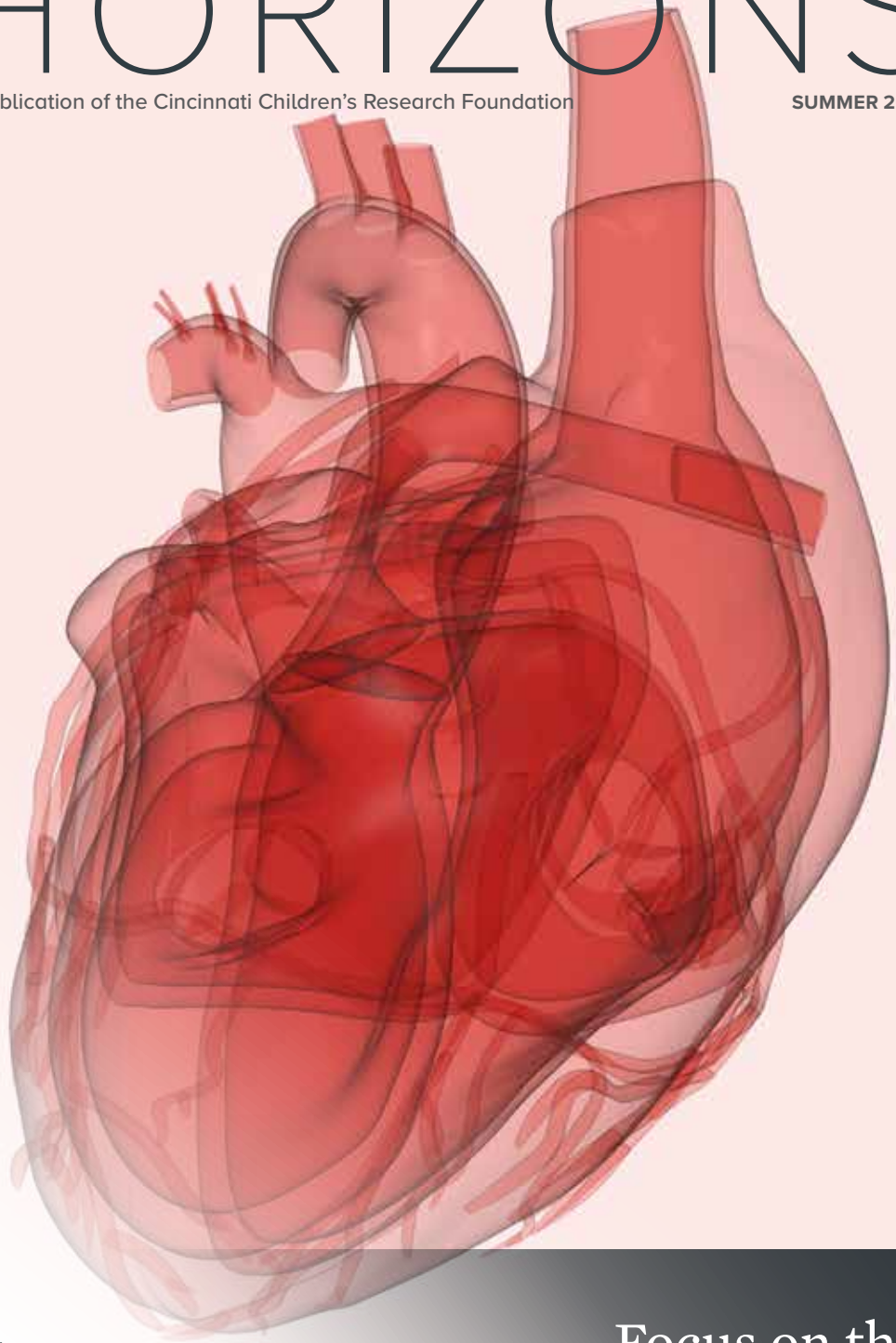
RESEARCH HORIZONS

A Publication of the Cincinnati Children's Research Foundation

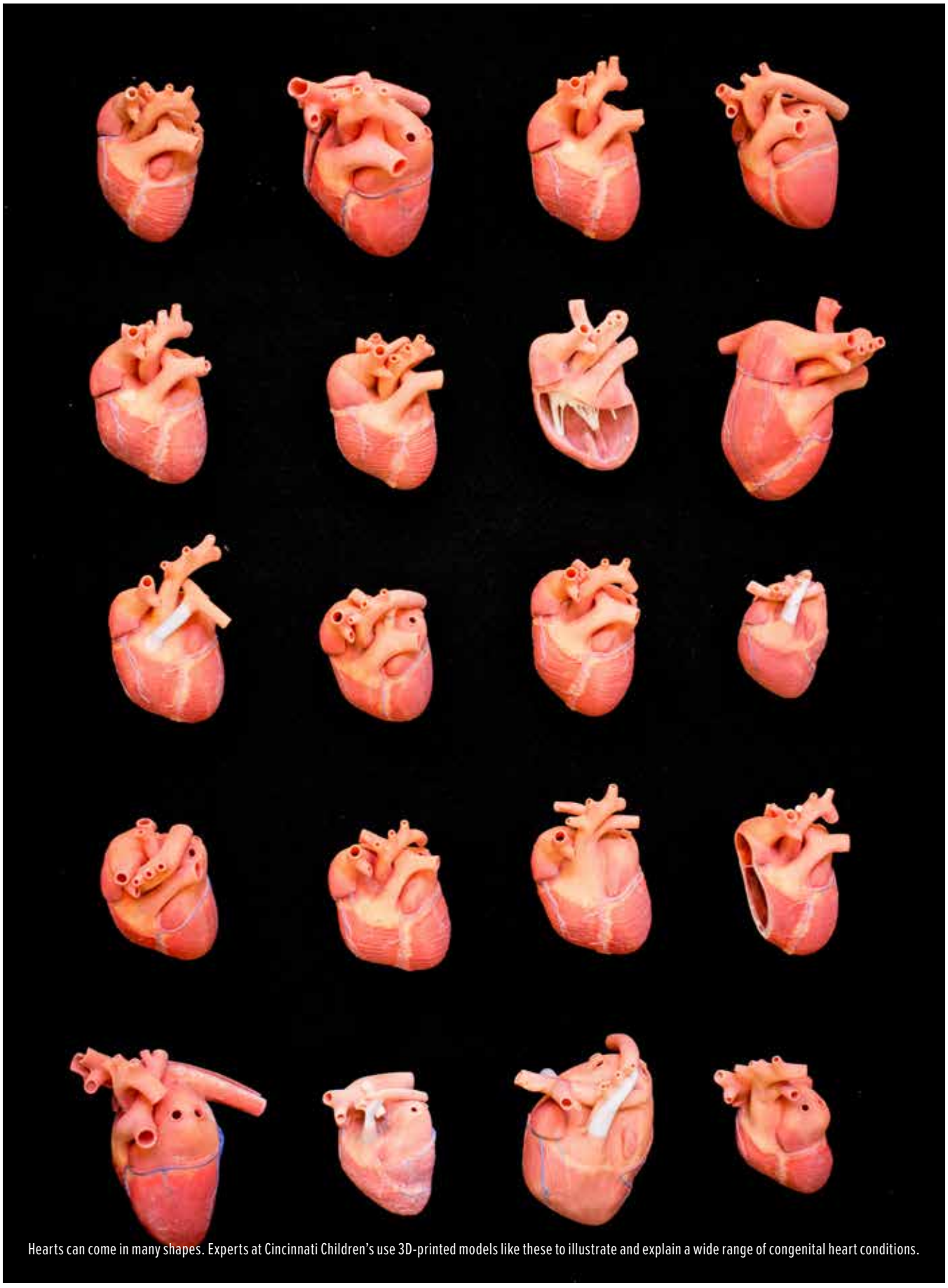
SUMMER 2017



Cincinnati Children's™
changing the outcome together

Focus on the Heart

Research to reduce risks, enhance life, and improve outcomes



Hearts can come in many shapes. Experts at Cincinnati Children's use 3D-printed models like these to illustrate and explain a wide range of congenital heart conditions.

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FEATURES

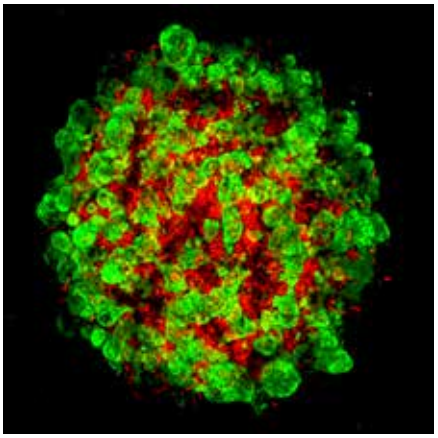
Colon and Liver Successes Accelerate Organoid Development

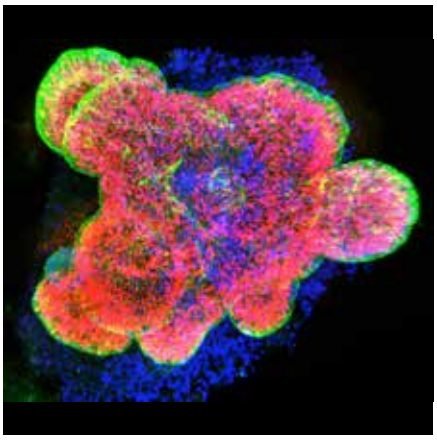
Scientists at Cincinnati Children's, working with a variety of research partners, have recently published significant steps forward in developing organoids that mimic colon and liver functions.

These projects, combined with previously reported progress at producing stomach and intestinal organoids, moves the medical center closer to being able to mimic an entire human gastrointestinal system—a potentially powerful tool for drug development and disease research.

Growing Colons from Stem Cells

A team including Jorge Munera, PhD, James Wells, PhD, and Michael Helmrath, MD, reported a breakthrough in coaxing human pluripotent stem cells to form colon organoids. In mice, transplanted organoids went on to form larger structures that mimicked several key properties of the human colon. Detailed findings were published June 22, 2017, in *Cell Stem Cell*.





Someday, such organoids may become useful for producing tissue transplants based on a patient's own cells. Shorter-term, however, the new organoids may support improved studies of colitis, colon cancer, irritable bowel syndrome, Hirschsprung's disease and more.

"We've been limited in how we can study these diseases, in significant part because animal models like mice don't precisely recreate human disease processes in the gastrointestinal tract," Wells says. "This system allows us to very effectively model human diseases and human development."

Budding Liver Organoids

Meanwhile, Cincinnati Children's scientist Takanori Takebe, MD, worked with the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, to bioengineer human liver "buds" that revealed previously unknown networks of genetic-molecular crosstalk that control organ development.

The findings, reported online June 14, 2017, in *Nature*, could advance efforts to generate healthy human liver tissue from human pluripotent stem cells.

Using single-cell RNA sequencing, the team observed a dramatic change in how the cells behave when they all develop together in a 3D microenvironment. More fine-tuning will be needed to produce liver tissues that could be used in clinical trials, but if the team can produce self-organizing human tissues, it would provide new hope to people with end-stage liver disease who currently depend upon transplants from limited numbers of donated organs.

"The ability to bioengineer transplantable livers and liver tissues would be a great benefit," Takebe says. "Our data give us a new, detailed understanding of the intercellular communication between developing liver cells, and shows we can produce human liver buds that come remarkably close to recapitulating fetal cells from natural human development."

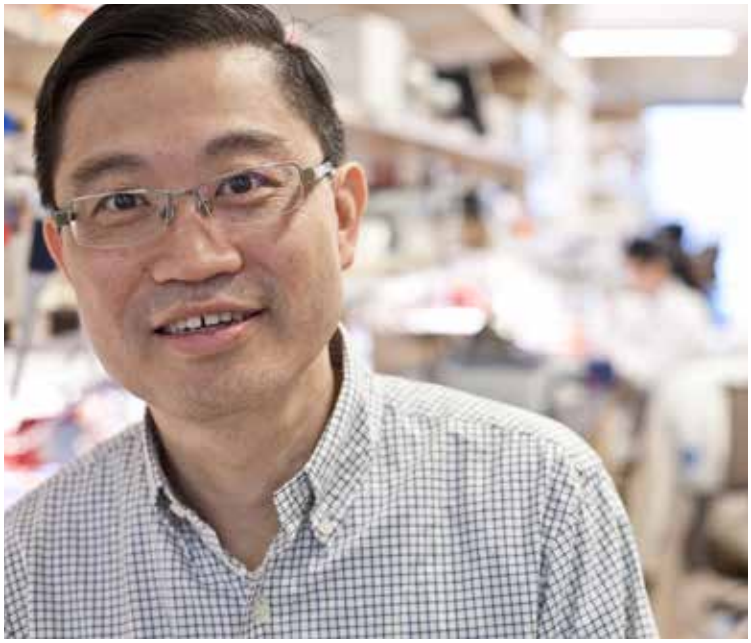
Mimicking the GI Tract

Since 2009, Wells and colleagues have reported successes at producing functional intestinal organoids, as well as connecting them to a nervous system. The team also has produced organoids that display the cell types and functions of the antrum and fundus regions of the human stomach.

The researchers have much more work ahead of them, but the latest findings advance a larger goal of mimicking an entire human digestive tract in the lab—and to do so for individual patients. This could become a highly useful tool for evaluating new oral medications and planning drug regimens for a wide range of diseases.

