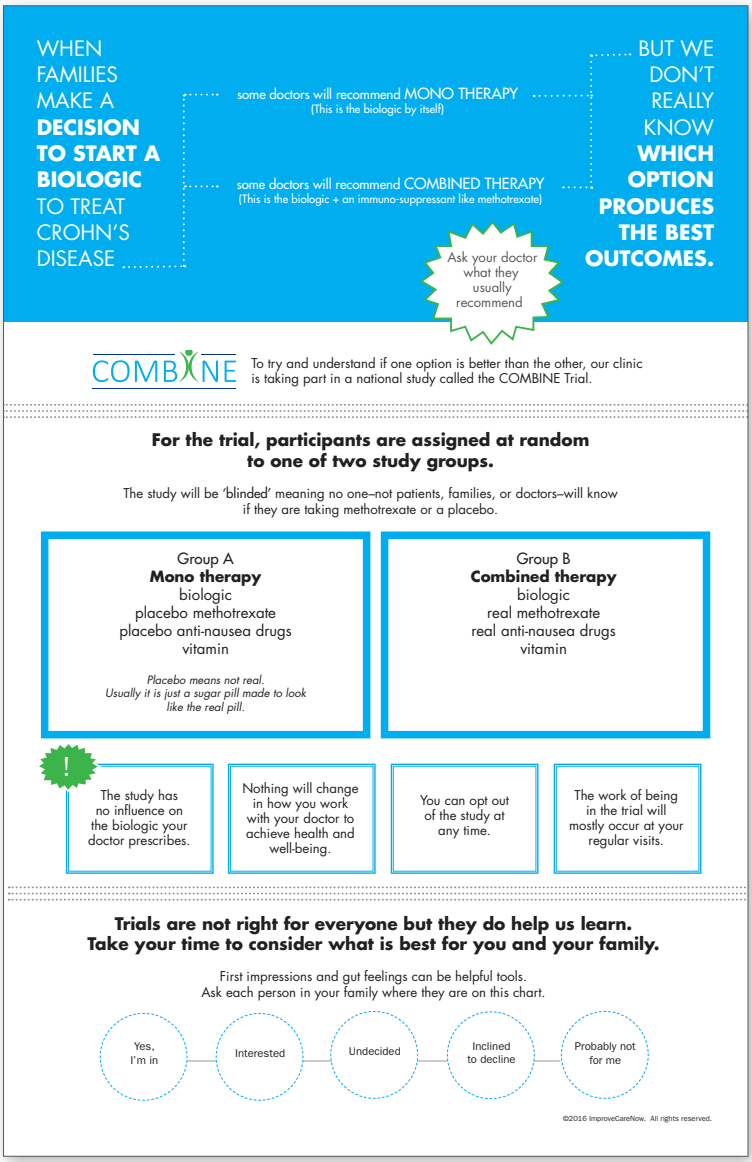
"Although the intervention was well-liked, we found no differences in knowledge, perceptions of decision support or study enrollment rates between arms of our study," Lipstein says. The researchers say possible reasons for why the study showed no clear impact include wide variation in use of the technique among clinicians and a lack of sensitivity in the outcome measures.

However, there is value to a well-liked approach. The study demonstrates that incorporating an in-person shared decision-making intervention into the consent process is feasible, Lipstein says. Next, the team plans to work on more robust measurement strategies to better evaluate the technique in other trials.

RESEARCH & TRAINING DETAILS

Faculty	11
Joint Appointment Faculty	29
Research Fellows & Post Docs	1
Total Annual Grant Awards	$891,070
Total Annual Industry Awards	$775,717

Lipstein EA, Breslin M, Dodds CM, Kappelman MD, Ollberding NJ, Margolis P, Xu Y, Brinkman WB. Integrating shared decision making into trial consent: A nested, cluster-randomized trial. Patient Educ Couns. 2021 Jul;104(7):1575-1582. doi: 10.1016/j.pec.2020.12.018. Epub 2020 Dec 25. PMID: 33386187.



Cincinnati Children's co-authors included Cassandra Dodds, MA, Nicholas Ollberding, PhD, Peter Margolis, MD, PhD, and Yingying Xu, PhD. The study also included collaborators from Smaller Sanities Studio, New York, NY, and the University of North Carolina at Chapel Hill.

Increased Vigilance, Training Needed to Identify Child Abuse in Infants

Robert Shapiro, MD

PUBLISHED DECEMBER 2021
Pediatric Emergency Care

A physician in an emergency room or urgent care center is in an excellent position to identify possible child abuse in an infant who cannot yet speak or walk. By recognizing sentinel injuries, physicians can take appropriate—possibly lifesaving—action.

Research by Robert Shapiro, MD, and colleagues indicates targeted training of physicians may be needed. The study found that fewer than 50% of infants presenting to a pediatric emergency room or urgent care clinic with visible injuries were evaluated for child abuse. Children who were evaluated by a physician or nurse practitioner trained in pediatric emergency medicine were more likely to be evaluated for signs of abuse.

The study included infants aged 6 months or younger with visible injury who presented to pediatric hospital-affiliated emergency departments or urgent care in Ohio between July 2013 and January 2017. Visible injury was identified in 378 infants, 47% of whom did not receive a skeletal survey.

Many of the infants with bruising, burns or intraoral injuries who were evaluated for child abuse were indeed found to have further injuries: 25% had an occult fracture and 24% had intracranial hemorrhage. Occult fractures were also found in infants with apparently isolated abrasion/laceration (14%), subconjunctival hemorrhage (33%) and scalp hematoma/swelling (13%).

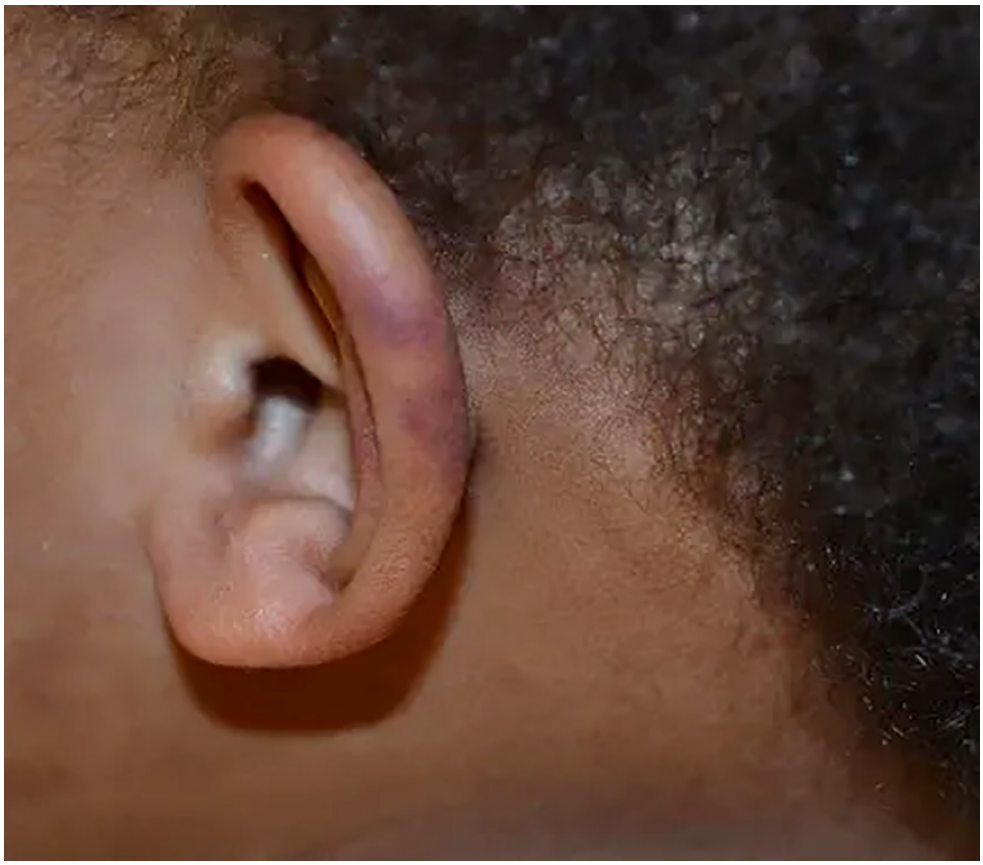
"In a preambulatory infant, injuries found on physical examination are important," Shapiro says. "They're often referred to as sentinel injuries because they indicate that additional trauma may exist. In such cases, X-rays of the entire skeleton and a computed tomography (CT) scan of the brain should be obtained to make sure there are no additional injuries that would indicate concern for physical child abuse."

RESEARCH & TRAINING DETAILS

Faculty	3
Joint Appointment Faculty	3
Total Annual Grant Awards	$313,384

Eismann EA, Shapiro RA, Makoroff KL, Theuerling J, Stephenson N, Duma EM, Fain ET, Frey TM, Riney LC, Thackeray JD. Identifying Predictors of Physical Abuse Evaluation of Injured Infants: Opportunities to Improve Recognition. Pediatr Emerg Care.2021 Dec 1;37(12):e1503-e1509. doi: 10.1097/PEC.0000000000002100. PMID: 32433455

Example of a Sentinel Injury



Minor cutaneous trauma in a preambulatory child may indicate physical child abuse. The Mayerson Center is one of 600 child abuse centers in the United States known as Child Advocacy Centers (CAC). All CACs must be accredited by the National Children's Alliance and meet specific requirements. Our center is one of only a few in the nation housed within a children's hospital and has treated children from 22 Ohio counties, as well as children from Kentucky and Indiana.

Automated System Predicts Children at High Risk for Acute Kidney Injury

Stuart Goldstein, MD

PUBLISHED MAY 2022
Kidney International Reports

Research led by Stuart Goldstein, MD, and colleagues integrates the Renal Angina Index (RAI) developed at Cincinnati Children's with an automated clinical decision support program to improve its ease of use at the bedside.

A three-year prospective trial called TAKING FOCUS 2 (TF2) is testing the program. First-year TF2 data demonstrated improved prediction of severe acute kidney injury (AKI) when the urinary biomarker neutrophil gelatinase-associated lipocalin (NGAL) is evaluated in critically ill patients with an RAI ≥8.

TF2 integrates the RAI into the Epic™ electronic medical record. Epic™ automatically calculates the RAI at the first 12 hours of admission to the pediatric intensive care unit (PICU). If the RAI ≥8, a clinician simply releases a reflex order for an NGAL test. Clinicians use the results to guide treatment, which can include fluid management and renal replacement therapy initiation.

Goldstein hopes that the TF2 study leads to the universal availability of an automated RAI tool that clinicians everywhere can use.

AKI occurs in about 25% of critically ill children admitted to the PICU. Severe AKI occurs in 11% of PICU cases and is independently associated with morbidity and 28-day mortality. The RAI-NGAL clinical decision support system lets clinicians quickly guide therapy for patients likely to develop severe AKI and avoid unnecessary interventions for patients not likely to develop AKI.

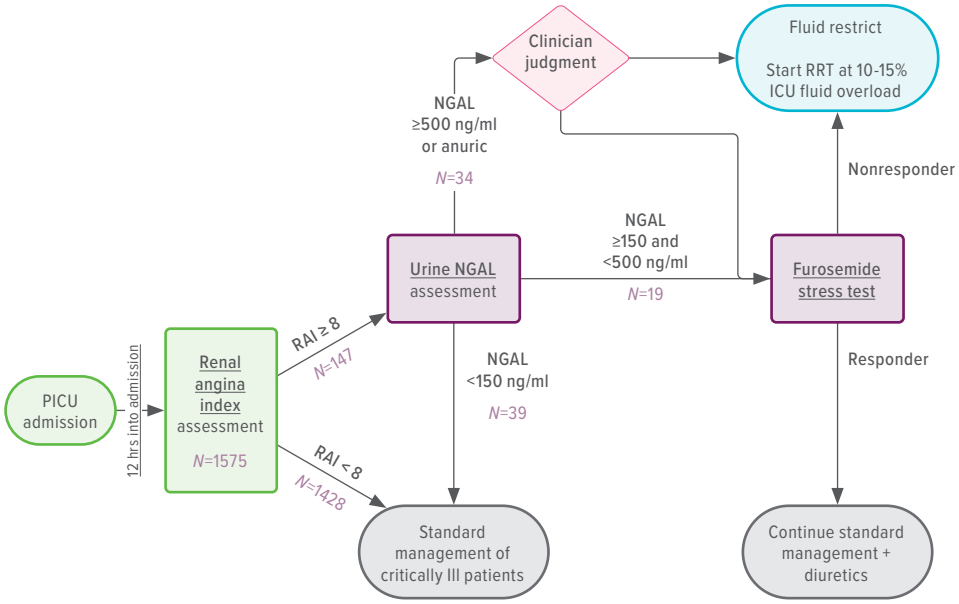
The system "provides real-time data that helps intensivists and nephrologists support patients with severe AKI in a standardized way earlier than they did before," Goldstein says.

