QUALITY, OUTCOMES AND RESEARCH

ANNUAL REPORT

2021

Children's Wisconsin

Herma Heart Institute

Joy Lincoln, PhD,
Peter Sommerhauser
Chair for Cardiac Quality,
Outcomes and Research,
Children's Wisconsin

Read Dr. Lincoln's Lab Spotlight on page 16.

Exceeding Expectations

Throughout the COVID-19 global pandemic, our physicians, researchers, trainees and staff have continued to work together to support our community, transitioning to a hybrid work environment where possible. We reached record quality, outcomes and research (QOR) milestones, maintained a healthy workforce, and further enhanced the collaborative culture in ways we could not have envisioned. The situation also reminded us why we are here: to improve outcomes for every child and adult with congenital heart disease who enters the doors at the Herma Heart Institute (HHI).

Our research portfolio now exceeds that of any other year. Over the past five years, the HHI-led QOR program, including lead investigators, trainees, administrators and staff, has grown exponentially to ensure that HHI continues to work at the cutting-edge of discoveries in congenital heart disease. In 2021, we recruited two national leaders in the field to join the collaborative HHI research team: John LaDisa Jr., PhD, professor of Pediatric Cardiology, is at the forefront of cardiovascular fluidic technology. Lu Han, PhD, assistant professor of Pediatric Cardiology is noted as a rising star of cardiomyocyte biology. Dr. LaDisa and Dr. Han bring innovative technology and conceptual ideas to the HHI QOR community.

We are grateful to have grown more than 280 percent in dollars received to support QOR projects since 2016. This includes six times more dollars from the National Institutes of Health, and three times more from private funding agencies and foundations. In 2021, HHI published more than 80 papers in peer-reviewed publications, and we continue to be impactful and prolific in national arenas related to pediatric heart disease.

Our program could not achieve these highlights without the support of our gracious families and community partners. Through their generosity, we have been able to support the development of high-risk endeavors that promise to transform the way we treat our patients. Through the HHI Precision Medicine Program, which includes our Cord Blood Repository and Tissue Bank, we are working together to gain a better understanding of individual differences in people's genes, environments and lifestyles, and how these might influence personalized treatment plans. Philanthropic funds also have supported the introduction of two new Endowed Chair Funds: the Patricia and Paul Jones Endowed Chair in Adult Congenital Heart Disease, awarded to Scott B. Cohen, MD, and the Albert O. Nicholas Endowed Chair in Heart Transplant, awarded to Ronald K. Woods, MD, PhD. There are now five endowed chairs within the HHI.

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"We are grateful to have grown more than 280 percent in dollars received to support QOR projects since 2016."

—Joy Lincoln, PhD

The COVID-19 pandemic has significantly impacted us all and continues to transform the way we work, connect with colleagues, interact with our patients and manage work/life effectiveness. Despite this, HHI has continued to demonstrate strong teamwork and dedication to developing innovative ideas that improve the clinical management and outcomes of our patients and their families. In addition, we are pioneering educational pathways for exceptionally talented individuals who strive to become world-class clinicians, researchers and physician-scientists. I am optimistic that 2022 will bring even greater successes, which will turn into hope for our HHI families and those impacted by congenital heart disease.

Sincerely,

Joy Lincoln, PhD

Peter Sommerhauser Chair for Cardiac Quality, Outcomes and Research, Children's Wisconsin

Director of Cardiovascular Research, Herma Heart Institute

Professor, Associate Chief and Research Director, Pediatric Cardiology, Medical College of Wisconsin

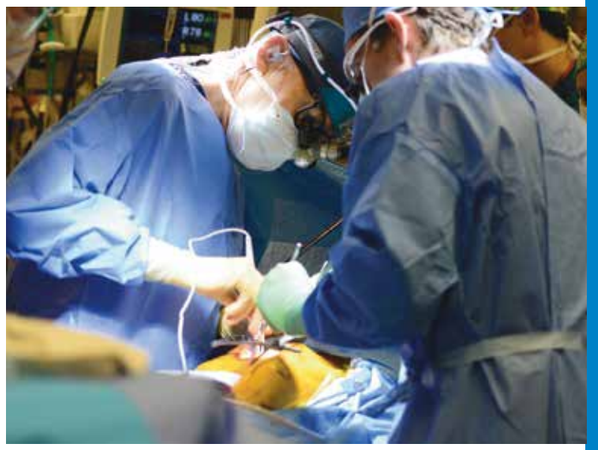
A Career of Collaboration and Education

Pediatric cardiovascular surgeon **Viktor Hraska, MD, PhD**, is working to develop a library of three-dimensional cardiovascular surgical videos for educational purposes. **Matthew Hietpas, MS, CCP**, a cardiovascular perfusionist at HHI, is assisting with this project.