Top: These liver buds developed by Takanori Takebe and colleagues could advance efforts to grow healthy human liver tissue. Bottom: These colon organoids developed by Jorge Munera, James Wells and colleagues move scientists a step closer to mimicking an entire GI tract.

MicroRNA Treatment Shows Promise for Neurodegenerative Disease



Q. Richard Lu, PhD

Scientists at Cincinnati Children's partially repaired damaged nerves and restored limb function using microRNA injected into mice with induced multiple sclerosis (MS).

The work was reported online March 27, 2017, in *Developmental Cell*.

MicroRNAs regulate gene expression in cells. This microRNA, miR-219, restarted production of myelin, a protective sheath, in nerves of the central nervous system.

"MiR-219 targets the processes that inhibit myelin formation after nerve injury, and treatment with this microRNA partially restores myelination and limb function," says Q. Richard Lu, PhD, lead investigator and Scientific Director of the Brain Tumor Center. "Augmenting miR-219 treatment with other blockers of myelin regrowth may provide a multi-point treatment strategy for people with diseases like MS."

Earlier research has pointed to the absence of miR-219 in the damaged nerves and tissues of people with neurodegenerative diseases like MS.

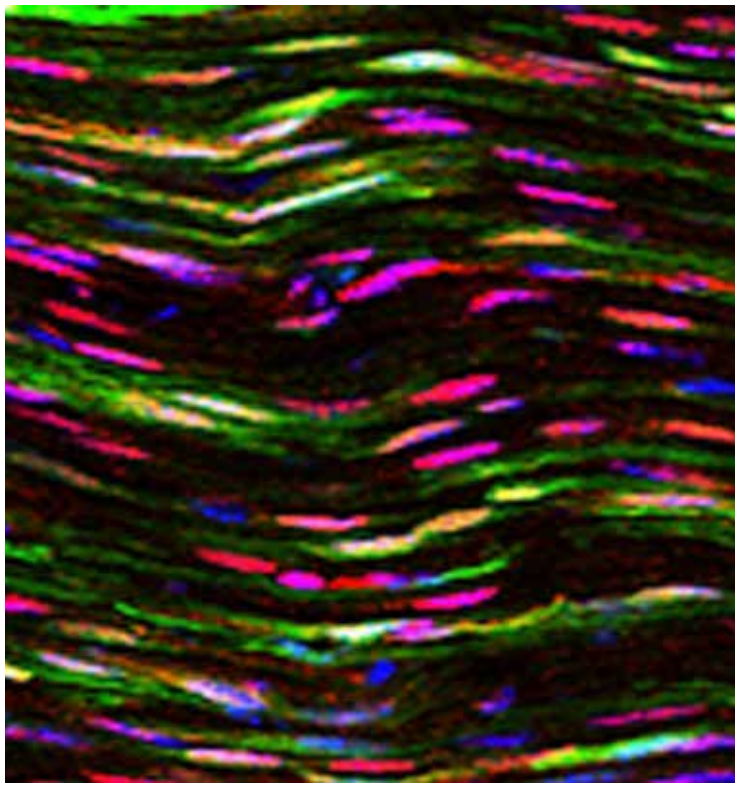
Protecting Nerves for Better Function

An estimated 20 million people in the United States have some form of peripheral nerve damage interfering with their lives.

Now, a study published April 26, 2017, in *Nature Communications,* suggests a way to fine-tune molecular signals so that peripheral nerves stay properly insulated and functioning normally.

A research team at Cincinnati Children's focused on Schwann cells, which protect nerves and ensure transmission of neural signals to limbs and other parts of the body. They discovered that genetic dysfunction in the HIPPO-TAZ/YAP and Gas-protein feedback circuit disrupts balanced production of Schwann cells, resulting in insufficient nerve insulation.

"These findings will lead to future studies aimed at fine tuning the balance between YAP/TAZ and Gas, and this may lead to new therapeutic strategies," says Q. Richard Lu, PhD, co-lead investigator and Scientific Director of the Brain Tumor Center.



This microscopic image shows molecular signs of insulation forming on the sciatic nerve of a 14-day old mouse.

Combination Drug Eliminates Hepatitis C in Adolescents

The first pediatric study of a combination drug to treat hepatitis C virus (HCV) was 100 percent effective, according to an online report in *Hepatology*.

The antiviral agents ledipasvir and sofosbuvir (marketed as Harvoni®) eliminated the virus in nearly 100 children ages 12 to 17 across the United States, United Kingdom and Australia.

Each received Harvoni once daily for 12 weeks, a dosage already proven effective in adults. All but two patients completed treatment and were "cured," meaning that HCV was not detected in their blood 12 weeks after treatment.

HCV infection is increasing in young populations, largely due to increasing use of injected opioids, says William Balistreri, MD, Director Emeritus of the Pediatric Liver Care Center and study lead author.

"In our area, there has been an increase of more than 350 percent in HCV infection among people 12 to 29 years old, including women of childbearing age who may pass the infection on to their newborn infants."

Nearly 80 percent of the children in the study had been infected during the perinatal period.

William Balistreri, MD

Melinda Mahabee-Gittens, MD

Study Finds a Surprising Source of Nicotine Exposure: Kids' Hands

Children can acquire significant levels of nicotine on their hands just by touching surfaces contaminated with tobacco smoke residues, even when no one around them is smoking at the time.

The findings were reported in the journal *Tobacco Control*. Melinda Mahabee-Gittens, MD, Division of Emergency Medicine, co-authored the study with researchers at San Diego State University.

The study involved 25 children and is being followed up with data from more than 700 additional children.

This is the first study to show tobacco exposure even without active smoking, Mahabee-Gittens says. "These findings emphasize that the only safe way to protect children from smoke exposure is to quit smoking and ban smoking in the home."

The children, aged 5 on average, also had significant levels of the harmful tobacco metabolite cotinine in their saliva. They were tested with parents' consent during emergency room visits for illnesses possibly related to second-hand smoke exposure.

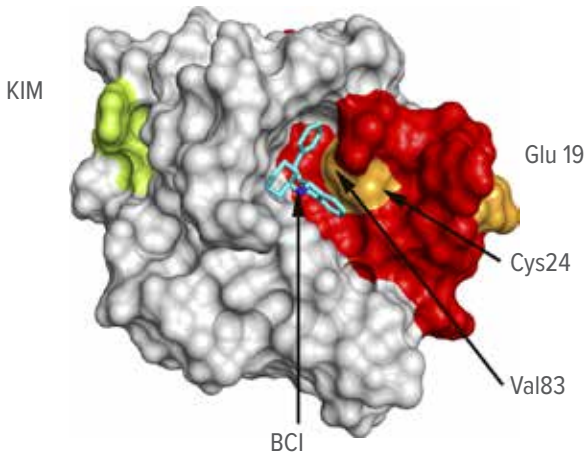
Preclinical Study Shows Promise in Treatment-Resistant Leukemia

A treatment that combines blocking two signaling proteins, plus chemotherapy, has been effective in eliminating human leukemia in mouse models, Cincinnati Children's researchers reported March 20, 2017, in *Nature Medicine*.

Their findings suggest that blocking the signaling proteins c-Fos and Dusp1 as part of combination therapy might cure several types of kinase-driven, treatment-resistant leukemia and solid tumor cancers.

These include acute myeloid leukemia (AML) fueled by the gene FLT3, lung cancers driven by the genes EGFR and PDGFR, HER2-driven breast cancers, and BCR-ABL-fueled chronic myeloid leukemia (CML), says Mohammad Azam, PhD, lead investigator and a member of the Division of Experimental Hematology and Cancer Biology.

"We think that within the next five years our data will change the way people think about cancer development and targeted therapy," Azam says. "This study identifies a potential Achilles' heel of kinase-driven cancers and what we propose is intended to be curative, not just treatment."



A study led by Mohammad Azam, PhD, reports detecting a molecular binding pocket that could help scientists develop therapies to block several types of kinase-driven, treatment-resistant cancers.

Senad Divanovic, PhD

Molecular Driver of Inflammation May Trigger Preterm Birth

Scientists at Cincinnati Children's have identified a molecular driver of inflammation that may finally answer a key question about what causes mild systemic prenatal infections to trigger preterm birth.

The findings, published March 9, 2017, in *The Journal of Clinical Investigation,* may lead to new approaches to address an entrenched global health problem.

Researchers say a molecular signaling receptor that helps regulate the immune system, type I Interferon (IFNAR), signals when a woman may have a mild viral or bacterial infection that could trigger infection-driven preterm birth.

In mouse models, deleting or neutralizing the IFNAR receptor protected the animals from preterm birth.

"Preterm birth is a leading worldwide cause of illness and death in infants," says Senad Divanovic, PhD, lead investigator on the study and a member of Division of Immunobiology. "Identifying active type I IFN/IFNAR as an immunological driver provides an actionable biomarker and potential therapeutic target for reducing preterm birth risk in these circumstances."

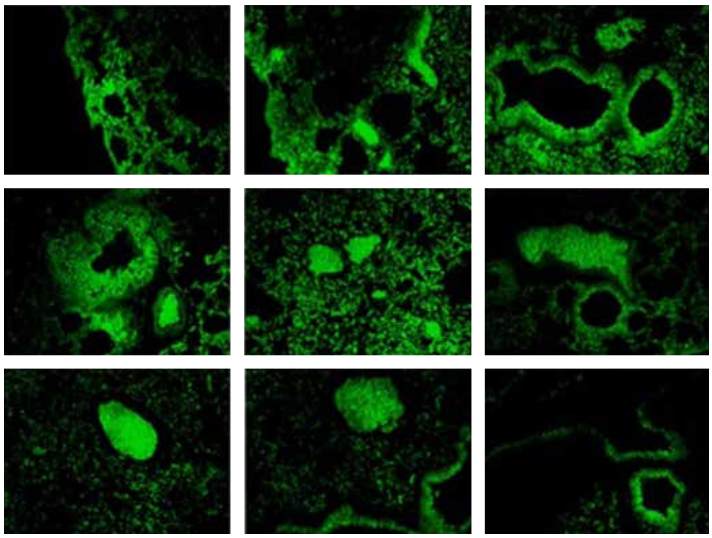
New Gaucher Disease Approach Would Suppress Inflammation-Promoting Protein

Blocking a molecule that drives inflammation in Gaucher disease may be an effective treatment with fewer risks and lower costs than current therapies, scientists say.

A research team led by Cincinnati Children's and including investigators from the University of Lübeck in Germany studied lysosomal storage disease in mouse models and in cells from blood samples donated by people with Gaucher. They reported their results in February in *Nature*.

Normal levels of glucosylceramide protect cells and promote their proliferation. Too much can lead to Gaucher, a buildup of fatty substances in organs such as the spleen and liver that can enlarge the organs and affect their function.

"Current enzyme replacement and substrate reduction therapies are expensive and still associated with inflammation, increased risk of malignancies and Parkinson's disease," says Manoj Pandey, PhD, study first author and a scientist in the Division of Human Genetics at Cincinnati Children's. "We suggest that targeting a molecule called C5aR1 may serve as a viable treatment option for patients with Gaucher disease and possibly other lysosomal storage diseases."



These microscopic images depict complement 3b deposition in lung sections from nine mice that were bred to mimic Gaucher disease. Targeting the molecule C5aR1 appears to block excess production of glucosylceramide, a hallmark of the disease.

Tracy Glauser, MD

Genes Determine Response to Epilepsy Treatment

A recent study in the *Annals of Neurology* reports on identified genes that may determine why any two children with childhood absence epilepsy (CAE) can have vastly different responses to the same drug.

The results suggest that knowing gene variants in children with CAE may help predict what drugs work best for them.

As part of a 32-center clinical trial, a team led by Tracy Glauser, MD, Director of the Comprehensive Epilepsy Center at Cincinnati Children's, investigated responses to three drugs used for CAE - ethosuximide, valproic acid and lamotrigine. They compared the effects of these drugs in 446 children with CAE.

Doctors focused on three genes that code for T-type calcium channels, which control the firing rate of brain cells, and on one gene that helps transport drugs from the brain. The team identified two calcium channel genes that occur in children for whom ethosuximide does not work. They also found variants of the genes in children for whom lamotrigine was effective.

Poor Motor Skills Linked to Gene Mutations

Some 6 percent of children worldwide suffer from developmental disabilities that affect skilled motor control. For many, this may be due to failure of two genes critical to developing motor skills.

Scientists from Cincinnati Children's and the City University of New York School of Medicine reported their findings May 3, 2017, in *Neuron*.