RESEARCH & TRAINING DETAILS

Faculty	12
Joint Appointment Faculty	4
Research Fellows & Post Docs	2
Total Annual Grant Awards	$1.7M
Total Annual Industry Awards	$1.5M

Goldstein SL, Krallman KA, Kirby C, Roy JP, Collins M, Fox K, Schmerge A, Wilder S, Gerhardt B, Chima R, Basu RK, Chawla L, Fei L. Integration of the Renal Angina Index and Urine Neutrophil Gelatinase-Associated Lipocalin Improves Severe Acute Kidney Injury Prediction in Critically Ill Children and Young Adults. Kidney Int Rep. 2022 May 25;7(8):1842-1849. doi: 10.1016/j.ekir.2022.05.021. PMID: 35967111; PMCID: PMC9366367.

TAKING FOCUS 2 AKI



The TAKING FOCUS 2 AKI clinical decision support flow algorithm can predict whether a child will develop severe AKI within three days of admission to the pediatric intensive care unit and can guide physicians in applying treatment. The clinical support algorithm suggests patients at low risk, RAI– and RAI+/NGAL–, receive standard management per PICU. Patients at high risk, RAI+/NGAL+, with NGAL 150–500 ng/ml, can have further risk stratification with a furosemide stress test (FST), unless contraindicated, whereas those with >500 ng/ml can either have an FST or initiate renal replacement therapy (RRT) if there is an emergent indication or if it is deemed better/urgent by the primary team. FST responders have a lower risk of requiring RRT, so management with diuretic and fluid restriction is suggested, although FST nonresponders are likely to fail diuretic management and an initiation of RRT is suggested if FO >10% to 15% cannot be prevented by fluid restriction alone.

Machine Learning Improves Early Surgery Referrals for Epilepsy Patients

Judith Dexheimer, PhD

Hansel Greiner, MD

RESEARCH & TRAINING DETAILS

Faculty	47
Joint Appointment Faculty	3
Research Fellows & Post Docs	2
Research Graduate Students	6
Total Annual Grant Awards	$4.9M
Total Annual Industry Awards	$740,672

Wissel BD, Greiner HM, Glauser TA, Pestian JP, Kemme AJ, Santel D, Ficker DM, Mangano FT, Szczesniak RD, Dexheimer JW. Early identification of epilepsy surgery candidates: A multicenter, machine learning study. Acta Neurol Scand. 2021 Jul;144(1):41-50. doi: 10.1111/ane.13418. Epub 2021 Mar 26. PMID: 33769560; PMCID: PMC8178229.

PUBLISHED JULY 2021
Acta Neurologica Scandinavica

An artificial intelligence algorithm developed at Cincinnati Children's can identify epilepsy surgery candidates earlier in the disease process.

Judith Dexheimer, PhD, and colleagues Hansel Greiner, MD, and Ben Wissel, PhD, MD-PhD candidate at the University of Cincinnati, have completed multiple studies to verify the algorithm's methods, check for racial bias, and guide the tools to improve the technology.

The algorithm runs on a software program embedded into a hospital's electronic health record (EHR). Using natural language processing techniques, it analyzes previous provider notes for each patient with an upcoming appointment in the epilepsy clinic. The algorithm considers the words, tone, and themes in the notes, and uses a scoring system to identify patients who meet neurosurgical criteria.

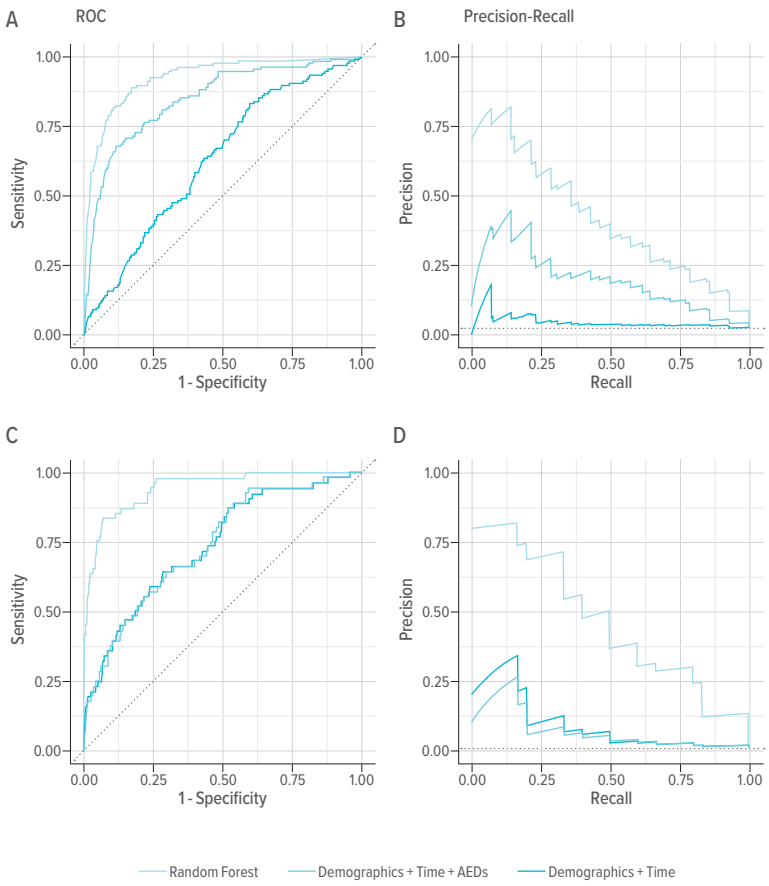
When patients are identified, the algorithm sends reminders to providers. Doctors who receive notices are three times more likely to refer patients for a surgery consult, Dexheimer says.

The team soon will deploy the device at UC Health in Cincinnati and at other pediatric centers and community hospitals to verify its use at other centers and answer the question, "Can we use it at a community hospital and indentify patients who should be referred to a specialty hospital?" Greiner says.

Currently there is no universal standard for neurosurgical intervention referrals for adults or children. The goal is to reduce the time to initial surgery evaluation for patients with intractable epilepsy. The national average in pediatrics is 10 years.

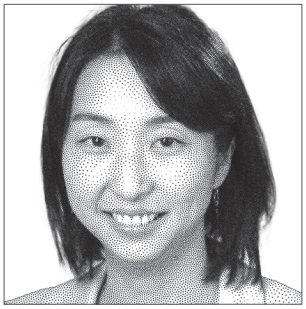
The machine learning algorithm is a collaborative project from the John Pestian Lab at Cincinnati Children's and the hospital's divisions of Biostatistics and Epidemiology, Emergency Medicine, Biomedical Informatics, Neurology, and Neurosurgery.

Evaluating an Epilepsy Surgery Algorithm



Receiver operating characteristic (ROC) and precision-recall curves for the pediatric (A, B) and adult (C, D) datasets. The gray dotted line represents the performance of a random classifier. "Demographics + Time + AEDs" represents the baseline logistic regression model that included anti-epileptic drug prescriptions, and "Demographics + Time" represents the baseline model without anti-epileptic drugs

Bindarit: A Potential Treatment for Protecting Neural Development in Neonatal Hydrocephalus



June Goto, PhD

Francesco Mangano, DO

RESEARCH & TRAINING DETAILS

Faculty	8
Research Fellows & Post Docs	1
Research Graduate Students	1
Total Annual Grant Awards	$560,343
Total Annual Industry Awards	$166,691

Iwasawa E, Brown FN, Shula C, Kahn F, Lee SH, Berta T, Ladle DR, Campbell K, Mangano FT, Goto J. The Anti-Inflammatory Agent Bindarit Attenuates the Impairment of Neural Development through Suppression of Microglial Activation in a Neonatal Hydrocephalus Mouse Model. J Neurosci. 2022 Mar 2;42(9):1820-1844. doi: 10.1523/JNEUROSCI.1160-21.2021. Epub 2022 Jan 6. PMID: 34992132; PMCID: PMC8896558.

PUBLISHED MARCH 2022
Journal of Neuroscience

The anti-inflammatory agent bindarit may restore cognitive and motor function damaged by neonatal hydrocephalus, investigators at Cincinnati Children's have found.

Research led by Francesco Mangano, DO, and June Goto, PhD, finds that administering bindarit significantly supports healthy postnatal cerebral cortical development. The findings, based on a mouse model, go beyond what is commonly known about neonatal hydrocephalus—that neuroinflammation and glial cell activation occur as a reaction to pressure.

"It's not been studied whether it's also related to cognitive or motor dysfunction in those patients," Goto says. "We thought we could find a new target to help improve neural cell development and brain function." Mangano and Goto identified cortical neuropil maturation defects such as:

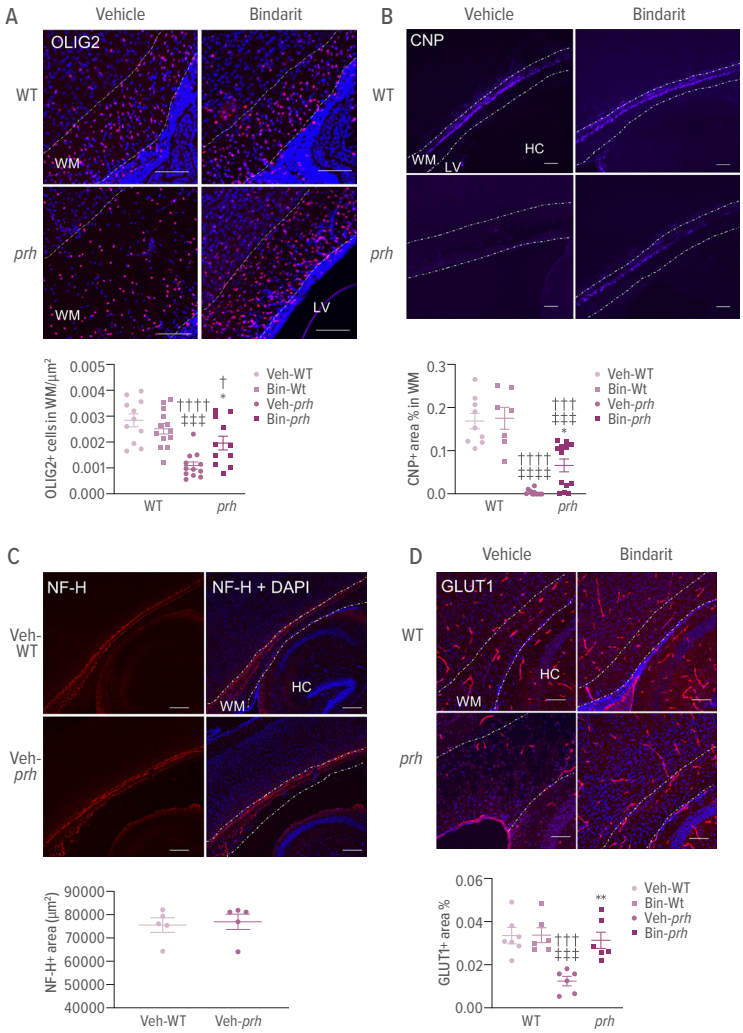
- Impaired maturation of excitatory synapses
- Dendritic arborization of inhibitory neurons
- Loss of homeostatic microglia
- Hindlimb locomotor defects

"The hydrocephalus mice showed spastic hind limb movements in the swim test," Goto says. "The bindarit treatment supported both neuronal and glial cell development and improved those movements."

Hydrocephalus prevents proper myelination and development of cortical neuronal cells. Bindarit blocks nuclear factor (NF)-kB activation and pro-inflammatory microglial activation. This restores the cortical neuropil thinning and synaptic maturation defects in *prh* mutant mouse brains.