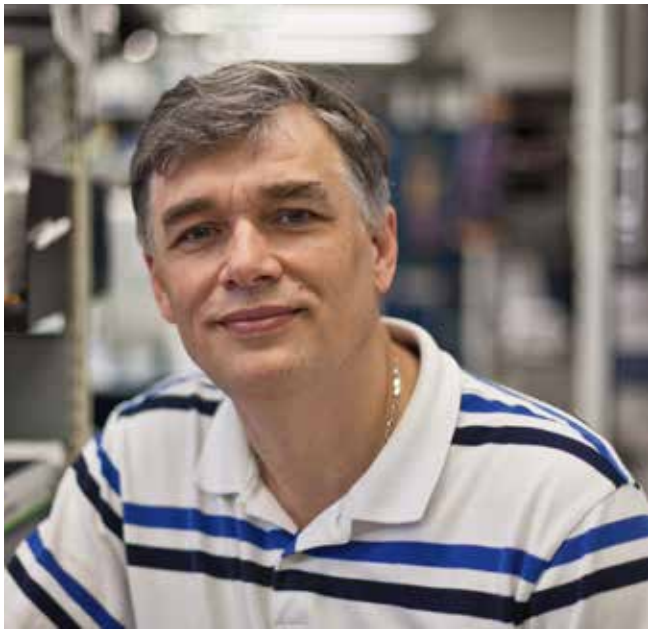
The researchers bred mice to lack molecular signaling from the Bax/Bak genetic pathway, and demonstrated how Bax/Bak's downstream molecular targets are vital to developing connections between the motor cortex, spinal circuits and opposing muscle groups.

They recommend that people with certain motor development disabilities be tested for mutant forms of these genes.

"Mutations in the Bax/Bak pathway in patients with developmental motor disabilities could translate to possible medical application," says Yutaka Yoshida, PhD, Division of Developmental Biology and study lead author. "Our goal is to determine whether disruptions in the pathway are implicated in skilled motor disabilities, and whether it regulates reorganization of other circuits in the central nervous system."

Yutaka Yoshida, PhD

Compound Hits Hard-to-Reach Target to Block Asthma Inflammation



Vladimir Kalinichenko, MD, PhD

Researchers at Cincinnati Children's have discovered a compound that blocks the inflammatory activity of the transcription factor FOXM1 in asthma.

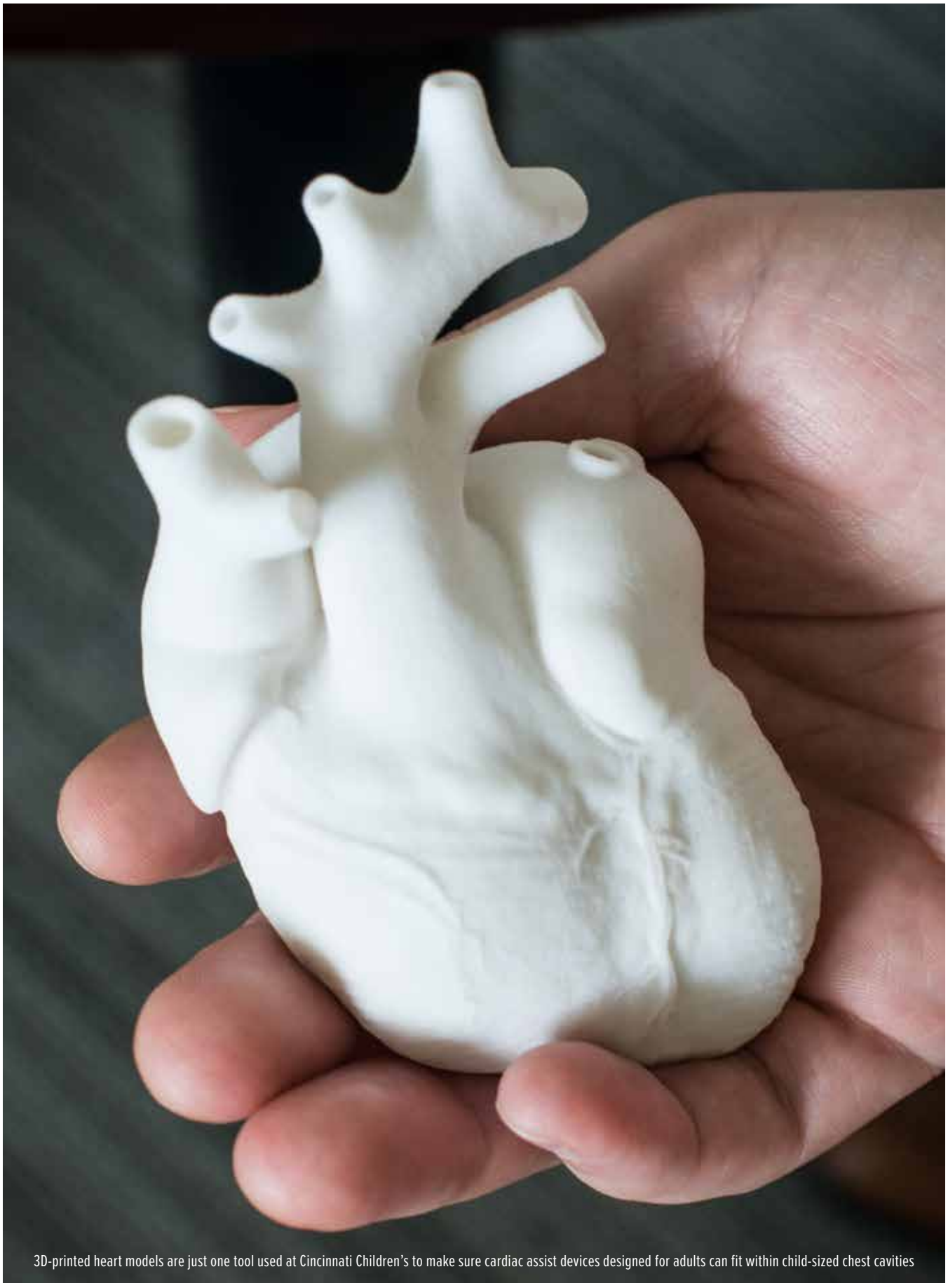
The finding was reported April 18, 2017, in *Science Signaling*.

The compound, RMC-1, prevents excess inflammation and mucous in mouse models and human respiratory cells.

Transcription factors, tiny proteins that switch genes on and off in cell nuclei, have long been considered unreachable targets for drug treatments.

"Traditional targets for drugs are receptors on cell surfaces, which are easy to reach. Transcription factors are inside cell nuclei and difficult to reach," says Vladimir Kalinichenko, MD, PhD, the study's lead investigator and a member of the Division of Pulmonary Biology. "RCM-1 keeps FOXM1 from entering the cell nucleus by activating cell machinery called proteasomes that degrade the transcription factor. This was very efficient at reducing lung inflammation and production of mucous-generating goblet cells in our tests."

Kalinichenko's team believes the discovery could lead to clinical trials for asthma, cystic fibrosis and chronic obstructive pulmonary disease.



3D-printed heart models are just one tool used at Cincinnati Children's to make sure cardiac assist devices designed for adults can fit within child-sized chest cavities

Devices Making a Difference

Ongoing research to improve mechanical assist devices helps more children and young adults with severe heart conditions live longer, better lives

by Tim Bonfield

Oregon resident Susie Arroyo is pursuing her dream of becoming a teacher even as she battles Duchenne muscular dystrophy (DMD), thanks to a life-saving device that keeps her heart pumping.

Not long ago, the heart complications caused by her disease would have amounted to a death sentence for Susie. Instead, in March 2013, she became the second person in the U.S. with DMD to receive a ventricular assist device (VAD).

Before the surgery, "I couldn't breathe. It was hard to even talk," Susie says. With the device, "I have a lot of energy. My color is back…I feel like Susie again."

In a world where donor organs for heart transplants remain in constant short supply, an evolving array of mechanical devices have begun to offer hope to more people with severe heart disease. Working together, doctors and scientists at Cincinnati Children's are helping to expand the populations of patients that can be helped by these devices.

- Teens who have survived cancer, only to suffer heart damage later as a side effect of radiation and chemotherapy.
- Children born with DMD and other conditions that make them unlikely candidates for organ transplants.
- People stricken by acute infections in which an assist device can support them long enough for their own heart to recover.

The Heart Institute at Cincinnati Children's has become one of the nation's largest pediatric programs for mechanical-assist devices. In addition to offering families access to surgeons versed in working with multiple types of devices, the program trains other surgeons in how to install them.

Experts here have developed and shared innovative computer imaging tools to fit devices in as many younger, smaller children as possible. Surgeons and support teams here also do the complex work needed to be allowed to mix and match parts from different manufacturers so that devices can function in smaller chest cavities.

Meanwhile, experts in multiple fields within Cincinnati Children's and colleagues in other medical centers are collaborating on research (see story, page 24) that could help patients live longer and better lives with mechanical devices.

"Even when children and teens get heart transplants, as many as 40 percent receive an assist device first. Otherwise, many would not make it to transplant," says Angela Lorts, MD, Medical Director, Mechanical Circulatory Support at Cincinnati Children's. "These devices can help some remain at home while they are on the waiting list, where they can focus on the nutrition and rehabilitation that will give them the strength they need for a successful transplant procedure."

OTHER SUCCESSES INCREASE DEVICE DEMAND

As more children grow into adulthood after surviving cancer, as treatments for muscular dystrophies extend life, and as more children survive Fontan surgery and other rigorous procedures to repair complex congenital heart defects (see story page 16), many of these patients encounter heart complications decades later.

Mechanical devices will play important roles in extending life for these patients, which make innovations in device design and in long-term medical support all the more important. So far, surgeons at Cincinnati Children's have implanted more than 50 cardiac-assist devices.

David Morales, MD, (left) and Angela Lorts, MD, (right) say improvements in mechanical-assist devices, along with better methods for fitting the devices, have made this rapidly evolving technology available to more children in need.

"We're now starting to explore new patient populations who before had little to no hope," says David Morales, MD, Chief of Cardiovascular Surgery at the Heart Institute. "We can support any child of any size with the best device for their particular heart failure."

CUSTOMIZED FITTING SAVES LIVES

Cardiologist Ryan Moore, MD, did not start college dreaming of becoming a doctor. He started out as an art major intending to pursue a career in digital media.

But he found that he enjoyed science and that he wanted to apply his skills to help people in more direct ways. So, he switched to become a biology major and pursued medical school. Now, as a cardiologist, he uses his artistic skills in life-saving ways.

Moore was a leading member of a small team at Cincinnati Children's that developed Heartpedia, a remarkable series of digital animations of major heart defects and the surgical procedures that can repair them. Moore also helped develop new software that allows experts to use CT and MRI scans to build rotating 3D images of an individual patient's chest cavity.

Now, Moore and colleagues can use these tools to determine with precision whether a device will fit properly in smaller, younger patients. This approach allows significantly more children to receive devices safely compared to the existing standard based on body surface area (BSA).

Using BSA, few children under the age of 14 would be considered grown enough to receive a Syncardia total artificial heart or other large cardiac devices, Moore says. But with 3D fitting technology, children as young as 12—even some as young as 10—have been successfully fitted with devices.

"BSA is an extremely limited form of measurement for this purpose," Moore says. "We have found that devices can be fitted in a number of children whose BSA measurements would preclude them. We also have found that the BSA measure sometimes can provide false positive results because it cannot account for chest cavities affected by scoliosis and *pectus excavatum*."

In a recent study published in the June 2016 issue of the *Journal of Heart and Lung Transplantation*, Moore and colleagues used the 3D techniques to evaluate 15 patients who were rejected for Syncardia devices because their BSA exceeded 1.7 m^2. The 3D imagery approach allowed eight of those patients to be fitted.

Looking ahead, Moore and colleagues are using these findings to begin rewriting the national eligibility criteria for heart devices.

A SOURCE OF EDUCATION AND TRAINING

Cincinnati Children's does not produce devices, but experts here play central roles in teaching both families and other medical centers about their use.

The Heartpedia mobile app provides clear visual depictions of heart conditions and procedures that many families find

The Heartpedia app, which helps educate families about heart conditions, was developed by Ryan Moore, MD, and a team of illustrators.

difficult to understand in other ways. The digital illustrations can be used in conjunction with 3D-printed heart models to explain how surgery will work.

"These visual tools have greatly enhanced our ability to communicate with families," Moore says. "Not only do these tools help us during in-person meetings, families can take these videos and models home and explain things to other relatives, friends and caregivers."

To measure the impact, Moore and colleagues are conducting follow-up studies to evaluate how much these visual tools improve understanding, in hopes that similar educational tools can be more widely shared.

Meanwhile, on the medical front, Cincinnati Children's has taken visual training to another level by developing advanced computer simulation tools to train heart surgeons and care teams on how to work with ventricular-assist devices. So far, the training has been provided to more than 30 other medical centers.

"Virtual implantation has been critical to our success," Morales says. "Until now, these devices have been designed almost exclusively with adults in mind. Now we are working with 11 other institutions to develop the pediatric protocols that will help standardize their use. This is an exciting and rapidly evolving field." ■

New Dimension: Lung Assist Devices

In addition to heart assist devices, the Heart Institute has made important strides in using lung assist devices to support children awaiting transplantation.

In July 2016, Morales and colleagues used NovaLung® and Quadrox® devices to serve as artificial lungs for two toddlers, each less than 2 years old, who were in lung failure due to severe pulmonary hypertension.

These external devices allowed the toddlers to be extubated, to receive nutrition therapy and physical rehabilitation, even to interact with parents, as they awaited surgery. Both survived to receive lung transplants.

"Neither child would have made it to transplant without these devices," Morales says.

Looking ahead, Morales predicts that lung assist devices will be increasingly common among children receiving transplants at Cincinnati Children's.

The Weight of the World

A POWERful national registry, a first of its kind, uses collaboration and big data to bring focus to pediatric obesity

by Tom O'Neill

In the fight against pediatric obesity, there is power in numbers and, increasingly, numbers in POWER.

When Shelley Kirk, PhD, RD, launched the Pediatric Obesity Weight Evaluation Registry (POWER) four years ago, there was no national registry of pediatric weight-management programs.

Today, POWER includes 33 medical institutions in 21 states, each contributing standardized data that can help determine which intervention strategies improve health for obese children, and just as importantly, which ones do not.

Cincinnati Children's serves as the Data Coordinating Center for the POWER project. Kirk, of the Heart Institute, and Eileen King, PhD, of the Division of Biostatistics and Epidemiology, lead the work.

"If you're starting a registry with limited resources, we have demonstrated that this can be done," Kirk says. "We proved that we could do it, as collaborators instead of competitors."

Now, the network has started producing meaningful results, including more accurate snapshots of the prevalence and impact of childhood obesity. This registry also highlights the valuable role for multi-component interventions to control body mass index (BMI) long-term. Those interventions can include medications, nutrition, physical activity and behavioral counseling.

OBESITY RATES LEVELING, BUT STILL TOO HIGH

In February 2017, a study based on POWER data appeared in the *Journal of Childhood Obesity*. The study analyzed data from 3,643 youths with obesity, including demographic and clinical parameters. Two-thirds of the children in the study were severely obese, in an era when one of every three children in the U.S. is overweight or obese.

With a four-fold increase in childhood obesity rates over the past several decades, there are reasons for guarded optimism. The data show that the rate of increase has slowed, but it has not stopped. This is particularly true for those with severe obesity, Kirk says.

IMPROVED INTERVENTIONS

In May, Kirk also gave a platform presentation at the annual meeting of the Pediatric Academic Societies in San Francisco.

She presented data showing that long-term monitoring by health professionals is crucial because so many kids struggle to adhere to the lifestyle recommendations for diet and exercise made by their weight-management programs.

Unlike electronic apps and other device-based tactics designed to engage kids in improving their eating habits and increasing activity level, Kirk says the data show that direct contact time with professionals actually works.

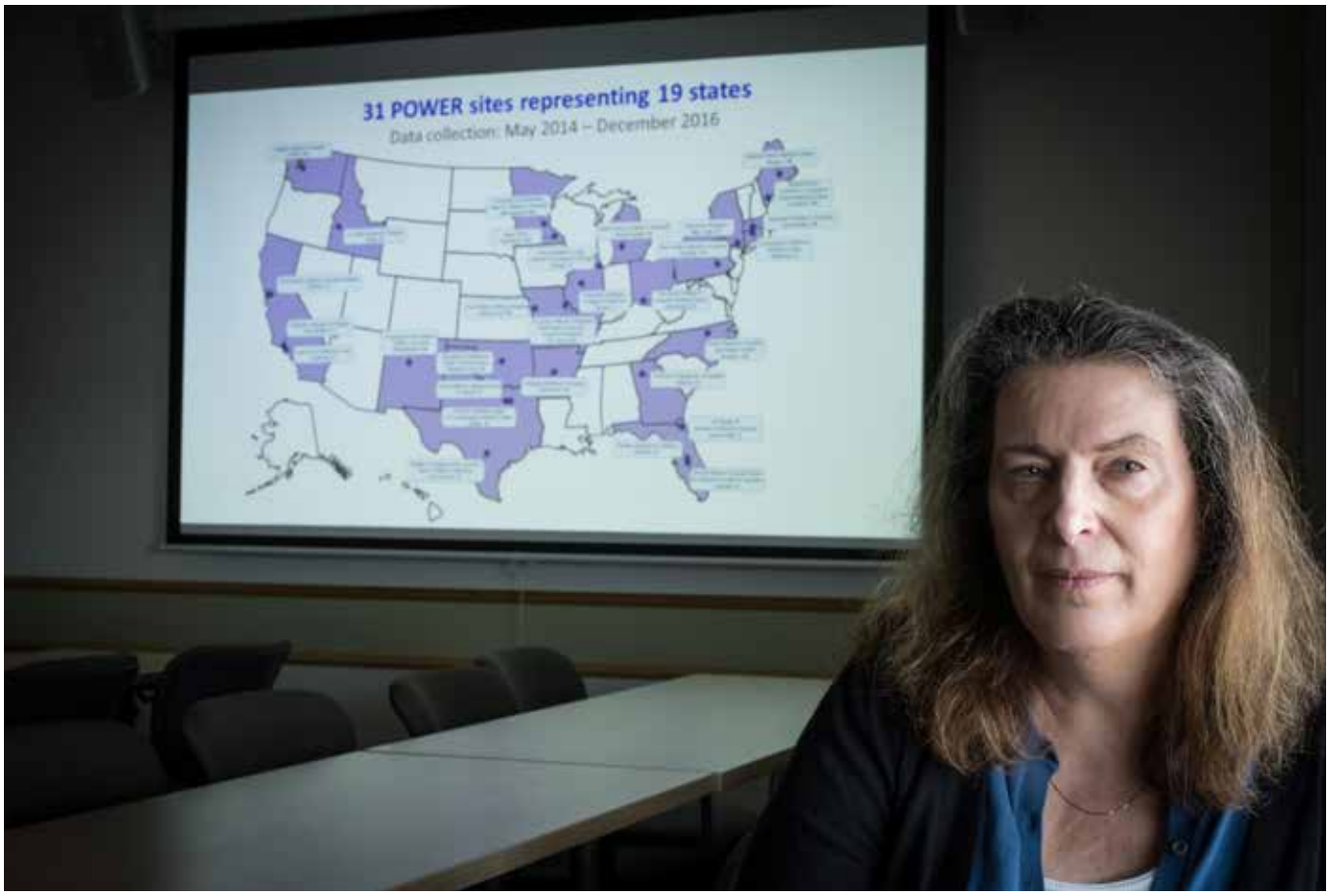
DIETITIANS MAKE A DIFFERENCE

In an April 2015 study published in the *Journal of Childhood Obesity*, Kirk worked with Robert Siegel, MD, Medical Director of the Center for Better Health and Nutrition to examine the impact of visits with registered dieticians on the BMI outcomes of obese children as part of their intervention program.

They found that each additional dietitian visit was associated with a 28 percent increased chance of successfully reducing BMI. Overall, the probability of success exceeded 78 percent with

"We're here to stay. Nobody knew we even had a future when we started. But Cincinnati Children's, including the Heart Institute, has been there the whole way."

– Shelley Kirk



Shelley Kirk, PhD, RD, launched the Pediatric Obesity Weight Evaluation Registry (POWER) four years ago. This year, two more institutions have joined.

monthly dietician visits, compared to 43 percent success rates with minimal exposure.

One big and frustrating challenge: "In some cases insurance coverage for a registered dietitian is limited to three 30-minute visits a year," Kirk says.

Still, the study was important because it helped set some precedents, Kirk and Siegel say.

"The biggest lesson is that success correlated with the number of dietitian visits," Siegel says. "Dietitians are very, very important. Exercise physiologists are very, very important. When the family does not meet with a dietitian and an exercise physiologist, the results are generally not good."

EARLY INTERVENTION MATTERS

In another paper, published in October 2015 in *Childhood Obesity*, Kirk and researchers from 13 of the institutions in POWER analyzed data on 6,737 obese patients ages 2-17.

The team studied laboratory tests, blood pressure and demographics. They also examined the relationships between BMI status and co-morbidities.

Their finding: By the time most obese youths enter weight management programs, it is too late to avoid significant co-morbidities. Yet convincing families to enroll kids earlier, at lower weights, has been an uphill battle, Kirk says.

POWER'S FUTURE, ONCE UNCERTAIN, IS NOW TAKING FLIGHT

Creating the POWER registry was long overdue, Kirk and Siegel say, but the effort has demonstrated that dozens of pediatric hospitals can team up to collect a valuable, uniform set of data. "We're here to stay," Kirk says. "Nobody knew we even had a future when we started. But Cincinnati Children's, including the Heart Institute, has been there the whole way."

The next step is to secure additional sources of funding. So far, the POWER project has been primarily funding by enrollment fees covering each two-year cycle ($5,000 for 2014-2016; $6,000 for 2016-2018) from each participating institution. However, additional funding provided by the Heart Institute to cover needed administrative and faculty support during the first cycle was key to the project's success.

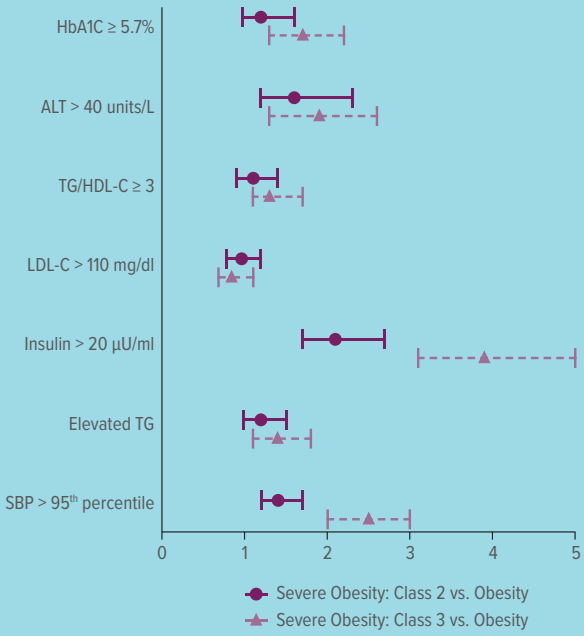
Kirk has been invited to speak about patient outcomes based on POWER at a September workshop sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases. The audience will include scientists with expertise in a range of specialties relevant to obesity, including genetics, endocrinology, epidemiology, psychology, behavioral medicine, and bariatric surgery.

She can't wait.

"We don't have National Institutes of Health funding now," she says, "but this meeting provides an opportunity to showcase the work of POWER and make important connections that can help secure future funding. We know that pediatric obesity research is important to NIH and we believe POWER offers a needed resource to address this important health issue. That's the vision we have for POWER going forward." ■

Dietitian Visits Show the Invaluable Role of Face-Time

From 2015 *Childhood Obesity* study titled "Increased Frequency of Dietitian Visits Is Associated with Improved Body Mass Index Outcomes in Obese Youth Participating in a Comprehensive Pediatric Weight Management Program":



Odds ratios for comorbidities of severe obesity (Class 2 and 3) versus obesity from logistic regression, adjusting for sex, age, race, ethnicity, insurance and site. Elevated triglycerides (mg/dL) determined as 75 (up to age 7); >90 (ages 8–11); or ‡110 (ages 12–17). HbA1C, hemoglobin A1c; ALT, alanine aminotransferase;TG, triglyceride; HDL, high-density lipoprotein; LDL-C, lowdensity lipoprotein cholesterol; SBP, systolic blood pressure.

The Doctor Will See You Now—At School

PEDIATRIC OBESITY TREATMENT SOMETIMES REQUIRES A CREATIVE TOUCH

Domika Dudley of Cincinnati is 13, inactive, and overweight. She often sleeps after school and mumbles answers to Robert Siegel, MD, with little eye contact.

The hallway grows quieter now that Rothenberg Preparatory Academy's school day has ended.

The soft-spoken Siegel, of the Heart Institute, gently pushes on, full of calm encouragement. He has better luck with Domika's grandmother, a bit of a firebrand who refuses to accept Domika's excuses.

Domika doesn't ride her bike because she can't find her helmet, which she doesn't look for. She watches far too much TV and eats unhealthy food daily.

"Oh," Helen Berry sternly tells her granddaughter, "we're going to find you things to do. I promise you that."

Siegel was encouraged. He conducts these visits at six inner-city schools as Medical Director of the Center for Better Health and Nutrition, a team of dietitians, nurses and exercise physiologists.

The previous week, he treated a young, overweight Guatemalan girl whose mother said through an interpreter that she has replaced soda with water in the home, a good step.

MOTIVATION DRIVES BETTER CHOICES

"Occasionally we will get a motivated teen who can do it alone, but it really takes the entire family being on board to make good progress," he says. "It is very discouraging when parents are not engaged. But I love being in schools and the community. It is where change can really happen."

Siegel is backed by research. For Domika, Siegel recommended a follow-up visit with the Division of Endocrinology at Cincinnati Children's, and possibly a future sleep-study.

Motivating overweight kids is a tricky landscape. In a February 2017 study in *Clinical Pediatrics*, senior author Siegel explored the success of an unusual program.

He found that offering small prizes such pencils, erasers, stickers and smiley-face emoticons to elementary-school kids improved their willingness to make healthier cafeteria choices by more than 300 percent. Food waste did not increase.

"I'm always amazed what a difference the prizes make," he says. Research, too.

Finding the Fontan of Youth

Heart procedure saves young kids' lives but over time blood circulation weakens. Research at Cincinnati Children's could help improve and extend their lives.

by Tom O'Neill

David Munro is a fairly unlikely first-time patient at Cincinnati Children's. For one thing, he's 23. For another, he lives in Nebraska.

However, his recent arrival illustrates our emergening prominence as a national leader in pediatric and adult congenital heart care. It also reflects the innovative research that is fueling better evaluation strategies for long-term patients like Munro who have been treated with Fontan procedures.