These study results open the potential for the therapeutic use of anti-inflammatory reagents like bindarit. There may be opportunities to prevent microglial activations or turn off damaging responses, Mangano says. Future studies of bindarit treatment combined with CSF diversion surgery may provide long-term benefits supporting neuronal development in neonatal hydrocephalus.

Myelination and Vascularization in *prh* White Matter with Bindarit Treatment.



(WM, white matter; LV, lateral ventricles; HC, hippocampus.)

A. Number of pan-oligodendrocyte lineage marker OLIG2+ cells per WM shows reduced oligodendrocyte density in veh-*prh* and improvement in bin-*prh*.

B. The mature myelination marker CNP positive staining area % in WM shows significant reduction of myelination in veh-*prh* and partial recovery in bin-*prh*.

C. Neurofilament-labeled axons (NF-H) positive area (μm2) in WM shows no significant difference between veh-WT and veh-*prh*.

D. Endothelial cell marker, GLUT1 positive staining area per WM (%) shows reduced vascular densities in veh-*prh* and significant recovery in bin-*prh*.

Non-Invasive Test Can Detect Uveitis Biomarkers in Tears

Sheila Angeles-Han, MD, MSc

Mekibib Altaye, PhD

RESEARCH & TRAINING DETAILS

Faculty	12
Joint Appointment Faculty	1
Research Fellows & Post Docs	5
Research Graduate Students	3
Total Annual Grant Awards	$631,258

Angeles-Han ST, Utz VM, Thornton S, Schulert G, Rodriguez-Smith J, Kauffman A, Sproles A, Mwase N, Hennard T, Grom A, Altaye M, Holland GN. S100 proteins, cytokines, and chemokines as tear biomarkers in children with juvenile idiopathic arthritis-associated uveitis. Ocul Immunol Inflamm. 2021;29(7-8):1616-1620. doi: 10.1080/09273948.2020.1758731. Epub 2020 May 28. PMID: 35169380; PMCID: PMC8842740.

PUBLISHED NOVEMBER 2021
Ocular Immunology and Inflammation

Sight-robbing eye damage is one of the most unfortunate outcomes for children diagnosed with juvenile idiopathic arthritis. JIA-associated uveitis (JIA-U) occurs in 10-20% of children with JIA and sight-threatening complications occur in up to 50% of affected children.

While clinicians can look for signs of eye inflammation during ophthalmic exams, experts have been hunting for a reliable biomarker that can more accurately detect early signs of JIA-U.

Previous research has found that certain S100 proteins, cytokines, and chemokines can serve as biomarkers. However, when these tests are conducted using serum the results are not accurate. When collected via aqueous humor (AqH), the results are accurate, but the invasive collection method makes it not feasible unless a child is having eye surgery.

Now, a team of researchers led by Sheila Angeles-Han, MD, MSc, Mekibib Altaye, PhD, and colleagues reports that these biomarkers can be collected from tears using Schirmer strips (small sterile slips of paper often used to measure tear volume).

In children with active uveitis, the biomarkers S100A12, IL-8, and sICAM-1 were all significantly increased compared to children with inactive uveitis.

"S100A12, IL-8, and sICAM-1 are associated with neutrophils. Neutrophil and mononuclear cell infiltration characterize endotoxin-induced uveitis in an animal model of acute anterior uveitis. Together, these data led us to speculate that neutrophils may play a role in the pathogenesis of anterior uveitis," Angeles-Han says.

Since the paper was published, Cincinnati Children's has provided internal funds to generate more pilot data to further pursue these findings. Validation in a large prospective cohort may better define the role of local inflammatory biomarkers in pediatric uveitis. These studies could lead to a non-invasive method of ocular screening of children with JIA and uveitis.

Using Tears to Collect Biomarkers

Key biomarkers of JIA-associated uveitis can be collected using non-invasive Schirmer strips, according to research from experts at Cincinnati Children's.

Stabilization Surgery for Hip Fractures Improves Outcomes for Some Pediatric Patients

Patrick Whitlock, MD, PhD

PUBLISHED MARCH 2022
Journal of Orthopedic Trauma

Surgical intervention could improve hip joint function for some pediatric and adolescent patients with hipbone socket (acetabulum) fractures, according to research conducted by Patrick Whitlock, MD, PhD, and colleagues.

These findings were based on the self-reported functional outcomes of 21 patients under age 18—one of the largest studies of its kind to date. Researchers found that open reduction internal fixation (ORIF) surgery could benefit patients who experience the same factors that support surgery in adults. They must have a fracture that is displaced by at least 2 mm in the weight-bearing portion of the hip, as well as hip instability.

"We strongly advocate for operative management of pediatric acetabulum fractures when adult displacement and instability criteria are present," Whitlock says. "We recommend urgent reduction of all pediatric and adolescent acetabulum fracture dislocations once diagnosed, given the high risks of poor outcomes associated with delayed reduction."

Few guidelines exist for treating this type of pediatric fracture. Most have been left to heal on their own. However, that can lead to complications. In fact, patients who have dislocated fractures for more than six hours have a 20-times higher risk of developing avascular necrosis than patients who receive prompt surgical intervention, Whitlock says.

The team used functional and health surveys to evaluate outcomes for pediatric patients who underwent ORIF surgery. Results included 86% reporting normal physical and mental component scores post-operatively, as well as normal bother scores. However, function scores were worse: 31.9 compared to the 12.7 population average, largely for patients who had delayed surgery.

"It's possible that younger, more active patients expect to have a higher level of function than an older adult population," he says. "That could account for the significant difference in scores."

RESEARCH & TRAINING DETAILS

Research Fellows & Post Docs	1
Total Annual Grant Awards	$497,705
Total Annual Industry Awards	$9,834

Southam BR, Schumaier A, Ramalingham W, Avilucea F, Denning JR, Whitlock, PW, Archdeacon MT. Pediatric and Adolescent Fractures of the Acetabulum Treated with ORIF: What Are Their Functional Outcomes? J Orthop Trauma. 2022 Mar; 36(3):137-141. Doi: 10.1097/BOT.0000000000002248. PMID: 34456313

Improving Outcomes for Hip Fractures

	Patient									Merle d'Aubigné				Length of Follow-Up (mo)	Complications
	Age	Sex	BMI	MOI	Fracture Type	Dislocation	Physes	Surgical Approach	QOR	Pain	Walking	ROM	Total		
1	11	F	18.2	MVA	PCPW	Y	Open	KL	A	6	6	6	18	118	None
2	12	M	26.2	Low fall	PCPW	N	Open	KL	A	5	5	6	16	11	None
3	12	F	28.7	Others	Transverse	N	Closed	KL	A	4	6	6	16	24	Cam lesion & labral tear—underwent hip arthroscopy
4	13	M	23.9	Low fall	PW	N	Open	KL	A	6	6	6	18	24	None
5	14	M	27.7	Low fall	PCPW	Y	Closed	KL	A	3	5	4	12	46	AVN & PTOA—converted to THA
6	15	M	24.5	Others	PC	N	Open	KL	A	6	6	6	18	57	None
7	15	F	25	MVA	T type	Y	Closed	KL	A	6	6	6	18	130	None
8	15	M	27.1	Others	PW	N	Closed	KL	A	6	6	6	18	24	None
9	16	F	28.7	MVA	BC	N	Closed	AIP	A	6	6	6	18	110	Abductor weakness
10	16	F	34.9	MVA	TPW	Y	Closed	KL	A	6	6	6	18	12	None
11	16	F	21.1	MVA	PC	Y	Closed	KL	A	6	6	6	18	13	Trochanteric bursitis
12	16	M	20.2	Low fall	T type	Y	Closed	AIP	A	6	6	6	18	27	None
13	16	M	35.2	Low fall	PW	Y	Closed	KL	A	3	5	5	13	26	AVN & PTOA—converted to THA
14	17	M	34.3	MVA	T type	N	Closed	II and KL	I	6	6	6	18	77	None
15	17	M	23.2	MVA	Transverse	N	Closed	KL	A	4	6	5	15	118	Postoperative infection
16	17	M	38.3	MVA	TPW	N	Closed	KL	A	5	5	5	15	70	Sciatic nerve pain
17	17	F	29.8	MVA	PW	Y	Closed	KL	A	6	6	6	18	15	None
18	17	M	21.8	MCA	PW	Y	Closed	KL	A	6	6	6	18	180	None
19	17	M	30.5	MCA	T type	Y	Closed	KL	A	5	5	5	15	83	Sciatic nerve pain, partial sciatic nerve palsy, and HO
20	17	F	31.9	MVA	PC	N	Closed	KL	A	6	6	6	18	26	None
21	17	F	36.1	MVA	PW	Y	Closed	KL	A	0	3	2	5	103	AVN & PTOA
Mean															
	15.4	—	28	—	—	—	—	—	—	5.1	5.6	5.5	16.2	61.6	—

A, anatomic; AIP, anterior intrapelvic; AVN, avascular necrosis; BC, both column; HO, heterotopic ossification; I, imperfect; II, ilioinguinal; KL, Kocher-Langenbeck; MCA, motorcycle accident; MVA, motor vehicle accident; PC, posterior column; PCPW, posterior column posterior wall; W, posterior wall; TPW, transverse posterior wall

How Intermittent Hypoxia Disrupts Circadian Rhythms

Bala S.C. Koritala, PhD

David Smith, MD, PhD

PUBLISHED OCTOBER 2021
Genes

More than 1 billion people worldwide experience episodes of oxygen desaturation (intermittent hypoxia) as a result of obstructive sleep spnea (OSA). Untreated OSA can cause a wide range of health conditions including heart disease, neurological, and metabolic disorders.

Scientists have suspected that IH interferes with circadian rhythms. But the body has many clocks operating in many tissues. Which ones are affected the most when IH occurs?

Circadian medicine researchers at Cincinnati Children's, led by Bala S.C. Koritala, PhD, and David Smith, MD, PhD, have shed light on this mystery by studying how exposure to IH affects the circadian rhythms of core clock genes in mice. These genes are known to play roles in regulating several physiological functions including daily activity, blood pressure, and core body temperature.

The team found that the brain's circadian clock was highly affected by IH as compared to the liver's clock. In particular, the *Arntl* and *Nr1d1* genes in the brain and *Cry2* in the liver lost their circadian gene expression as a consequence of IH exposure.

Future studies will seek to determine how disrupted clocks affect the OSA disease process.

"In summary, our results reinforce the concept that the clock response to IH is tissue-dependent," Smith says. "Our observations also provided insights to potential underlying etiologies of circadian rhythm-associated health conditions."

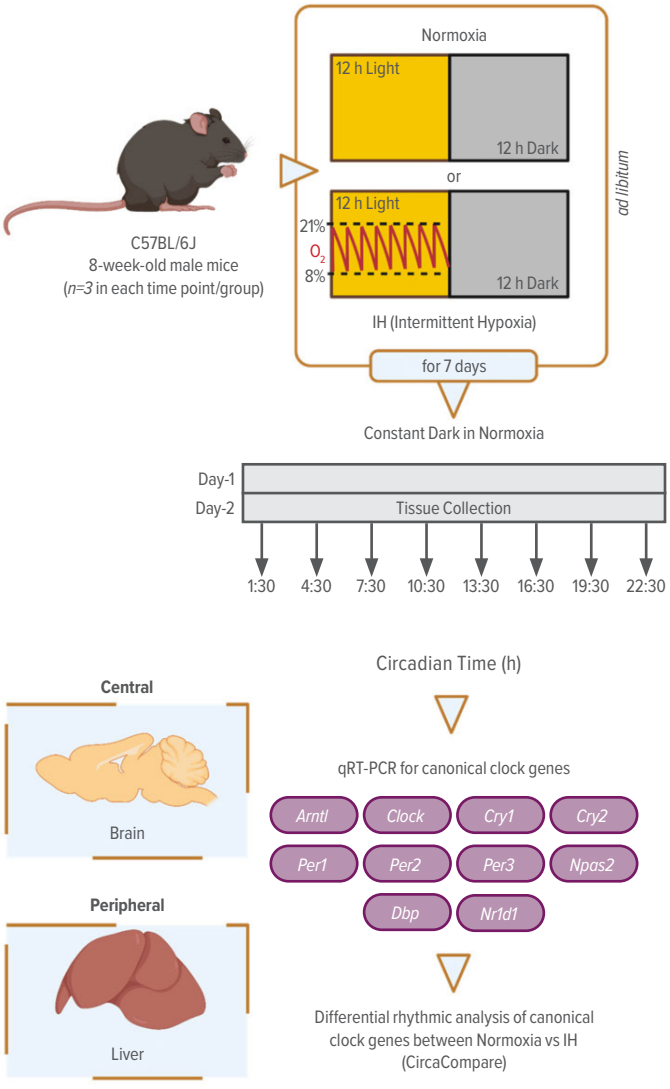
In addition to Koritala and Smith, seven people at Cincinnati Children's were contributing co-authors: Yin Yeng Lee, PhD, Shweta Bhadri, MS, Laetitia Gaspar, PhD, Corinne Stanforth, BS, Gang Wu, PhD, Marc Ruben, PhD, and Lauren Francey, MS.

RESEARCH & TRAINING DETAILS

Faculty	14
Joint Appointment Faculty	2
Research Fellows & Post Docs	1
Total Annual Grant Awards	$408,177
Total Annual Industry Awards	$65,104

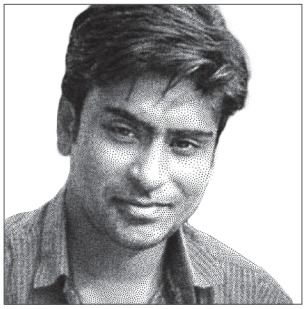
Koritala BSC, Lee YY, Bhadri SS, Gaspar LS, Stanforth C, Wu G, Ruben MD, Francey LJ, Smith DF. Intermittent Hypoxia Alters the Circadian Expression of Clock Genes in Mouse Brain and Liver. Genes (Basel). 2021 Oct 16;12(10):1627. doi: 10.3390/genes12101627. PMID: 34681021; PMCID: PMC8535273.

Sleep Apnea and Clock Genes



In this study, mice were exposed to seven days of normal breathing or intermittent hypoxia (IH). Animals housed under IH received hypoxic events only in the 12 h light phase (similar to nighttime for people). After day 7, both sets of mice spent 2 days of normal breathing in constant darkness. Feeding and temperature were controlled. Then brain and liver tissues were collected at three-hour intervals for analysis.

Momelotinib Inhibits FLT3-Mutant AML Without Major Side Effects



Mohammad Azhar, PhD

Mohammad Azam, PhD

PUBLISHED FEBRUARY 2022
Blood Advances

An estimated one third of patients with acute myeloid leukemia (AML) have mutations in the *FLT3* gene that often results in poor survival rates even when patients receive stem cell transplants. Yet two generations of *FLT3* inhibitors have failed to help people achieve lasting disease remission.

Now, another emerging drug called momelotinib appears to avoid problems encountered by other drugs such as gilteritinib (approved in 2018 for treating adults with *FLT3*-positive AML), according to a pre-clinical study led by first author Mohammad Azhar, PhD, and senior author Mohammad Azam, PhD.

This *JAK2* inhibitor potently inhibits *FLT3*, including preventing activation loop mutations that make AML resistant to quizartinib and a compound mutant form of *FLT3* that is fully resistant to gilteritinib.

"Because momelotinib showed equipotent inhibition of *JAK2* and *FLT3* and suppressed *ACVR1* to alleviate anemic response, we reasoned that it will be more effective in suppressing AML progression and may alleviate chemotherapy induced anemia," Azam says.

In addition, unlike gilteritinib, the drug does not inhibit *c-KIT*, an off-target side effect that can lead to heart damage, poor bone marrow function, and weak blood cell production.

"Its ability to impede the resistance conferred by growth factor signaling and activation loop mutants suggests that momelotinib treatment could provide a deeper and durable response and, thus, warrants clinical evaluation," the study concludes.

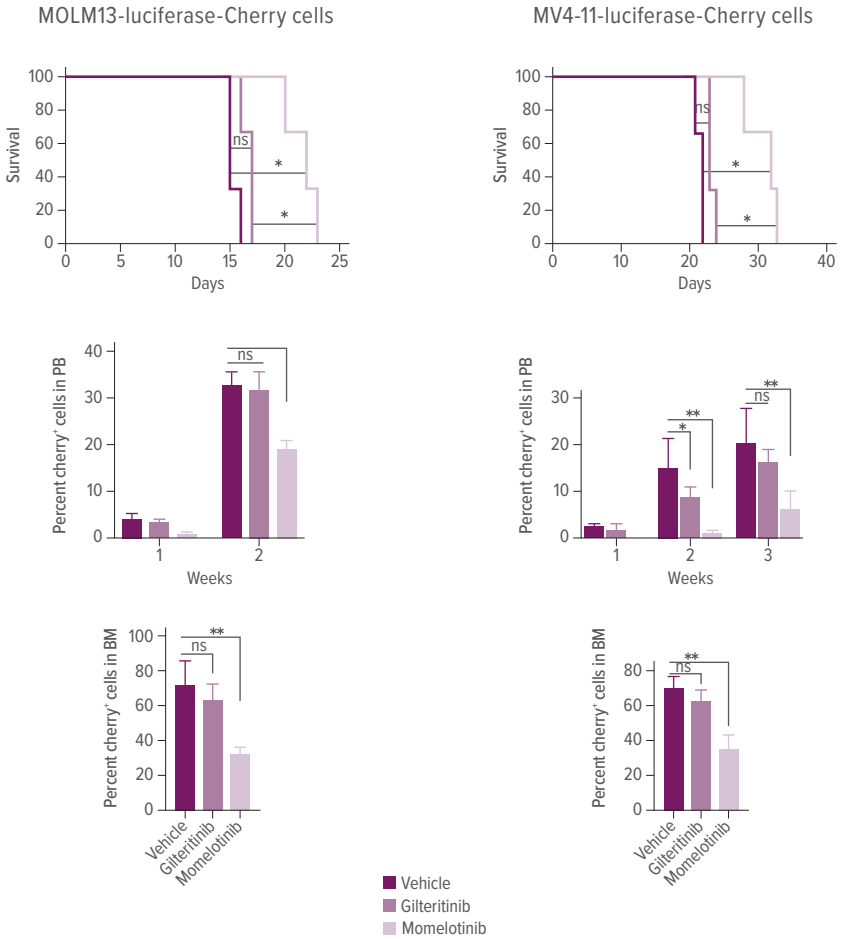
Cincinnati Children's and University of Cincinnati co-authors on this study included Zachary Kincaid, BS, Meenu Kesarwani, PhD, Arhama Ahmed, BS, Mark Wunderlich, Tahir Latif, MD, and Daniel Starczynowski, PhD.

RESEARCH & TRAINING DETAILS

Faculty	26
Joint Appointment Faculty	7
Research Fellows & Post Docs	3
Research Graduate Students	2
Total Annual Grant Awards	$1.2M

Azhar M, Kincaid Z, Kesarwani M, Ahmed A, Wunderlich M, Latif T, Starczynowski D, Azam M. Momelotinib is a highly potent inhibitor of FLT3-mutant AML. Blood Adv. 2022 Feb 22;6(4):1186-1192. doi: 10.1182/bloodadvances.2021004611. PMID: 34768286; PMCID: PMC8864657.

Momelotinib Shows Promise in Pre-Clinical Testing



These charts depict survival times and cancer cell volumes after mice were administered 1 million MOLM13-luciferase-Cherry cells (left panels) and MV4-11-luciferase-Cherry cells (right panels)

Laparoscopic Surgery is an Acceptable Alternative to Laparotomy for Pediatric Ovarian Dermoid Cysts

Lesley Breech, MD

Beth Rymeski, DO

PUBLISHED JUNE 2022
Journal of Pediatric Surgery

As surgeons have become more comfortable with laparoscopic surgery, these less-invasive procedures have become the standard for the treatment of many conditions. Many ovarian dermoid cysts are removed via more-invasive laparotomy procedures, but laparoscopic surgery is a safe and effective alternative for many children with ovarian dermoid cysts, according to research conducted by Lesley Breech, MD, director, Division of Pediatric and Adolescent Gynecology, and her colleagues.

This study relied on a review of 466 patients aged 2 to 21 who underwent ovarian dermoid resection over 10 years. Of these patients, 60% underwent laparoscopy, 30% laparotomy, and 10% laparoscopy converted to laparotomy.

In terms of efficacy, there were no differences between the two procedures in rates of tumor spillage. Importantly, especially for the pediatric population, those patients undergoing laparoscopy had a one-day hospital stay compared to two for laparotomy.

The study ultimately concluded that patients who underwent laparoscopy rather than laparotomy had no differences in tumor spillage, recurrence, or the need for reoperation. Moreover, these patients had a shorter hospital stay compared to laparotomy. As a result, a less-invasive laparoscopy is an acceptable approach for the resection of pediatric ovarian dermoid cysts.

"These results seem to demonstrate that pediatric and adolescent patients, like adults, benefit from the use of a minimally invasive approach to the resection of ovarian dermoid lesions," Breech says. "This paper validates the role of laparoscopy for this indication in this population, getting both kids and parents back to routine activities sooner."

Breech L, Midwest Pediatric Surgery Consortium. Laparoscopy versus laparotomy for pediatric ovarian dermoids. J Pediatr Surg. 2022 Jun;57(6):1008-1012. doi: 10.1016/j.jpedsurg.2022.01.053. Epub 2022 Feb 12. PMID: 35292164.

Outcomes For Dermoid Cyst Resection

	TOTAL		OPERATIVE APPROACH						
			Laparoscopy		Laparotomy		Laparoscopy converted to Laparotomy		
	N or Median	% or (Q1,Q3)	N or Median	% or (Q1,Q3)	N or Median	% or (Q1,Q3)	N or Median	% or (Q1,Q3)	p for difference
TOTAL	466	100%	279	60%	139	30%	48	10%	
AGE	14	(11, 17)	15	(11, 17)	14	(11, 17)	13	(9, 16)	0.08
Race/Ethnicity									0.92
Asian	12	3%	8	3%	2	1%	2	4%	
Hispanic	49	11%	29	10%	15	11%	5	10%	
Multiracial	12	3%	8	3%	3	2%	1	2%	
Non-Hispanic Black	89	19%	55	a	23	17%	11	23%	
Non-Hispanic White	266	57%	160	57%	82	59%	24	50%	
Other	38	8%	19	7%	14	10%	5	10%	
Specialty of Operating Surgeon									0.002
Pediatric and adolescent gynecology	122	26%	80	29%	39	28%	3	6%	
Pediatric surgery	260	56%	142	51%	77	55%	41	85%	
Adult gynecology	58	12%	44	16%	13	9%	1	2%	
Combination case or other specialty	26	6%	13	5%	10	7%	3	6%	
Size of lesion (cm)									
	7.6	(5.2, 11.1)	6.4	(5, 9)	11.4	(8, 17)	7.2	(6, 10)	<0.0001
Procedure									0.09
Ovarian-sparing surgery	303	65%	191	68%	80	58%	32	67%	
Oophorectomy	163	35%	88	32%	59	42%	16	33%	
Tumor spillage at the time of surgery									0.15
Yes	70	15%	48	17%	19	14%	3	6%	
No	379	81%	224	80%	112	81%	43	90%	
Unknown	17	4%	7	3%	8	6%	2	4%	
Length of stay (days)									
	1	(1, 2)	1	(0, 2)	2	(1,3)	2	(2, 3)	<0.0001

Less-invasive laparoscopic procedures are an acceptable alternative for pediatric ovarian dermoid cysts.

Dentists Can Influence COVID-19 Vaccine Uptake

Jennifer Cully, DMD, MEd

PUBLISHED SEPTEMBER 2021
Journal of the American Dental Association

The introduction of the COVID-19 vaccine has helped to curb many of the effects of the global pandemic. In healthcare settings, it has allowed for a safer environment for practicing dentistry, including aerosol-generating procedures, which can play a disproportionate role in spreading the disease.

Moreover, dentists can influence the uptake of the COVID-19 vaccine, according to research conducted by Jennifer Cully, DMD, MEd, Division of Pediatric Dentistry and Orthodontics, and her colleagues.