The Fontan procedure is an ingenuous yet imperfect treatment that helps children born with only one heart ventricle. This complex form of bypass surgery redirects pulmonary arteries so that blood can flow directly to the lungs without being driven by heart contractions, thus relieving strain on the single ventricle.

Patients typically undergo Fontan surgery between the ages of 2 and 5 as part of a three-stage series of operations. The procedure is life-saving but by adolescence, weak functional cardiac capacity begins to betray the patient's organs. The declining function can occur so gradually that it frequently escapes early detection.

"The average 11-year-old with Fontan looks pretty close to their peers," says Bryan Goldstein, MD, of the Heart Institute. "The average 18-year-old with Fontan, you could pick them out of a lineup if they all ran around a track."

But by then, many have aged out of pediatric care. Approximately 20 to 30 percent of Fontan patients eventually receive a heart transplant. However, many die on the waiting list due to lack of available organs.

INNOVATIVE EVALUATIONS SHED NEW LIGHT ON ORGAN FUNCTION

Our Fontan team has transitioned its focus from excitement about survival to long-term chronic management. This requires a broader approach to the impact of Fontan circulation. Cincinnati Children's new evaluation methods are a national model.

"The key is idealizing the circulation, anatomically and physiologically, and screening for problems with the kidneys, liver, neurodevelopmental function, bone growth, endocrine, all these things," Goldstein explains.

From his bed in the Cardiac Intensive Care Unit, Munro's body is extremely frail but his words are not. "My hope, long-term," he says, "is to get things fixed, essentially."

Mother, Susan Keisler-Munro: "Path forward, right?"

Son: "Yeah."

Mother with slight laugh: "He looks better in person than he does on paper."

THE JOURNEY TO CINCINNATI CHILDREN'S

The family spent two years trying to find the best experts in long-term Fontan care. Their cardiologists in Omaha ultimately referred them to Cincinnati Children's.

"There are things being done here that, you know, potentially aren't being done elsewhere," Keisler-Munro says. "There's a serious concentration of brainpower here."

That brainpower is driving first-of-its-kind research into earlier interventions and far more extensive assessments for Fontan management. The goal: faster identification of when and how declining circulation affects physical activity and organ function. Then, employ better medications and care methods to slow the rate of deterioration.

In trying to improve Munro's health to the point where he might be eligible for a transplant, Goldstein implanted covered stents into the Fontan circulation, where thrombus had formed, in an effort to improve blood flow.

He also dilated the shrunken Fontan conduit back to its original diameter. It had narrowed significantly over time, contributing to Munro's poor organ function.

If Munro becomes eligible for a transplant, the procedure would be considered high-risk, a risk Munro and his mother say they are willing to take.

LOSING PATIENTS TO ADULT CARE, AND GETTING THEM BACK

Cincinnati Children's has greatly expanded its reach through our Adult Congenital Heart Disease program, directed by Gruschen Veldtman, MD.

"One surprising thing is that anyone with a serious heart condition can get lost to care. It's not uncommon," he says. "But increasingly, we're reaching out to cardiologists to ensure that doesn't happen."

Behind every advancement in Fontan care, is research.

In a study published in September 2016 in the *Journal of the American Heart Association*, researchers examined 60 adolescent and young-adult Fontan patients to tease out the relationship between vascular function and clinical outcomes.

This had not been established previously. One key difference: instead of measuring blood flow while subjects are lying down, they measured it during cardiopulmonary exercise. Teen Fontan patients often face a Catch-22: the poorer their circulation, the less they exercise, and the weaker the heart structure becomes.

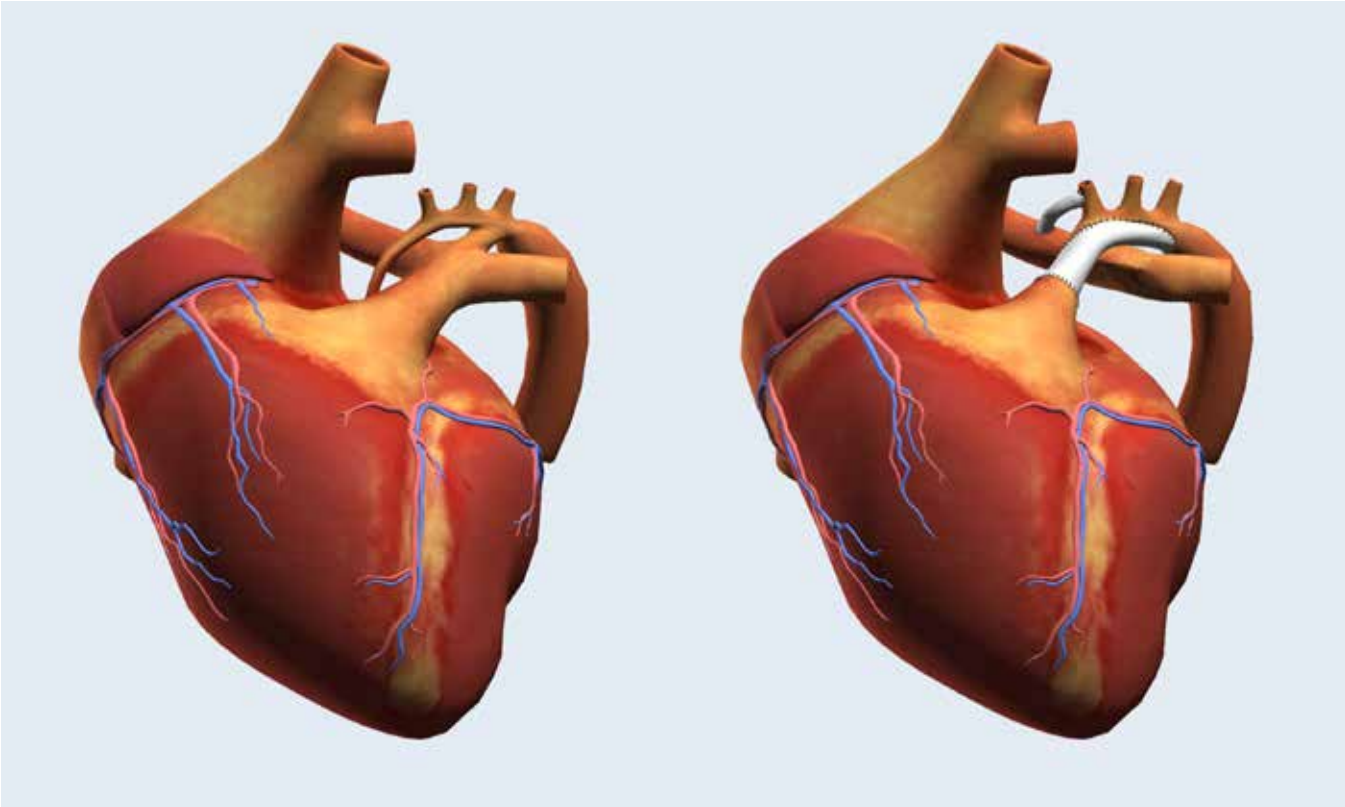
The team included first-author Goldstein and six colleagues at Cincinnati Children's, including Andrew Redington, MD, Executive Co-Director of the Heart Institute. They found that the poorest vascular measures were associated with the poorest functional measures, potentially identifying new avenues of treatment. Also, other organs were impacted.

"You can look at the brain, lungs, kidneys, liver, musculature, and see changes," Veldtman says.

SQUEEZING AND RELAXING, THE TWO-WAY STREET OF CARDIAC FUNCTION

The Fontan procedure fails over time in a number of different ways. One way is that the heart does not squeeze well, so it introduces less blood circulation through the lungs. The lungs too are implicated, commonly with abnormalities in pulmonary artery resistance.

Often though, the single ventricle has trouble refilling during the relaxation phase of the heartbeat. This results in decreased output,



These illustrations from the Heartpedia app show how the Fontan procedure corrects abnormal blood flow in hypoplastic left heart syndrome (left) with a modified flow (right) that allows the single right ventricle to eject blood primarily to the body.

Fontan expert at Cincinnati Children's humbled to meet … Dr. Fontan

Dr. Francois Fontan of Bordeaux, France, made medical history in 1971 when he performed a rather inventive surgical procedure for a life-threatening heart condition called tricuspid atresia.

That procedure now bears his name. In 2013, the website www.topmastersinhealthcare.com named him one of the 20 most innovative pediatric surgeons alive.

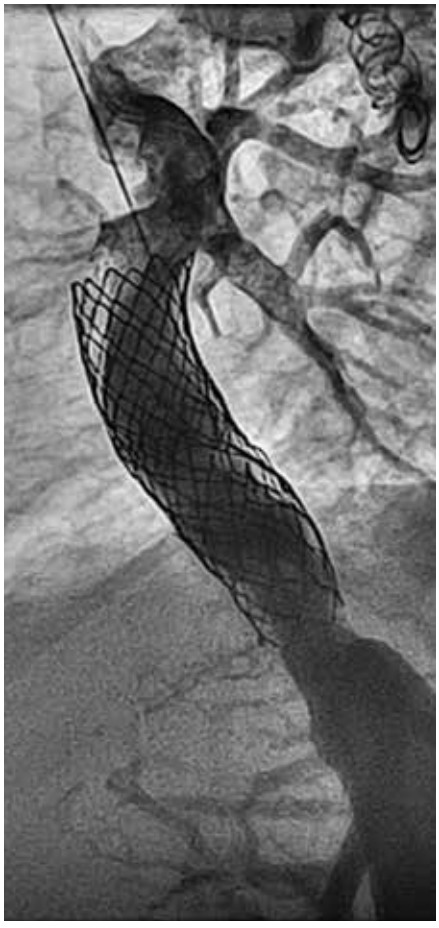
Fontan, now 88, still has sharp mental acuity. Gruschen Veldtman, MD, of the Heart Institute, and colleagues at the International Fontan Interest Group met with him informally in Bordeaux.

Veldtman's eyes lit up as he recalled his visit:

"I asked him his message to the many patients across the globe. He said to the effect, work with your expert physicians to get the best care. It was so simple. I think I was looking for something more profound.

"What he underscores is, this condition takes expertise. As physicians, we have to be confident and yet humble. It was one of the most incredible meetings. For him, seeing everyone focused on Fontan circulation in such an important way, I think it must have been very touching for him."

Veldtman, too.



These lateral angiograms of David Munro's Fontan pathway show before (left) and after (right) treatment with covered stents and balloon angioplasty.

"Diastolic dysfunction cannot be identified well non-invasively," says Goldstein, Associate Director of the Cardiac Catheterization Laboratory. "The right ventricle wasn't designed to pump against high pressure and resistance."

In a paper published in the June 2016 issue of *Heart*, senior author Goldstein and four Cincinnati Children's colleagues revealed that rapid-volume expansion was an important method of identifying "occult" diastolic dysfunction in Fontan patients.

Researchers were able to identify a large cohort of Fontan patients with high end diastolic pressure (diastolic dysfunction) that was only present with ventricular stress testing. This suggests that the longer duration of Fontan circulation, the worse the diastolic function.

In Munro's case, "we found substantial obstruction in his Fontan conduit due to thrombosis," says Goldstein, who often

Drs. Gruschen Veldtman, left, and Bryan Goldstein, are key physician/researchers in the Adolescent and Adult Congenital Heart Disease program, which was recently accredited by the Adult Congenital Heart Association. Veldtman directs the program.

collaborates—both clinically and academically—with Veldtman.

"Collaboration is utterly vital to our success," Veldtman says. Much like their teamwork in research, Goldstein and Veldtman applied their shared expertise to Munro's evaluation and care.

That reputation for collaboration was not lost on Keisler-Munro. Or her son.

"They're certainly encouraging. They wanted to see me in-person," he says. "So I don't look like the walking wounded, you know."

A heart transplant, even if a donor were available, is a tenuous option.

"In the past, people who have seen David were a bit gun-shy about considering him for a transplant," she says, "or even other major interventions. As we've gone down this journey, a transplant has been presented as the best alternative for an extended lifespan, but it's been so difficult."

In a systematic review of 28 studies, involving 6,707 patients, senior author Veldtman noted that assessing mortality rates is a challenge because outcome measures vary greatly. The findings were published in January, 2017, in *Heart*.

Of 697 late deaths, the five most common causes were heart/Fontan failure (22 percent), arrhythmia (16 percent), respiratory failure (15 percent), renal disease (12 percent) and thrombosis/bleeding (10 percent).

LONG-TERM CANCER CARE A TEMPLATE FOR FONTAN PATIENTS

Researchers know far more now than they did just a decade or so ago. In 2005, scientists saw what Veldtman calls a "startling" increase in rates of liver cancer in Fontan patients. "That started a revolution of thinking differently," he says. "That it was about more than just the heart."

Whether patients like Munro ever become eligible for heart transplants, Goldstein and Veldtman emphasize that their long-term care should look more like the care of a cancer survivor, where active organ surveillance is the norm, and not the exception.

"Every Fontan patient deserves that," Goldstein says.