The study involved administering a 41-point questionnaire about vaccine acceptance to caregivers of children receiving oral healthcare in a dental clinic in an urban pediatric teaching hospital. The questionnaire used the Health Belief Model—a tool aimed at predicting future health behaviors.

The results showed that 39.2% of caregivers would not allow their child to receive a COVID-19 vaccination. However, 27.8% of caregivers agreed that if their physician recommended a COVID-19 vaccination, they would allow their child to receive it. In total, 52.2% said that a healthcare professional could influence this decision.

"Although vaccine hesitancy has been researched in dental settings, this article was one of the first specifically looking at the COVID vaccination for children in the context of dentistry," Cully says. "We will continue to look at other areas of vaccination hesitance, such as the HPV vaccination, which continues to be controversial amongst caregivers."

Dentists are able to engage and advocate for vaccines because they already have a history of advocating for preventive health measures like fluoride and frequent check-ups.

Since this study was published, Cully and colleagues have launched other public health projects at the intersection of dentistry and medicine, including advocating for penicillin allergy testing.

RESEARCH & TRAINING DETAILS

Faculty	9
Total Annual Grant Awards	$299,999

Cully JL. Caregiver acceptance of an anticipated COVID-19 vaccination. J Am Dent Assoc. 2021 Sep;152(9):730-739. doi: 10.1016/j.adaj.2021.03.004. Epub 2021 Mar 24. PMID: 34059293; PMCID: PMC7988472.

Caregiver Responses to Questions on Health-Seeking and Health-Acceptance Behaviors

STATEMENT	RESPONSE	NO., n/N (%)	HEALTH BELIEFS MODEL DOMAIN
If My Child Gets COVID-19, They Will Get Sick.	Disagree Neutral Agree	11/96 (11.5) 42/96 (43.8) 43/96 (44.7)	Perceived severity of virus
If My Child Gets COVID-19, They Will Have to Go to the Hospital.	Disagree Neutral Agree	23/98 (23.5) 44/98 (44.9) 31/98 (31.6)	Perceived severity of virus
If My Child Gets COVID-19, They May Never Show Symptoms.*	Disagree Neutral Agree	12/95 (12.6) 35/95 (36.8) 48/95 (50.5)	Perceived severity of virus
My Child Is at Risk for Getting COVID-19.	Disagree Neutral Agree	28/97 (28.9) 39/97 (40.2) 30/97 (30.9)	Perceived susceptibility to virus
If My Child Gets COVID-19, Other Members of Our Family Will Get Sick.	Disagree Neutral Agree	14/96 (14.6) 34/96 (35.4) 48/96 (50.0)	Perceived susceptibility to virus
Wearing a Mask or Facial Covering Helps Prevent the Spread of COVID-19.	Disagree Neutral Agree	12/97 (12.4) 22/97 (22.7) 63/97 (64.9)	Perceived susceptibility to virus
Social Distancing (for Example, Keeping 6 Feet Apart from Others) Helps Prevent the Spread of COVID-19.	Disagree Neutral Agree	4/97 (4.1) 20/97 (20.6) 73/97 (75.3)	Perceived susceptibility to virus
Dentists and Dental Health Care Providers Are at High Risk for Getting COVID-19.	Disagree Neutral Agree	8/98 (8.2) 17/98 (17.3) 73/98 (74.5)	Perceived susceptibility to virus
I Am Worried My Child Will Get Sick or Have Side Effects from a COVID-19 Vaccine.	Disagree Neutral Agree	14/96 (14.6) 29/96 (30.2) 53/96 (55.2)	Perceived clinical barrier to vaccination
I Am Worried About How I Would Pay for the COVID-19 Vaccine for My Child.	Disagree Neutral Agree	55/96 (57.3) 19/96 (19.8) 22/96 (22.9)	Perceived clinical barrier to vaccination
It Would Be Difficult to Take Off From Work or School to Take My Child for the COVID-19 Vaccine.*	Disagree Neutral Agree	59/97 (60.8) 17/97 (17.5) 21/97 (21.6)	Perceived clinical barrier to vaccination
The COVID-19 Vaccine May Prevent My Child from Getting Sick.	Disagree Neutral Agree	21/95 (22.1) 49/95 (51.6) 25/95 (26.3)	Perceived benefits of vaccination
My Child Getting the COVID-19 Vaccine May Stop Other Children from Getting Sick with the Virus.	Disagree Neutral Agree	23/96 (24.0) 42/96 (43.8) 31/96 (32.2)	Perceived benefits of vaccination
The COVID-19 Vaccination May Prevent Dentists and Dental Health Care Providers from Getting Sick with the Virus.	Disagree Neutral Agree	17/98 (17.3) 37/98 (37.8) 44/98 (44.9)	Perceived benefits of vaccination
If My Doctor Recommends That My Child Receive the COVID-19 Vaccine, Then I Will Vaccinate My Child.	Disagree Neutral Agree	41/97 (42.3) 29/97 (29.9) 27/97 (27.8)	Cue to action

* Owing to rounding the values do not sum to 100%.

Dentists can play an important role in increasing the uptake of the COVID-19 vaccine.

Mechanisms Regulating Epithelial Integrity Directly Affect Facial Development

Yu Lan, PhD

Rulang Jiang, PhD

PUBLISHED FEBRUARY 2022

Current Topics in Developmental Biology

Two experts at Cincinnati Children's are helping write the book for future scientists to understand the latest discoveries about molecular mechanisms that lead to conditions such as cleft palate.

Craniofacial malformations, including cleft lip and cleft palate, are among the most common structural birth defects, but the etiology and pathogenic mechanisms underlying these birth defects are not well understood.

This book chapter co-authored by Yu Lan, PhD, and Rulang Jiang, PhD, summarizes a collection of mouse genetic studies that have been instrumental in unraveling the mechanisms regulating epithelial integrity and periderm differentiation during facial and palate development. The chapter describes the beginnings of embryonic facial development as cranial neural crest cells interact with the surface ectoderm to form the facial primordia, and the crucial differentiation steps that occur as the facial primordial tissues grow and merge around the oral cavity to form the face and palate.

Disrupting periderm differentiation causes aberrant inter-epithelial adhesions that can interfere with facial morphogenesis. While formation of the upper lip requires adhesion followed by dissolution of intervening epithelial seams, palate formation involves adhesion and fusion of bilateral palatal shelves. The co-authors summarize findings of many gene mutations affecting cell adhesion molecules or their regulation in patients with cleft lip/palate and describe how mouse genetic studies have revealed underlying molecular mechanisms involving these factors.

"Since proper epithelial integrity also plays crucial roles in wound healing and cancer, understanding the mechanisms regulating epithelial integrity during facial development has direct implications for improvement in clinical care of craniofacial patients," the co-authors state.

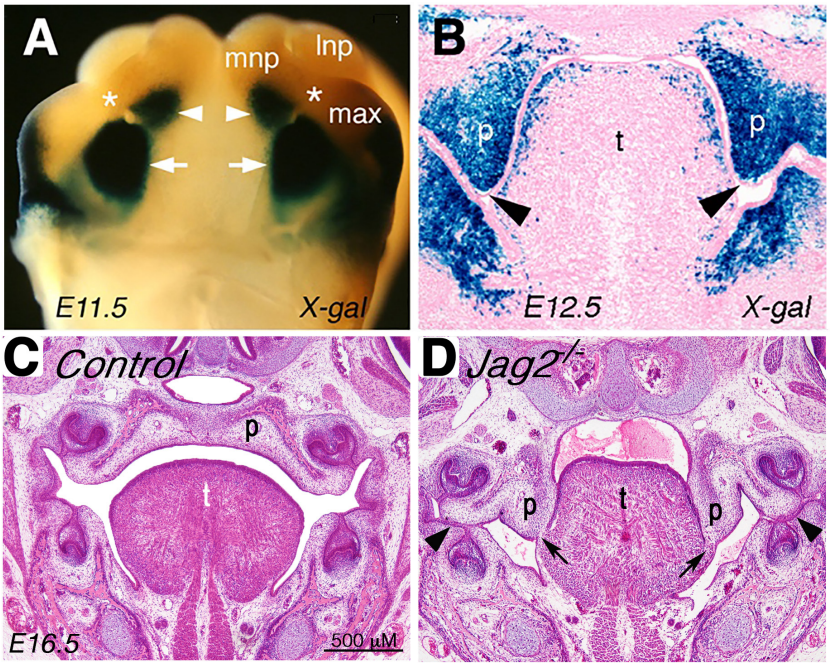
The chapter appears as part of a text entitled *Mouse Models of Development and Disease*, edited by Thomas Gridley and Leif Oxburgh.

RESEARCH & TRAINING DETAILS

Faculty	1
Joint Appointment Faculty	1
Research Graduate Students	1
Total Annual Grant Awards	$550,771

Lan Y, Jiang R. Mouse models in palate development and orofacial cleft research: Understanding the crucial role and regulation of epithelial integrity in facial and palate morphogenesis. Curr Top Dev Biol. 2022;148:13-50. doi: 10.1016/bs.ctdb.2021.12.003. Epub 2022 Feb 28. PMID: 35461563; PMCID: PMC9060390.

Mouse Genetic Studies Reveal a Critical Role of Periderm Differentiation in Palate Development



(A) Oral view looking at the developing upper jaw of an embryonic day (E) 11.5 mouse embryo. The blue color staining marks the bilateral primordia of the primary palate (arrowhead) and second palate (arrow). The asterisks mark the sites of adhesion and fusion of the maxillary processes (max) with the medial and laternal nasal processes (mnp and lnp) to form the intact upper lip. (B) A coronal section through developing secondary palate (p) and tongue (t) of an E12.5 mouse embryo. (C, D) Coronal sections through the same region of the embryonic oral cavity of an E16.5 control mouse embryo (C) and that of a *Jag2* mutant mouse embryo (D). By this developmental stage the bilateral palatal shelves had elevated to the horizontal position above the tongue and fused to form the intact palate in the control embryo. However, the *Jag2* mutant embryo had a disruption of the periderm differentiation and exhibited aberrant adhesion between the palatal shelves and lateral sides of the tongue (arrows), which results in cleft palate at birth. The *Jag2* mutant embryo also exhibited other aberrant inter-epithelial adhesions, such as oral adhesions between the upper and lower jaws (arrowheads).

Obstructive Sleep Apnea in Children Increases Levels of Cytokines Linked to Atherosclerosis in Adults

David Smith, MD, PhD

Raouf Amin, MD

RESEARCH & TRAINING DETAILS

Faculty	35
Joint Appointment Faculty	11
Research Fellows & Post Docs	7
Research Graduate Students	10
Total Annual Grant Awards	$15.3M
Total Annual Industry Awards	$431,871

Smith DF, Schuler CL, Hossain MM, Huang G, McConnell K, Urbina EM, Amin RS. Early Atherosclerotic Inflammatory Pathways in Children with Obstructive Sleep Apnea. J. Pediatri. 2021 Dec; 239:168-174. doi: 10.1016/j.jpeds.2021.08.031. PMID: 34450122. PMCID: PMC9020582 (Available 12/1/22).

PUBLISHED DECEMBER 2021
Journal of Pediatrics

Children who have obstructive sleep apnea (OSA) have increased levels of certain proinflammatory cytokines that are linked to atherosclerosis in adulthood, according to research conducted by David Smith, MD, PhD, Raouf Amin, MD, and colleagues. These findings, based on data from 96 children (53 healthy and 43 with OSA), offer details about arterial changes present before atherosclerosis appears. They could help explain the early groundwork of disease.

"The results of our study offer some significant insights into the link between OSA and inflammatory cytokines that we know play a role in cardiovascular disease in adults," Amin says. "An increase in the levels of these cytokines in children with OSA is an important indicator of the evolving landscape. These cytokines are complex, so our findings provide valuable information."

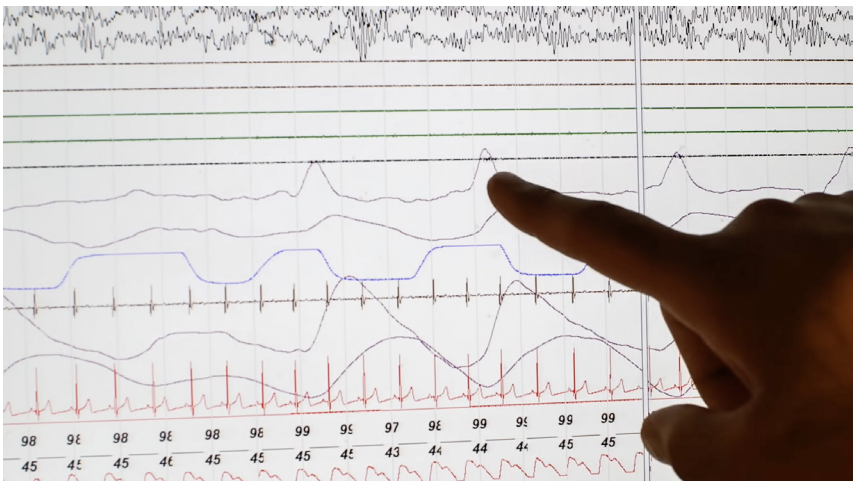
To identify cardiovascular differences in children with OSA, the team conducted sleep studies, collected blood samples to measure cytokine levels, and performed ultrasounds to measure the thickness and stiffness of the carotid arteries. The blood tests revealed children with OSA had higher levels of three cytokines associated with atherosclerosis: soluble cluster of differentiation-40 ligand, interleukin-6, and interleukin-8.

While the ultrasound scans did not identify clear differences in carotid arteries between children with OSA and healthy controls, the inflammatory mediators correlated with changes in the structure and function of the carotid arteries. The lack of typical atherosclerotic changes is likely because children have had less time to be impacted by OSA.

"What we've discovered about the levels of these cytokines is an important first step toward identifying biomarkers that we already know are linked to atherosclerosis in adults that may also be useful in detecting preclinical cardiovascular changes in kids with OSA," Amin says.

Being able to successfully make that connection, however, will require longitudinal studies.

Sleep Study



CRP, C-reactive protein; SSA, serum amyloid A. *P <.05.

Wide Price Variations Persist for Common Outpatient Imaging

Shireen Hayatghaibi, PhD

Andrew Trout, MD

PUBLISHED MARCH 2022
JAMA Network Open

In January 2021, the federal Hospital Price Transparency Rule began requiring hospitals to publish chargemaster rates, discounted cash prices, and payer-negotiated prices in a machine-readable file and publish costs for 300 common shoppable medical services in a consumer-friendly format.

However, a year later, only 39% of the 89 children's hospitals ranked by *U.S. News & World Report* were fully compliant with the rule, according to research led by first author Shireen Hayatghaibi, PhD, and colleagues. While 98% of the hospitals complied with the shoppable services requirement, only 39% were fully compliant with both requirements. Many did not provide machine-readable files; 53% omitted minimum and maximum negotiated rates, 51% omitted payer-negotiated rates, 40% omitted cash prices, and 9% omitted chargemaster rates. Medical imaging is an especially common shoppable service, but pricing for similar exams still varies widely based on initial charges, discounted cash prices and negotiated rates with insurers. In many cases, cash prices exceed negotiated rates, exposing the least insured families to the highest costs.

Among fully compliant hospitals, the greatest cash price variation was for retroperitoneal ultrasound (CoV: 84%), computed tomography (CT) of the head without contrast (CoV: 82%), and complete abdominal ultrasonography (CoV: 74%). CoV represents standard deviation divided by the mean, higher numbers mean more variation.

"Most hospitals are not compliant with the transparency law. We were also surprised that hospitals were charging our most vulnerable population, those without insurance, more than those with insurance," Hayatghaibi says. "It may take more time than many patient advocates had hoped to see more equitable pricing."

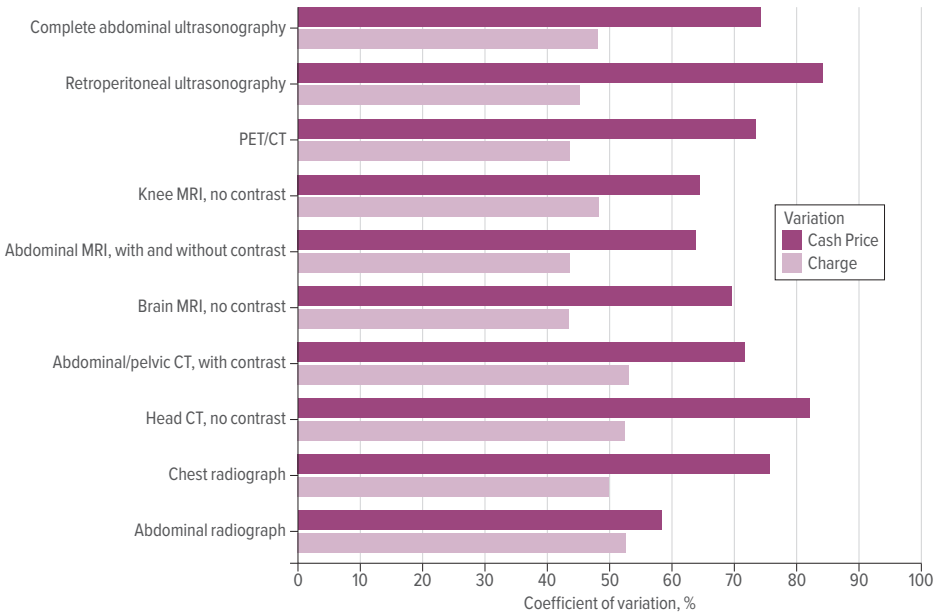
Cincinnati Children's complies with the transparency law, but now staff are using these learnings to work with families to better understand the financial burden associated with imaging.

RESEARCH & TRAINING DETAILS

Faculty	54
Joint Appointment Faculty	5
Research Fellows & Post Docs	4
Total Annual Grant Awards	$4.2M
Total Annual Industry Awards	$223,121

Hayatghaibi SE, Alves VV, Ayyala RS, Dillman JR, Trout AT. Transparency and Variability in Pricing for Pediatric Outpatient Imaging in US Children's Hospitals. JAMA Netw Open. 2022 Mar 1;5(3):e220736. doi: 10.1001/jamanetworkopen.2022.0736. PMID: 35234885; PMCID: PMC8892227.

Charge and Cash Price Variation for 10 Common Outpatient Imaging Examinations



CT indicates computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

Mining Electronic Health Records to Develop Better Systems of Care for Children with Cerebral Palsy

Brad Kurowski, MD, MS

PUBLISHED NOVEMBER 2021
Developmental Medicine & Child Neurology

Research led by Brad Kurowski, MD, MS, and colleagues highlights the complex healthcare navigation requirements for children with cerebral palsy (CP).

Investigators set out to characterize the patterns of care for children with CP in a tertiary healthcare system. They used electronic health record data from 2009 to 2019 for 6,369 children with CP.

"An overall challenge for this project was understanding the complexity of interactions that children with CP and their families had with the healthcare system," Kurowski says. "We had to apply modeling methods uniquely to this question and use data visualization to characterize hotspots where interaction occurred."

By using medical informatics, machine learning. and a "big data" approach, researchers uncovered clusters of care. The ratio of in-person visits to care coordination visits was calculated for each specialty. Study results include:

- The identification of seven primary clusters of care: musculoskeletal and function, neurological, high frequency/urgent care services, procedures, comorbid diagnoses, development and behavioral, and primary care.
- The in-person to care coordination visit ratio was 1:5 overall for healthcare encounters.
- Most interactions with care teams occur outside of in-person visits.
- The ratio of in-person to care coordination activities differ by specialty.

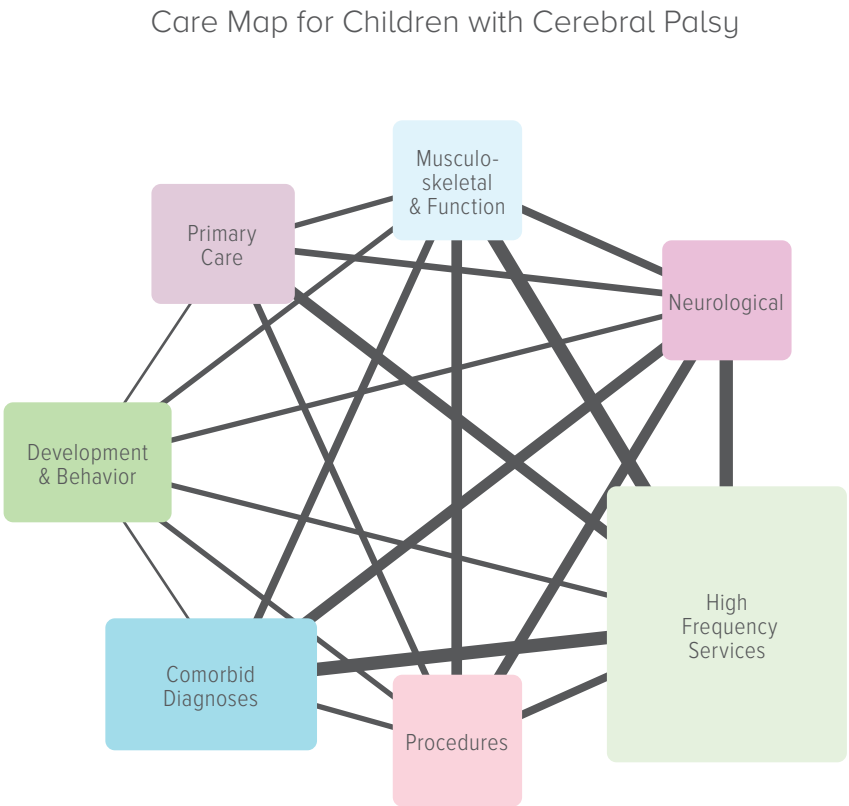
These findings provide a foundation for the development of better systems of care for these patients and to improve outcomes for children with CP and their families.

"Streamlining care, clustering services, and reducing frequent acute visits has the potential to decrease the burden of care on families and reduce healthcare costs through more efficient utilization of services," Kurowski says.

RESEARCH & TRAINING DETAILS

Faculty	11
Research Fellows & Post Docs	1
Research Graduate Students	4
Total Annual Grant Awards	$2.0M

Kurowski BG, Greve K, Bailes AF, Zahner J, Vargus-Adams J, Mcmahon MA, Aronow BJ, Mitelpunkt A. Electronic health record and patterns of care for children with cerebral palsy. Dev Med Child Neurol. 2021 Nov;63(11):1337-1343. doi: 10.1111/dmcn.14867. Epub 2021 Mar 25. PMID: 33768551; PMCID: PMC9037045.



Care map diagram depicting the breadth of healthcare visits across the hospital for children with cerebral palsy. Clusters are presented in each box with the size of the box symbolizing the total load of in-person visits. The height of the box signifies the total number of visits in the last 10 years. The width of the box denotes the mean number of visits in a year per patient and the width of the line exemplifies the number of shared children treated in both clusters.

Cystic Fibrosis and Ototoxic Meds Linked with Hearing Loss

Chelsea Blankenship, AuD, PhD

Lisa Hunter, PhD

RESEARCH & TRAINING DETAILS

Faculty	5
Joint Appointment Faculty	8
Research Fellows & Post Docs	2
Research Graduate Students	2
Total Annual Grant Awards	$3.7M
Total Annual Industry Awards	$166,935

Blankenship CM, Hunter LL, Feeney MP, Cox M, Bittinger L, Garinis AC, Lin L, McPhail, Clancy JP. Functional Impacts of Aminoglycoside Treatment on Speech Perception and Extended High-Frequency Hearing Loss in a Pediatric Cystic Fibrosis Cohort. Am J Audiol. 2021 Oct 11;30(3S):834-853. doi: 10.1044/2020_AJA-20-00059. Epub 2021 Jan 19. PMID: 33465313.

PUBLISHED OCTOBER 2021
American Journal of Audiology

Aminoglycoside antibiotics such as gentamicin, amikacin and tobramycin—often used to treat infections in children and adults with cystic fibrosis (CF)—are known to have an ototoxic effect. Lisa Hunter, PhD, scientific director of the Audiology Division, led one of the first studies to evaluate the functional impact of this ototoxicity.

Not only do those with CF have a higher prevalence of hearing loss, they also are more likely to have impaired speech-in-noise understanding, balance problems and tinnitus compared to typically developing controls. Almost half the CF patients had a history of middle ear infections, despite frequently receiving antibiotics.