Munro and his mother agree. ■

FONTAN CAN PUSH THE LIVER INTO SURVIVAL MODE

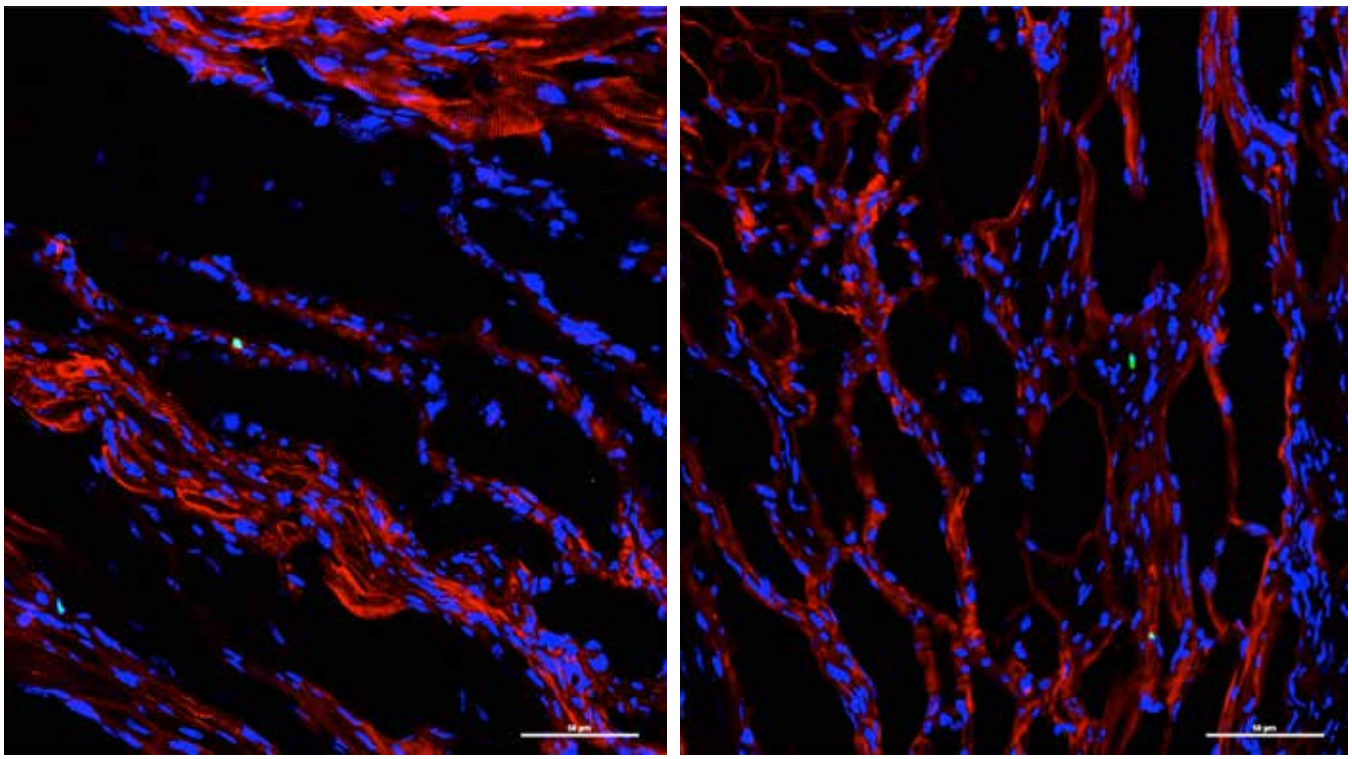
Organs can show some clever ways of adapting to the lack of sufficient circulation. Research here has shown that the liver protects itself from excessive pressure by developing barriers around the large veins inside it.

"It creates a structure of scar tissue, almost like braces, that contains the pressure," Gruschen Veldtman, MD, says. "It's quite extraordinary."

Teaching an Old Dogma New Tricks

To get hearts to heal themselves

by Nick Miller



These confocal microscope images show that activating Tbx20 overexpression produces cell proliferation in fetal and post-MI adult cardiomyocytes.

One seemingly impassable barrier on the path to one of medicine's Holy Grails—regenerating heart muscle injured by heart attack or disease—has been the long-held belief that mature heart muscle cells do not regrow.

Based on studies in mice, cardiomyocytes undergo a few cycles of mitotic cell division after birth, end up with a double nucleus, then forever stop regenerating—or so the dogma goes.

But heart researchers at Cincinnati Children's are trying to upend what has been one of the hard facts of life after cardiac infarction, or being born with a serious heart anomaly. The effort is producing some exciting, but still preliminary, results. This includes one finding that developed in such an unexpected manner that the scientists initially did not believe what they found.

Led by Katherine Yutzey, PhD, Division of Molecular Cardiovascular Biology, and Fu-li Xiang, PhD (a former member of Yutzey's lab, now at Novartis), the research team found that over-expression of the transcription factor Tbx20 in the infarcted and damaged hearts of mice prompted the hearts to partially regenerate. Treated mice regained 60-75 percent of their heart function.

Transcription factors are proteins that tell other genes what do to. From a surprising laboratory observation by Santanu Chakraborty, PhD, (Yutzey's post-doctoral fellow at the time) the scientists learned Tbx20 sets off a cascade that gets mature cardiac muscle cells to act more like fetal cardiomyocytes. Scientists know that fetal cardiomyocytes, which help spur initial heart development, are able to regenerate and proliferate.

These heart samples, harvested 4 weeks after experimental treatment, show that treated heart tissue (bottom) exhibited cell growth not seen in untreated tissue (top).

Katherine Yutzey, PhD

The potential implications of the team's discovery were startling enough that it prompted investigators to check and recheck the data for the reality of the findings to set in.

"When the observation was first reported to me I didn't believe it," Yutzey says. "I've had three different postdocs work on this now, trying to show the same finding in different ways, and finally it became evident that it was working.

"The old dogma was you can't get new heart muscle, and now we and some other groups in the field are finding that you can," she says. "The question is how you make that work so it's therapeutically beneficial to patients."

HIGH-RISK, HIGHER STAKES

The research clearly falls into a high-risk category, which essentially means the chances of failure are considerable, according to Yutzey. Also considerable are the potentially high benefits if the research leads to useful therapies.

According to the U.S. Centers for Disease Control and Prevention, unhealed heart attack damage is the leading cause of heart failure, contributing to 287,000 deaths a year in the United States alone. Meanwhile, congenital heart defects affect about one percent—or about 40,000—births a year in the U.S. The estimated hospital costs for people with congenital heart disease exceeds $1.9 billion.

And while today's advancing surgical techniques can reconfigure some malformed hearts to allow more children born with cardiac defects to survive into adulthood, those survivors often need complex, life-long follow-up care.

WHEN AGE MATTERS

One of the questions Yutzey and her colleagues want to answer is what age and health status would be best for performing complex corrective procedures in children. Should children be younger or older? Much could depend on the amount of time after birth that human cardiomyocytes start to lose their fetal characteristics and regenerative potential.

"Mice have this ability to regenerate heart muscle if they are injured for about a week after birth. We have no idea when it stops in humans, and obviously you can't study this in human babies," Yutzey explains.

"When the surgeons do these repairs it's a pretty severe operation. They have to move things around and make connections that didn't exist before. If there was a way to optimize the growth of new heart muscle after a repair like this, a huge basic question becomes finding out how long the human heart can heal itself after birth."

Yutzey is part of a wide-ranging collaborative research project with Cincinnati Children's Heart Institute, including cardiac surgeon Farhan Zafar, MD, and senior research assistant Scott Baker to try and find out. The planned work includes experimental surgical processes dovetailing with detailed laboratory analyses.

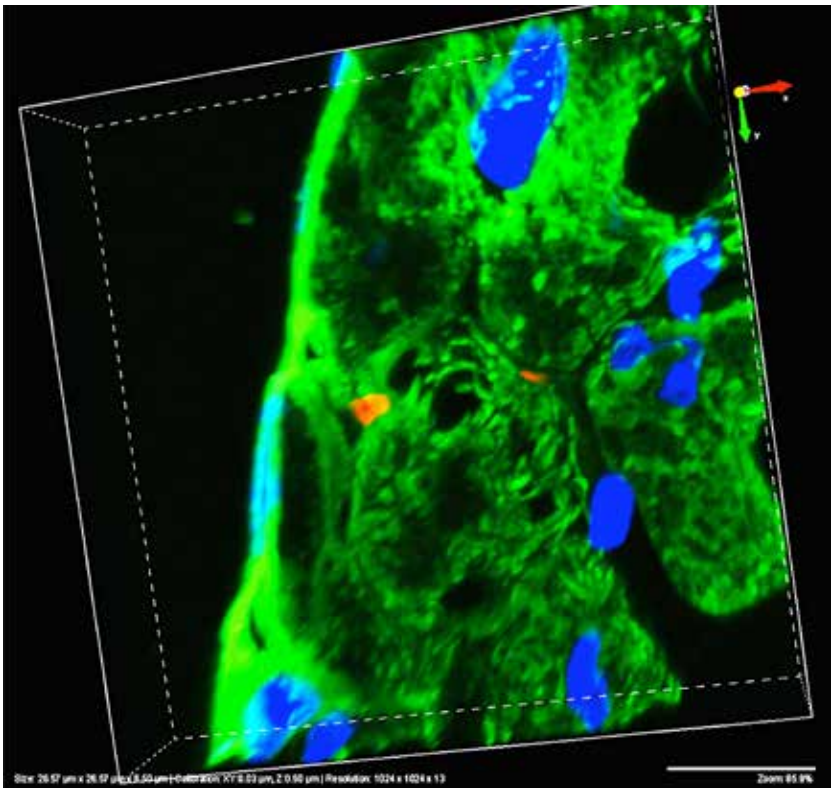
"The surgeons tell us that younger infants can do better after having these complex surgeries and there is more plasticity in their hearts and tissues, but none of us have any data on this," she says.

A LONG JOURNEY AHEAD

The next phase of the team's research will involve testing Tbx20 in preclinical models that offer closer comparisons to the human heart. For its initial work, the team studied mice that were engineered to overexpress Tbx20. Going forward, researchers plan to employ a viral vector to deliver Tbx20 to injured heart tissue. If successful, this approach has more potential for clinical use.

These steps will take time, but at least now, a pathway to that Holy Grail of heart research appears to be open for exploring. ■

"The question is how you make that work so it's therapeutically beneficial to patients."



This representative Z-stack of confocal microscope images indicates locations where cardiomyocytes are dividing after treatment to overexpress Tbx20. Further research will explore how a viral vector can be used to induce this process.

A New Kind of Clot Blocker

A promising approach that could limit clot formation without increasing bleeding risk could transform life for children—and adults—who depend on heart devices

by Tim Bonfield

Every surgeon who has connected a patient to a heart-lung bypass machine, placed an infant on an ECMO pump, or installed one of the growing number of mechanical heart support devices on the market has faced this battle:

How to prevent deadly blood clots from forming without creating an also deadly risk of bleeding?

Decades ago, doctors and scientists learned that blood rapidly begins to clot when it contacts metal parts, glass and plastic tubing, and other non-biological materials. For many years, doctors have reduced the risk of clots by employing large doses of heparin, warfarin or other anti-coagulants.

The well-known problem has been that the balancing act can easily fail, leading either to clot-triggered strokes or severe internal bleeding events. The longer a person's blood is in contact with a device, the harder it becomes to avoid a complication.

"When the first Berlin Hearts were introduced, there was a very high clotting rate, as high as 20 to 25 percent," says James Tweddell, MD, Executive Co-Director of the Heart Institute at Cincinnati Children's. "If it were possible to prevent clots effectively without incurring a bleeding risk that would be an enormous improvement."

Now, just such a solution may be on the horizon.

Tweddell, an internationally-prominent cardiac surgeon, is collaborating with Joseph Palumbo, MD, an expert on blood and blood diseases at Cincinnati Children's, on early-stage research that zeroes in on blocking "contact activation" of the clotting cascade. Their work indicates that inhibiting the function of coagulation factor XII (F12) can prevent device-related blood clotting while not affecting the body's ability to heal wounds.

A KEY FACTOR FOR THE FUTURE OF CARDIAC DEVICES

With only a few thousand donated organs available per year, receiving a full heart transplant is not a realistic option for the hundreds of thousands of people in the United States coping with heart failure. These include children born with severe heart defects, young adults battling diseases such as Duchenne muscular dystrophy, and legions of seniors with hearts weakened by previous heart attacks, coronary disease, and age.

For most who reach advanced heart failure, the hope of extended life depends heavily on mass-producing practical cardiac support and replacement devices. When that day arrives, device recipients might be able to live on for years, even decades—but they will not live well if they must depend on existing anticoagulation therapy.

"Even the newer anticoagulants that have been developed in the past five to 10 years come with significant bleeding risks," Palumbo says.

In the last decade, however, researchers have been learning more about how F12 works, and how it relates to other clotting factors. That work has led Palumbo, Tweddell and colleagues to evaluate a compound made by California-based Ionis Pharmaceuticals.

TARGETING FACTOR XII TO BLOCK PATHOLOGICAL CLOT FORMATION

Clot formation, Palumbo says, is the final step of a cascade of activity involving multiple blood proteins.

Older anticoagulant drugs, such as heparin and warfarin, act like massive dams toward the bottom of this cascade. (see figure, page 27.) They interfere with the production and/or function of thrombin, the central protein in the clotting cascade needed for making fibrin, the material that actually forms clots.

By blocking the activity of proteins later in the clotting process, current anticoagulants significantly impair patients' ability to form any kind of clot, desired or not. The new approach would place the dam on a side stream—before it joins the larger cascade, Palumbo says.

While F12 is crucial to how the blood reacts to foreign surfaces, it plays no role in stopping the bleeding associated with wounds. Thus, blocking only F12 would allow the rest of the cascade to flow unimpeded, and carry no surgical bleeding risk.

"If this approach succeeds, a person receiving a cardiac device would be protected from contact-mediated clotting but could still undergo future surgeries, or heal from accidental trauma, with greatly reduced risk of bleeding," Palumbo says.

Joesph Palumbo, MD, (left) is working with James Tweddell, MD, (right) on a promising approach to preventing clots caused when blood contacts foreign device surfaces.

To test their hypothesis, these researchers are using an exciting potential treatment that relies on a "gapmer," a type of antisense oligonucleotide (ASO) that can be used to silence the function of a specific gene. Gapmers are highly specific, and can be used for extended periods. The gapmer produced by Ionis specifically targets the gene controlling F12.

"By suppressing the contact activation pathway, this treatment could allow use of bypass machines, ECMO, ventricular-assist devices, and so on, with much less than standard anticoagulation," Tweddell says.

EARLY-STAGE TESTING UNDERWAY

A lab team including Farhan Zafar, MD, research associates Scott Baker, Leah Rosenfeldt, and Malinda Frederick, clinical veterinarian Brenda Wynn, and surgical veterinary technician Savannah Walters have begun testing the F12-blocking compound in preclinical models.

So far, the work is showing promising results that appear to serve as a basic proof of concept. However, much more testing is needed before clinical trials can begin, Palumbo says.

NEXT STEPS

More testing is needed to verify the early results, Palumbo says. Further rounds of study would likely involve longer time frames and more types of cardiac assist devices.

The highly-specific gapmer approach could be ideal for long-term management of ventricular assist devices. Patients (or caregivers) would even be able to administer treatments at home. However, the weeks-long build-up period needed before surgery could be a limiting factor for the gapmer approach when it comes to bypass surgery. A faster-acting F12 inhibitor would be beneficial for patients facing more urgent situations.

"Even if this approach cannot fully replace the need for heparin or warfarin, any large reduction in the dosages of those drugs would have a potentially dramatic impact on bleeding risks," Palumbo says. ■

Top: Research assistant Leah Rosenfeldt prepares a syringe for the anti-clotting experiment with assistance from student intern Jessica Shafer. Bottom: Team notes track the project's progress.

Targeting the Clotting Cascade

A) This illustration shows that contact-activated clotting follows a different pathway than clotting caused by wounds, which suggests that blocking Factor 12 could could limit the risk of device-related blood clots without triggering other bleeding risks. B) This chart shows how pressure across a cardiopulmonary bypass oxygenator is affected in preclinical models of different forms of anticoagulation therapy. When heparin treatment is stopped (red and purple), the pressure across the oxygenator increases dramatically, consistent with blood clot formation in the device. However, treatment with the factor XII gapmer (blue) produced minimal clotting, similar to maintaining typical high doses of heparin (yellow). C) These post-bypass tissue section images show extensive damage without heparin anticoagulation (control) but minimal necrosis following treatment with fXII Gapmer.

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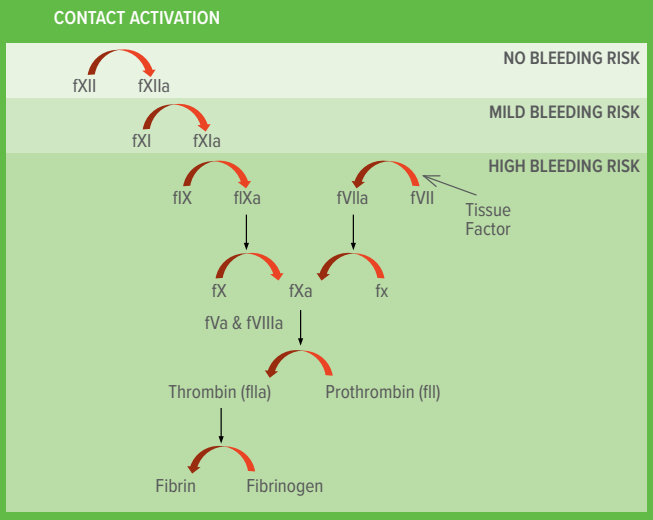

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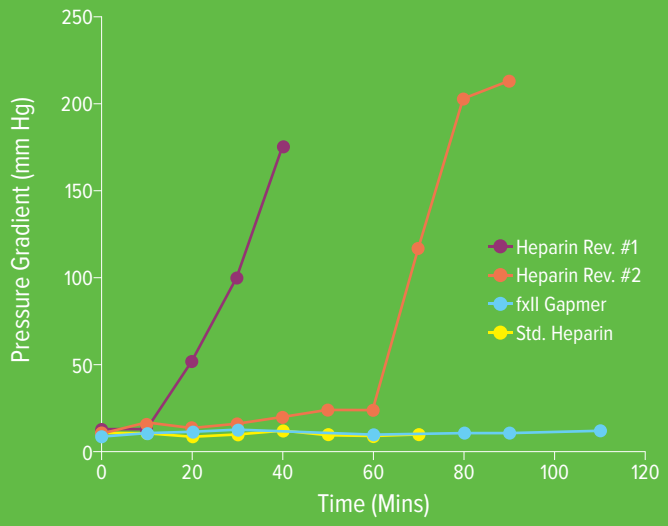

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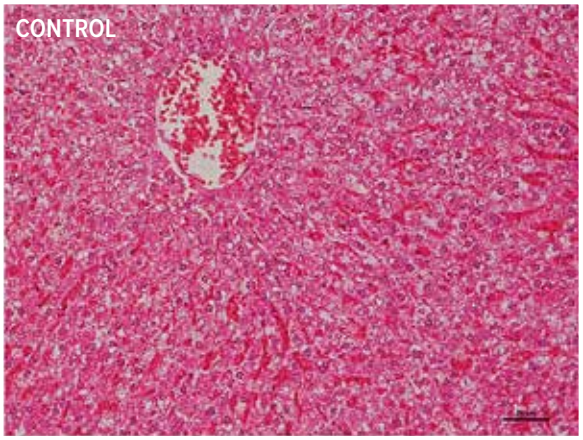
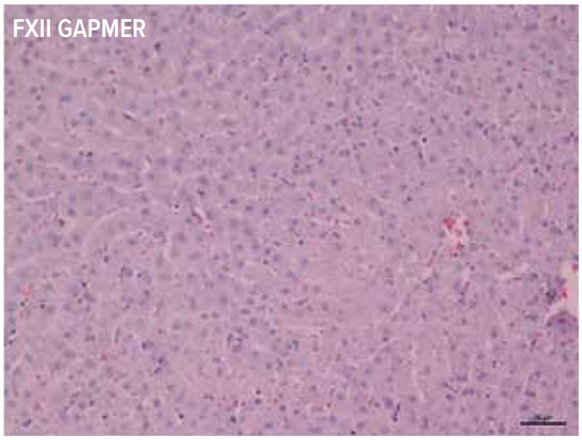




GRANTS

From Feb. 1 to June 30, researchers at Cincinnati Children's were awarded 214 grants valued at $105.8 million in total costs. Here are the recipients of grants exceeding $1 million:

David I. Bernstein, MD, MA,

Infectious Diseases, received a three-year, $1.3 million grant from the National Institute of Allergy and Infectious Diseases, to study the implementation of the Vaccine and Treatment Evaluation Units, a national group of institutions that conducts clinical trials of promising candidate vaccines and therapies for a variety of infectious diseases.

Samantha A. Brugmann, PhD,

Plastic Surgery, will study the role of primary cilia in murine craniofacial development, using a six-year, $2 million grant from the National Institute of Dental and Craniofacial Research.

Robert C. Coghill, PhD,

Director of Research, Anesthesia, received a three-year, $2.8 million grant from the National Institute of Neurological Disorders and Stroke, to study the brain mechanisms that account for individual differences in pain.

Steve Danzer, PhD,

Anesthesia, received a five-year, $1.8 million grant from the National Institute of Neurological Disorders and Stroke, to study the identification and reversal of primary and secondary epileptogenic changes in patients with epilepsy. He also received a three-year, $2 million grant from the same agency to study mTOR regulation of aberrant neuronal integration and epilepsy.

Stella Davies, MBBS, PhD,

Director, Bone Marrow Transplant and Immune Deficiency, received a five-year, $1.1 million grant from the National Cancer Institute for her role with the Childhood Cancer Survivor Study. The project examines the late effects of patients who have survived five years or more following a pediatric cancer diagnosis.

Matthew J. Flick, PhD,

Experimental Hematology & Cancer Biology, received a five-year, $2.3 million grant from the National Cancer Institute to study the thrombin-dependent mechanisms of pancreatic ductal adenocarcinoma disease.

Patricia Fulkerson, MD, PhD,

Allergy and Immunology, will study the role of Aiolos in eosinophilic asthma, using a five-year, $2 million grant from the National Institute of Allergy and Infectious Diseases.

Richard Gilman, PhD,

Child and Adolescent Psychiatry, received a three-year, $1.2 million grant from the Department of Justice for his work in the Campbell County (Ky.) School District's efforts to reduce violence.

John Harley, MD, PhD,

Director of the Center for Autoimmune Genomics and Etiology (CAGE), will study gene regulation as a foundation for autoimmune disease prevention, using a five-year, $2.7 million grant from the National Institute of Allergy and Infectious Diseases.

Rashmi Hegde, PhD,

Developmental Biology, received a five-year, $1.9 million grant from the National Cancer Institute, to study the linked regulation of tumor angiogenesis.

Michael Helmrath, MD, MS,

General and Thoracic Surgery, received a five-year, $1.9 million grant from the National Institute of Diabetes and Digestive and Kidney Diseases, to investigate the regional identity in human intestinal stem cells.

Kevin Hommel, PhD,

Behavioral Medicine and Clinical Psychology, received a five-year, $1.3 million grant from the National Institute of Child Health and Human Development, for his work in enhancing patient adherence to treatment and health outcomes.

Vivian Hwa, PhD,

Endrocrinology, will study the roles of STAT5b in IGF-1 production and human growth, with a two-year, $1.6 million grant from the National Institute of Child Health and Human Development.

Edith Janssen, PhD,

Immunobiology, received a five-year, $1.5 million grant from the National Institute on Aging, to study metabolic alterations in age-associated dendritic cells.

Rulang Jiang, PhD,

Developmental Biology, will study the molecular regulation of palate development, using a four-year, $1.2 million grant from the Shriners Hospital for Children.

Heather Kaplan, MD, MSCE,

Neonatology and Pulmonary Biology, received a two-year, $2.6 million grant from the Patient-Centered Outcome Research Institute, to study the use of single subject (N-of-1) designs to answer patient-identified research questions.

GRANTS

Susmita Kashikar-Zuck, PhD,

Behavioral Medicine and Clinical Psychology, received a five-year, $7.7 million grant from the National Institutes of Arthritis and Musculoskeletal and Skin Diseases, for her role with the multi-site randomized clinical trial of FIT Teens for juvenile fibromyalgia.

Satish Madala, PhD,

Pulmonary Medicine, will study the WT1 regulation of pulmonary fibrosis, using a five-year, $2 million grant from the National Heart, Lung, & Blood Institute.

Stephen Meuthing, MD,

Co-Director, James M. Anderson Center for Health Systems Excellence, will study ways to improve the safety of patients, using a one-year, $3 million grant from the Ohio Children's Hospitals' Solutions for Patient Safety.

Lou Muglia, MD, PhD,

Co-Director, Perinatal Institute, received a five-year, $3 million grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, to advance the systems-biology approach to discovery of biological pathways in placental development and parturition. He also received a one-year, $2 million grant from the March of Dimes for his work with its Prematurity Research Center Ohio Collaborative.

Satoshi Namekawa, PhD,

Reproductive Sciences, received a four-year, $1.9 million grant from the National Institute of General Medicine Sciences, to study DNA damage response pathways in meiotic sex chromosome I.

Ernest Pedapati, MD,

Child and Adolescent Psychiatry, will study anomalous sensorimotor physiology in Fragile X Syndrome, using a five-year, $1.3 million grant from the National Institute of Mental Health.

Brenda Poindexter, MD, MS,

Perinatal Institute, received a four-year, $1.7 million grant from the National Institute of Child Health and Human Development, for her work with its Cooperative Multicenter Neonatal Research Network.

Saulius Sumanas, PhD,

Developmental Biology, will study the role of collagen COL22A1 in intracranial aneurysms, using a four-year, $1.9 million grant from the National Heart, Lung, and Blood Institute.

Takuji Suzuki, MD, PhD,

Pulmonary Biology, will study genome-edited iPS cell-derived macrophages, using a four-year, $1.6 million grant from the National Heart, Lung, and Blood Institute.

Takanori Takebe, MD,

Gastroenterology, Hepatology and Nutrition, received a three-year, $1.3 million grant from Ono Pharmaceutical Co., Ltd., to study the directing of multi-visceral organ budding from induced pluripotent stem cells.