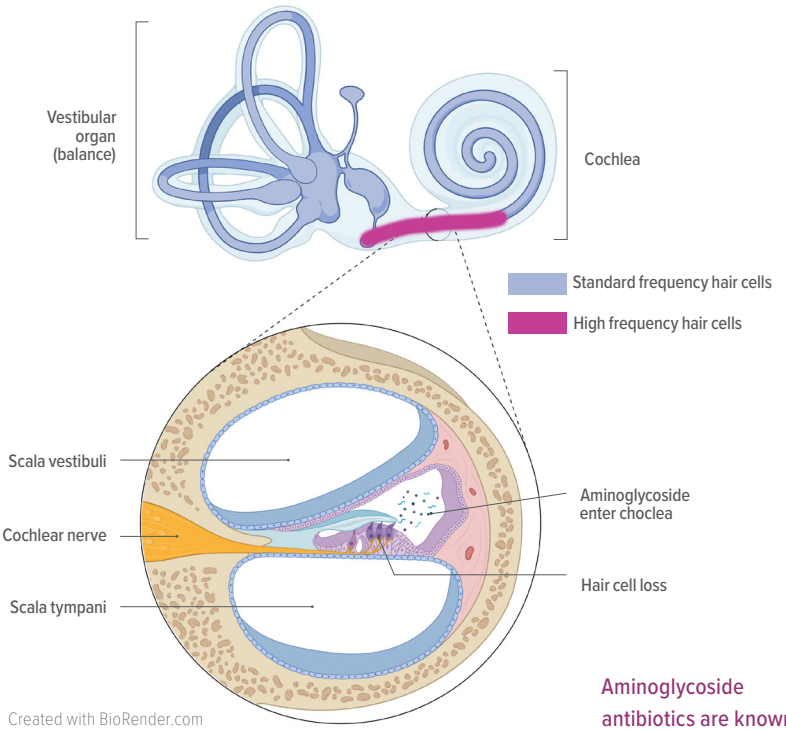
The study concludes that children with CF should be asked about these symptoms and have a baseline hearing assessment before being treated with aminoglycosides, and then be assessed regularly so that hearing problems can be identified and treated.

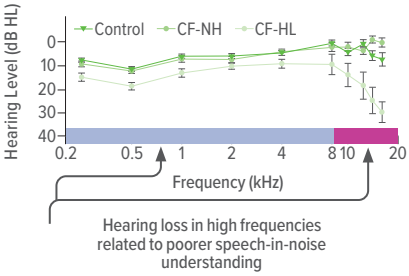
"Due to medical advancements, individuals with CF are living longer," Hunter said. "Therefore, they are at a higher risk for developing hearing loss that can progress and ultimately impact speech and language skills, literacy development, scholastic achievement and quality of life."

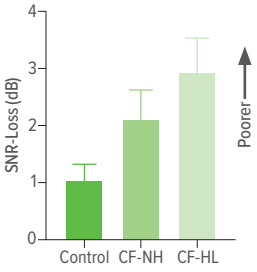
The study was originally funded by a Cincinnati Children's Place Award, and has been expanded into a larger multisite study, "Prevention of Ototoxicity with Effective Monitoring or POEM," funded by a five-year NIH grant.

"We are collaborating with Dr. Gary McPhail, director of the cystic fibrosis program, Dr. Sander Vinks and Dr. Min Dong in clinical pharmacology, and Drs. Patrick Feeney and Angela Garinis at Oregon Health and Science University in Portland," Hunter said. "We hope to validate and refine monitoring tools for use in the clinic."

Impact of Aminoglycosides on the Inner Ear in Cystic Fibrosis (CF)







Aminoglycoside antibiotics are known to cause cochlear damage that can lead to poorer speech-in-noise understanding and other hearing-related symptoms. Baseline testing and regular hearing loss assessment can help identify problems so they can be treated to reduce their functional impact.

Clinical Trial Leads to Approval for Tofacitinib to Treat Children With pcJIA

Hermine Brunner, MD

Daniel Lovell, MD

RESEARCH & TRAINING DETAILS

Faculty	12
Research Fellows & Post Docs	1
Total Annual Grant Awards	$2.9M
Total Annual Industry Awards	$3.6M

Ruperto N, Brunner HI, Synoverska O, Ting TV, Mendoza CA, Spindler A, Vyzhga Y, Marzan K, Grebenkina L, Tirosh I, Imundo L, Jerath R, Kingsbury DJ, Sozeri B, Vora SS, Prahalad S, Zholobova E, Butbul Aviel Y, Chasnyk V, et al; Paediatric Rheumatology International Trials Organisation (PRINTO) and Pediatric Rheumatology Collaborative Study Group (PRCSG). Tofacitinib in juvenile idiopathic arthritis: a double-blind, placebo-controlled, withdrawal phase 3 randomised trial. Lancet. 2021 Nov 27;398(10315):1984-1996. doi: 10.1016/S0140-6736(21)01255-1. Epub 2021 Nov 9. PMID: 34767764.

PUBLISHED NOVEMBER 2021
The Lancet

The Janus kinase (JAK) inhibitor tofacitinib is available today as an effective, affordable treatment for children with polyarticular course juvenile idiopathic arthritis (pcJIA) thanks in large part to a Phase 3 clinical trial co-coordinated by experts at Cincinnati Children's.

Until now, treating JIA typically required administering intravenous or subcutaneous doses of synthetic and biological drugs. This international study was the first to evaluate a JAK inhibitor for this form of JIA, which affects five or more joints. Among the potentially exciting benefits: this disease modifying anti-rheumatic can be delivered orally.

The double-blind study included 225 children treated at 64 centers in 14 countries. At 44 weeks post-treatment, 53% of those receiving tofacitinib experienced reduced disease flares, compared to 29% of those receiving placebo.

Tofacitinib was approved in 2012 for adults with rheumatoid arthritis, but further study was needed to evaluate its effects in children. Based on data from this trial, the US FDA approved the drug for children in September 2020. European Commission approval occurred in August 2021. Full study results were published about three months later by *The Lancet*.

The study was organized by the Paediatric Rheumatology International Trials Organisation (PRINTO) and Pediatric Rheumatology Collaborative Study Group (PRCSG). The PRCSG, launched in 1973, was led for many years by Daniel Lovell, MD. Now, Hermine Brunner, MD, director, Division of Rheumatology, serves as its chair and scientific director. Brunner and Lovell were two of the four senior leaders on the study.

"Although there are already several advanced treatments available, oral tofacitinib will be an appealing new option. Injected and infused treatments can be quite burdensome to both children with pcJIA and their caretakers," Brunner says.

Tofacitinib (sold as Xeljanz) received US FDA approval for children in September 2020 and European Commission approval in August 2021. Image courtesy of Pfizer Inc.

Confident Athletes More Likely to Experience Second ACL Injury After Return-to-Play

Mark Paterno, PT, PhD

PUBLISHED JANUARY 2022
Journal of Orthopedic Research

Young athletes who return to sports (RTS) with high confidence in their knees after anterior cruciate ligament (ACL) reconstruction are more likely to experience a second ACL injury within two years, according to research conducted by occupational and physical therapy specialist Mark Paterno, PT, PhD, and colleagues.

The findings, based on data from nearly 160 young athletes, indicate that mental status could play a larger role in safe return-to-play than previously anticipated.

"In all likelihood, these results show us the current return-to-sports criteria really aren't doing a good job of measuring who's ready to return to sport," Paterno says. "They work well in adults, but we're not seeing the same results in kids. It could be that adolescents typically return to a higher level of play than most adults."

Strength and functional test scores are currently used to clear an athlete for safe RTS. However, the study results also show that having high confidence increases the risk of ACL re-injury. Findings indicate confident players are twice as likely to experience another injury. The risk spikes to 10 times for confident players who meet all RTS criteria.

"The million-dollar question is how do we intervene for improvement? We want to reach beyond the current RTS tests and identify better measures for successful return to play," Paterno says. "With that, we could put a tool in the clinician's hand that would give them a better roadmap to determine if someone is ready to safely return to activity."

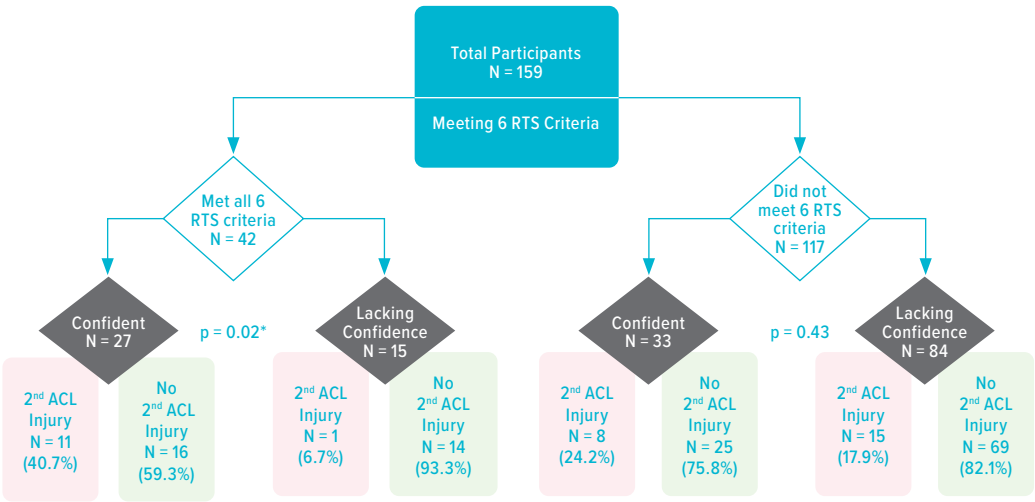
To reach that goal, Paterno's team is examining different sets of criteria that could provide a more accurate RTS analysis.

RESEARCH & TRAINING DETAILS

Faculty	6
Total Annual Grant Awards	$7,500

Paterno MV, Thomas S, VanEtten KT, Schmitt LC. Confidence, ability to meet return to sport criteria, and second ACL injury risk associations after ACL-reconstruction. J Orthop Res. 2022 Jan; 40(1):182-190. doi: 10.1002/jor.25071. PMID: 33930209.

Distribution of Second ACL Injury by Meeting RTS Criteria and Confidence



Confidence, ability to meet return-to-sport criteria, and second ACL injury risk associations after ACL-reconstruction.

ACL anterior cruciate ligament; RTS return-to-sport

Children with Bladder Exstrophy Need Long-Term Kidney Health Monitoring

Pramrod Reddy, MD

PUBLISHED APRIL 2022
Journal of Pediatric Urology

For children born with bladder exstrophy, a rare condition in which the bladder develops outside the body, continuous kidney monitoring is a necessity. Follow-up is especially important after surgical reconstruction of the bladder, according to research conducted by Pramod Reddy, MD, director, Division of Pediatric Urology, and colleagues.

Surgical reconstruction is an important treatment for severe cases of bladder exstrophy, but it comes with complications. Regardless of the technique used for the initial repair, children with this condition remain at high risk for chronic kidney disease and other complications later in life, including incontinence and sexual dysfunction.

This study analyzed upper urinary tract deterioration or chronic kidney disease after complete primary repair of exstrophy (CPRE) in 104 children over a 10-year period. The project was part of the US-India Bladder Exstrophy Collaboration, with relevant data collected from patients in India.

"The result of this research is a recommendation for a follow-up plan to ensure proper surveillance of patient kidney health," Reddy says. "The study provides a framework on how to counsel the families of these patients on their long-term health outcomes."

Follow-up studies evaluating ongoing kidney outcomes of these patients are already in the works. Of particular interest is how children with this condition achieve urinary continence as they get older—particularly through puberty.

Next steps for this research include analyzing patient and family reported outcomes on quality of life, including mental health, as these children grow, as well as continuous monitoring for chronic kidney disease.

RESEARCH & TRAINING DETAILS

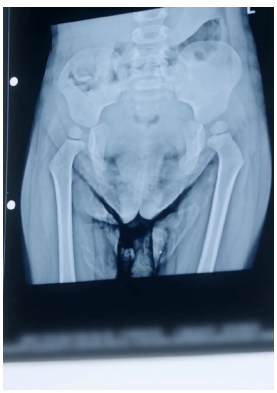
Faculty	6
Joint Appointment Faculty	1
Total Annual Grant Awards	$1.8M
Total Annual Industry Awards	$40,964

Reddy PP, DeFoor, WR. Kidney Function Outcomes in Patients After Complete Primary Repair of Bladder Exstrophy And Penopubic Epispadias: Results From The International Bladder Exstrophy Consortium. J Pediatr Urol. 2022 April. doi: 10.1016/j.jpurol.2022.04.018

International Collaboration

The US-India Bladder Exstrophy Collaborative provides world-class care to every child, and novel research is informing care plans for children with bladder exstrophy.

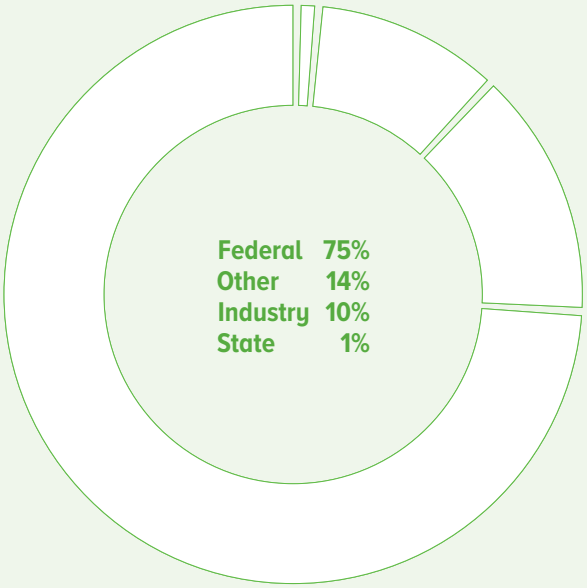
https://www.bladderexstrophy.com/indiacollaboration/



By the **Numbers**

Funding and Awards, Faculty, Fellows & Staff

Sources of External Funding



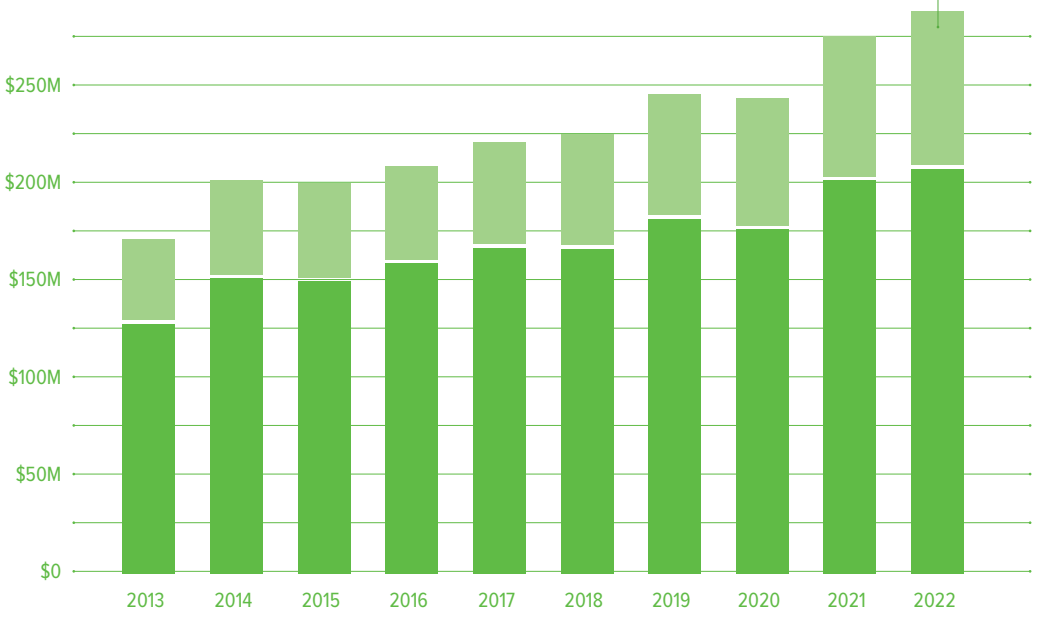
Sources of Federal Funding

National Institutes of Health	$190.2M
Ctr for Disease Control and Prevention	$5.8M
Health Resources & Services Admin	$5M
Food and Drug Administration	$2.6M
Department of Defense Army	$2.2M
Administration for Community Living	$1.5M
Department of Defense	$1.3M
Agcy for Healthcare Research and Quality	$980,223
Substance Abuse & Mental Hlth Svc Admin	$921,476
Department of Health and Human Services	$916,648
US Department of Education	$746,777
Ntl Inst for Occupational Safety & Hlth	$636,000
National Science Foundation	$558,437
US Army	$393,188
Department of Veteran Affairs	$364,990
Department of Health and Human Services	$234,424
Administration for Children and Families	$233,537
Department of Justice	$43,000
Ctr for Medicare/Medicaid Services	$33,619
Maternal & Child Health Bureau	$32,000
US Depart of Housing & Urban Development	$24,732
Cincinnati Veterans Administration	$6,644
Total	**$214,977,482**

State & Other Funding Sources

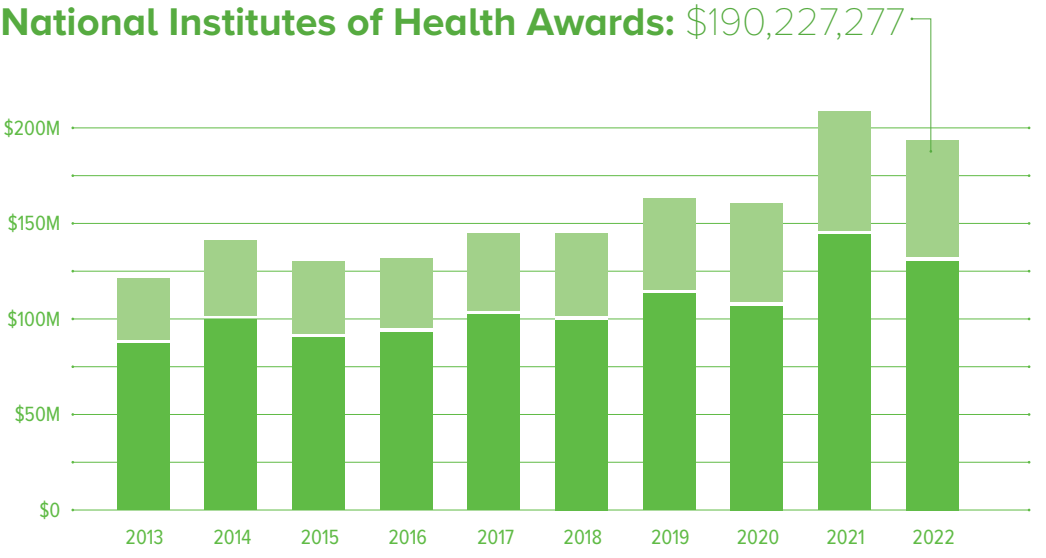
Cystic Fibrosis Foundation	$6.8M
Patient-Centered Outcome Research Inst.	$3.2M
Leona M & Harry B Helmsley Charitable	$3.1M
Bill & Melinda Gates Foundation	$2.3M
The Cure Starts Now Foundation	$1.7M
Doris Duke Charitable Foundation	$1.5M
March of Dimes National	$1.5M
Ohio Department of Health	$1.4M
American Heart Association – National	$1.3M
Burroughs Wellcome Foundation	$977,501
Ntl Inst of Dental & Craniofacial Res	$955,616
National Institute for Health Research	$820,695
Dr. Ralph & Marian Falk Med Res Trust	$807,582
Simons Foundation	$765,448
State and Other Funding	$14.7M
Total	**$42,091,292**

Sponsored Program Awards: $283,070,671



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

National Institutes of Health Awards: $190,227,277



Indirect Funds

Direct Funds

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 $45.1 MILLION RAISED THROUGH PHILANTHROPY IN 2022, 48% 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.

$21,593,062

DONATED TO RESEARCH IN 2022

Child Health Research Career Development Awards

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

John Erickson, MD, PhD
Neonatology

Laura Peterson, MD
Neonatology, Perinatal, and Pulmonary Biology

Strauss Fellows

The Arnold W. Strauss Fellow Award is a one-year $10,000 award instituted in 2014 in honor of his tireless championship of higher education at Cincinnati Children's.

Courtney Sump, MD
Hospital Medicine

Rebecca Henkel, MD
Neonatology and Pulmonary Biology

Alison Murray, MD
Endocrinology

Hank Wirth, MD
Heart Institute

Oto Inoue, PhD
Endocrinology

Karis Kosar, PhD
Gastroenterology

Ashley Turner, PhD
Biostatistics and Epidemiology

Procter Scholars

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

LaQuita Jones, DO
Oncology

Jasbir Dhaliwal, MBBS
Gastroenterology, Hepatology & Nutrition

Justin Schwartz, MD, PhD
Allergy & Immunology

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.

Andrea Beaton, MD, MS
Cardiology

Brittany Rosen, PhD, MEd
Adolescent and Transition Medicine

Robert Siegel, MD
Cardiology

Katherine Auger, MD, MSc
Hospital Medicine

John Hutton, MD, MS
Reading and Literacy Discovery Center

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.

Timothy Chlon, PhD
Experimental Hematology and Cancer Biology

Benjamin Tourdot, PhD
Experimental Hematology and Cancer Biology

Patricia Vega Fernandez, MD, MSc, RhMSUS
Rheumatology

Mayur Sarangdhar, PhD, MRes
Biomedical Informatics and Oncology

Hisako Fujiwara, PhD
Neurology

Alister Bates, BA, M Eng, PhD
Pulmonary Medicine

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.

Nicole Weaver, MD
Human Genetics

Meghan McGrady, PhD
Behavioral Medicine and Clinical Psychology

MEDICAL RESIDENTS
228

Our Faculty

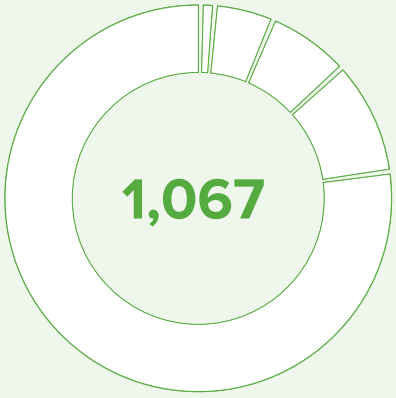
Pediatrics
826 total [772 full time / 54 part time]

Surgery
102 total [92 full time / 10 part time]

Anesthesia
73 total [54 full time / 19 part time]

Radiology
54 total [47 full time / 7 part time]

Patient Services
12 total [5 full time / 7 part time]



Research Graduate Programs

Biomedical Informatics	Immunology Program	MSTP Program	BRT Graduate Program - MS	MDB Graduate Program - PhD
40 Students (20 PhD, 20 GC)	**49** Students (44 PhD, 5 MS)	**74** Students	**8** Students	**62** Students

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.

Audrey Crowther, BS
Office of Graduate Education

Alexander Meithke, MD
Gastroenterology, Hepatology, and Nutrition

Lisa Shook, DHPE, HCHES
CBDI

Rick Ittenbach, PhD, MEd, MHS
Biostatistics and Epidemiology

Elizabeth Bien, PhD, MSN
Biostatistics and Epidemiology

Sang Lee, MD, MEd
Pediatric Emergency Medicine

Elanchezhian Somasundaram, PhD
Radiology

Christina Gross, PhD
Pediatrics

Juan Sanchez Gurmanches, PhD
Endocrinology

Nicholas Nassar, PhD
CBDI

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Experimental Hematology

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EDITORS

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EDITORIAL ADVISOR

Kristine Justus, PhD
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DATA CONTRIBUTORS

Linda Gold and Akshay Pillai
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WRITING & EDITING CONTRIBUTORS

WriterGirl & Associates, Leighanne Toole, and Mary Beth Weaver

GRAPHICS & PHOTOGRAPHY

Reed DeWinter and Michael Wilson
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Cincinnati Children's Hospital Medical Center
3333 Burnet Ave., MLC 9012
Cincinnati, OH 45229-3026
513-636-4420

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3333 BURNET AVE, MLC 9012
CINCINNATI, OH 45229-3026