Sing-Sing Way, MD, PhD,

Infectious Diseases, received a five-year, $2 million grant from the National Institute of Allergy and Infectious Diseases, to study the functional immune tolerance to non-inherited maternal antigen.

Matthew Weirauch, PhD,

CAGE, will study how the binding of Epstein Barr Virus EBNA2 unifies multiple sclerosis genetic mechanisms, using a four-year, $1.1 million grant from the National Institute of Neurological Disorders and Stroke.

Jeffrey Whitsett, MD,

Co-Director, Perinatal Institute, received a four-year, $2.2 million grant from the National Heart, Lung, and Blood Institute, to study the role of EMC3/TMEM111 in alveolar epithelial cell function. He also was awarded a one-year, $1.4 million grant from the agency to study lung and cardiovascular development and disease.

Yutaka Yoshida, PhD,

Developmental Biology, received a five-year, $1.1 million grant from the National Institute of Neurological Disorders and Stroke, to study a novel approach to restoring motor function.

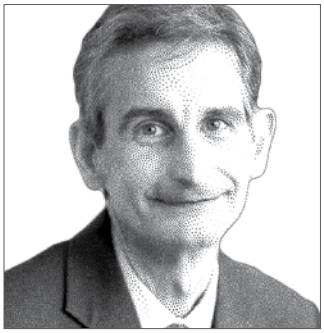
HONORS

Muglia to Direct Human Genetics

Louis Muglia, MD, PhD, has been appointed to the role of A. Graeme Mitchell chair and Director of the Division of Human Genetics.

Muglia, who trained in pediatrics and pediatric endocrinology at Boston Children's, came to the Perinatal Institute at Cincinnati Children's in January 2012 after faculty positions at Washington University in St. Louis (1996-2008) and Vanderbilt University Medical Center (2008-2012), where he also served as vice chair for research.

Muglia's bibliography includes more than 215 peer-reviewed publications and chapters. His expertise in the genetics of preterm birth has been nationally and internationally recognized with a Lucille Markey Charitable Trust Scholar award, a Burroughs-Wellcome Fund Career Development Award, and multiple NIH R01s since 2001.



Louis Muglia, MD, PhD

Lee Denson, MD,

Director, Schubert-Martin IBD Center, received a $100,000 Sherman Prize from the Bruce and Cynthia Sherman Charitable Foundation in recognition of his career of achievements in improving the health and wellness of people living with Crohn's disease and ulcerative colitis.

Todd Florin, MD, MSCE,

Emergency Medicine, was elected to represent Emergency Medicine on the Society for Pediatric Research Council.

Maryam Fouladi, MD, MSc,

Oncology, was selected to participate in the Executive Leadership in Academic Medicine (ELAM) program.

Victor Garcia, MD,

Founding Director, Trauma Services, was recently named a Great Living Cincinnatian by the Cincinnati USA Regional Chamber.

Mike Gittelman, MD,

Emergency Medicine, was named President-Elect for the Ohio Chapter of the American Academy of Pediatrics.

Haleh Heydarian, MD,

Cardiology, was inducted as a Fellow of the American College of Cardiology.

James McCarthy, MD, MHCM,

Director, Pediatric Orthopaedics, was elected President of the Pediatric Orthopaedic Society of North America.

HONORS

Mary McMahon, MD,

Director, Division of Physical Medicine and Rehabilitation, was elected Secretary of the American Board of Physical Medicine and Rehabilitation.

Halima Moncrieffe, PhD,

Center for Autoimmune Genomics and Etiology (CAGE), was named a TEDMED Research Scholar and was selected as part of a Black Science Network feature for Black History Month.

Jennifer O'Toole, MD, MEd,

Hospital Medicine, received the inaugural Brendan Kelly Award from the Medicine-Pediatrics Program Directors Association.

Joe Real, MD,

General and Community Pediatrics, recently received the APA Young Investigator Award, the Ray Helfer Presentation Award, and the Children's Journal Travel Award.

Paul Spearman, MD,

Director, Infectious Diseases, was elected President (2017-18) of the Pediatric Infectious Diseases Society.

Sandy Staveski, PhD, RN, APRN,

Heart Institute, was elected President of the Pediatric Cardiac Intensive Care Society.

Sarat Thikkurissy, DDS, MS,

Dentistry, was named Pediatric Dentist of the Year by the American Academy of Pediatric Dentistry.

Jilda Vargus-Adams, MD, MSc,

Physical Medicine and Rehabilitation, was elected President (2018) of the American Academy of Cerebral Palsy.

McAuliffe named Anesthesiologist-in-Chief

John McAuliffe III, MD, MBA, has been appointed anesthesiologist-in-chief at Cincinnati Children's after serving as interim chief since last March.

McAuliffe replaces Dean Kurth, MD, who after 13 years at Cincinnati Children's returned to Children's Hospital of Philadelphia.

McAuliffe began his career at Cincinnati Children's in 1985 in the Department of Anesthesia. By 1994, he was named associate director. From 2002-2014, he served as research director. Beginning in 2008 until last year, he added the role of director of the Division of Neurobiology. Since 2010, he has been section chief of Intraoperative Neurophysiological Monitoring.

John McAuliffe III, MD, MBA

REGISTER TODAY FOR THE

27th International Symposium on Adult Congenital Heart Disease

In its 27th year, the International Symposium on Adult Congenital Heart Disease (ACHD) brings experts from around the world to deliver the latest findings of cutting-edge research as well as practical advice for the treatment of these patients. The program is intended for pediatric and adult medical providers, including nursing and allied health professionals, seeking to improve ACHD care.

SEPTEMBER 14-16, 2017

at the Westin Hotel Cincinnati

FEATURED TOPICS INCLUDE:

- Advanced medical and surgical strategies for treating heart failure
- Fontan circulation and its multi-organ consequences
- Maternal-fetal care for women with ACHD
- Neurodevelopmental assessment and outcomes
- Advanced therapies in pulmonary arterial hypertension
- Electrophysiology and hybrid interventions
- Multimodality imaging integration: virtual surgery and virtual reality in CHD

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For event details, contact:
Continuing Medical Education office
cme@cchmc.org or 513-636-6732

www.cincinnatichildrens.org/ACHDsymposium

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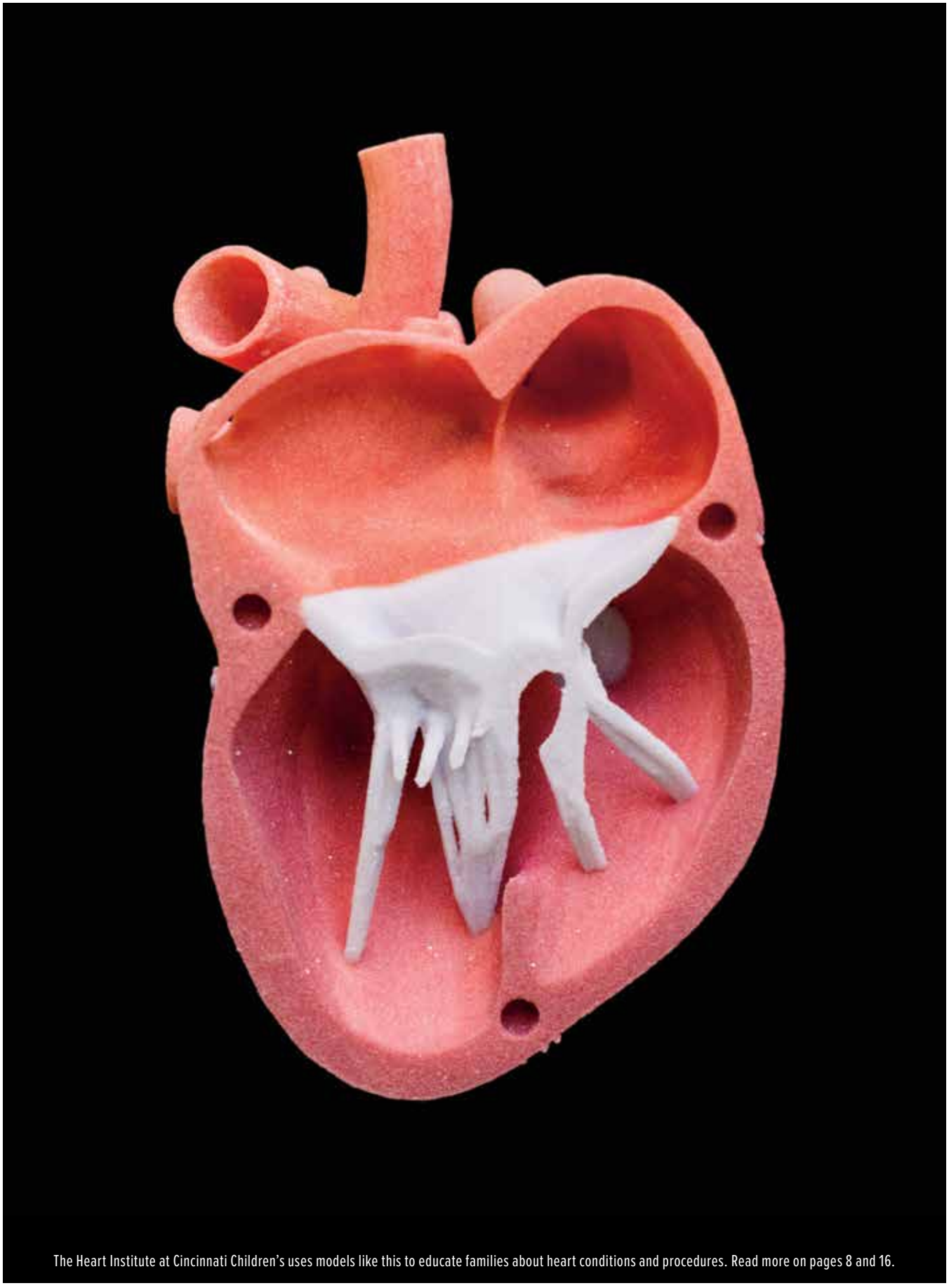

The Heart Institute at Cincinnati Children's uses models like this to educate families about heart conditions and procedures. Read more on pages 8 and 16.

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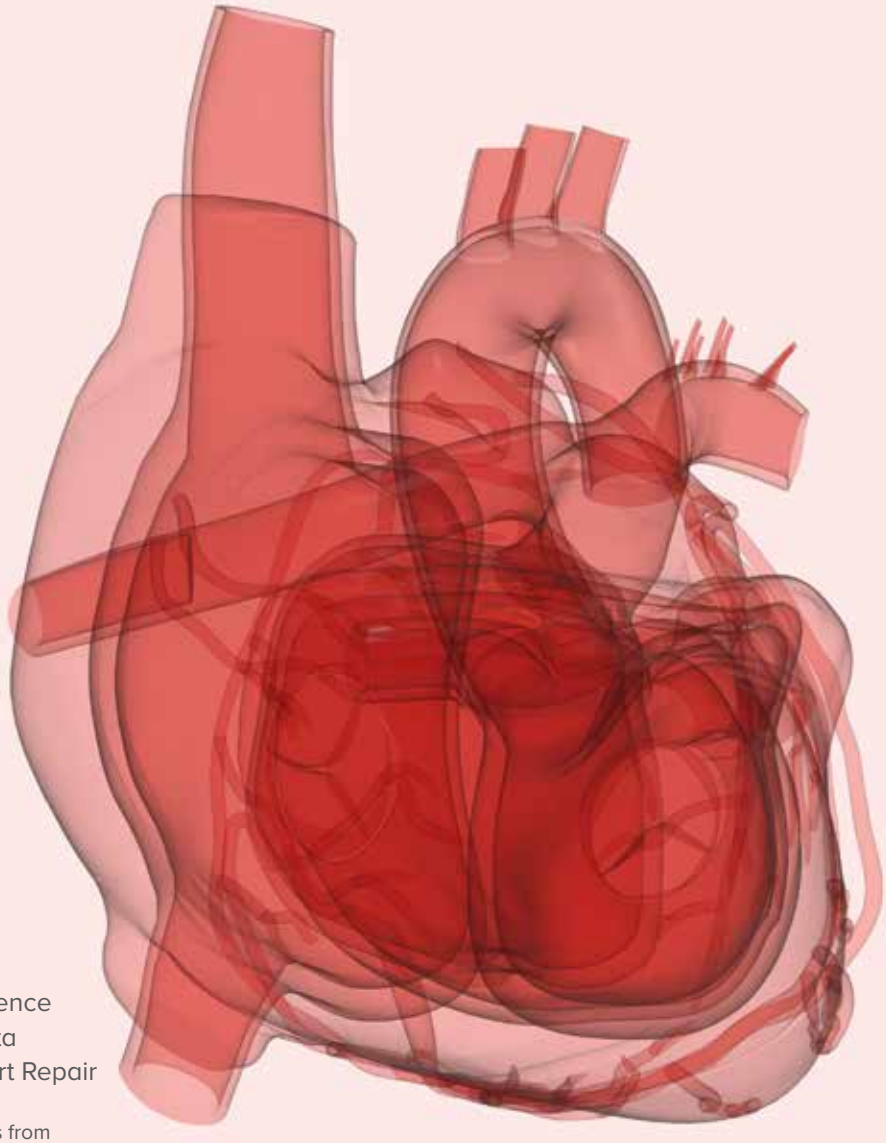

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