Dr. Hraska has previously produced a textbook on pediatric congenital heart surgery, which included a DVD of surgical videos in which he described the planning and etiology of each procedure. With this new encyclopedia, Dr. Hraska and Hietpas hope to make highly specialized and informative videos that can be useful to surgical professionals, as well as allied health professionals. "With congenital heart surgery, there are so many different reasons that these children are having surgery and so many unique operations," said Hietpas. "Depending upon where you are, you might do one or two of these procedures a year, whereas other places can be doing one or two a week."

HHI is committed to collaboration and learning and has recently appointed new staff and leaders who align with these values. **Michael Mitchell, MD**, will be HHI's new surgical director. "His ability to bring all parties together is a very strong point of his," said Hietpas.

Viktor Hraska, MD, PhD, previously produced a textbook on pediatric congenital heart surgery.



Above: Dr. Hraska and his team perform heart surgery on a young patient.

By the Numbers

- **3** psychologists
- **10,000+** cardiac patients treated annually
- **500+** heart surgeries each year
- **400+** cardiac catheterizations performed each year
- **280%** growth in research funds in five years
- **2,700+** ACHD patients currently followed
- **27** pediatric cardiologists
- **80+** papers in peer-reviewed publications in 2021
- **3** surgeons
- **11** pediatric cardiology fellows
- **5** endowed chair holders
- **7** principal investigators with **20+** research staff
- **14** anesthesiologists and intensivists

Cardiologist Dan McLennan, MD, bonds with a patient born with congenital heart disease.

2021 Innovation Fund Awards

Grants support research and innovative programs to improve outcomes for people with congenital heart disease

The Innovation Fund was launched when the Herma family committed to donating $8 million to Children's Wisconsin on the condition that the hospital raised enough donor funds to match it. The following year, Children's was able to raise more than $9 million from donors, and the Herma family directed that these funds be designated for research and innovation related to improving outcomes for patients born with congenital heart disease.

Today, the Herma family has donated in excess of $25 million. According to Maryanne Kessel, HHI executive director of development, they are not only the largest benefactors to HHI, but the largest benefactor to children's health care systems overall.

The HHI Innovation Fund was created in 2018 to ensure that these funds explicitly support research, quality improvement, and innovations in education and training. Including this year's recipients, the HHI Innovation Fund has awarded $4 million across multiple projects. The purpose of funding varies from research to quality improvement to optimizing programming.

"The Herma family are committed to working with us in partnership as philanthropic supporters and also as thought leaders to develop systems and strategies to conquer congenital heart disease and improve the quality of life for those living with congenital heart disease."

— Maryanne Kessel, HHI executive director of development

The 2021 Innovation Fund Award Winners

HERMA HEART INSTITUTE RESEARCH GRANTS

- Exploring endothelial restoration as a therapeutic target in the treatment of congenital bicuspid aortic valve disease — Joy Lincoln, PhD; Michaela Patterson, PhD; Michael Mitchell, MD
  - This is the second year of funding for Dr. Lincoln's research. She and her collaborators are exploring healing restoration as the therapeutic target in the treatment of bicuspid aortic valve disease.
- Pulmonary arteriovenous malformations (PAVM) in univentricular congenital heart disease — Andrew Spearman, MD
  - Dr. Spearman, a pediatric cardiologist at Children's, has received a one-year pilot award to develop a novel PAVM mouse model and use a previously published AVM mouse model to determine whether sVEGFR1 prevents and resolves PAVMs.

HERMA HEART INSTITUTE QUALITY IMPROVEMENT GRANT

- MI-SMART Plan Improvement Project for School-Aged Cardiac Patients — Kyle Landry, MS
  - The Education Achievement Partnership Program (formerly the School Intervention Program) intends to improve its MI-Smart Plan for school-aged patients who have congenital heart disease. Funds from the Innovation Award will aid in optimizing the program.

HERMA HEART INSTITUTE PROGRAMMATIC GRANTS

- Cardiogenetics Program Support — Donald Basel, MD
  - The aim of research in the cardiogenetic service is multifaceted, varying from assessing the impact of genetic diagnoses on the outcomes data of the transplant service to improving the diagnostic rate and discovery of new genetic etiologies in affected patients. Dr. Basel is the lead on this project, which supports the work being done between the genetics team and HHI.
- Herma Heart Institute Tissue Repository — Precision Medicine Program
  - The Precision Medicine Program is developing a bank of discarded tissue, blood or cell samples donated at the time of birth or during corrective surgery from patients diagnosed with congenital heart disease. Research and clinical studies are focused on utilizing patient cells to develop surgical material that can be implanted back into the child to fix congenital structural malformations of the heart in the future.

Thousands of children born with congenital heart malformation could benefit from precision medicine.

Bringing Precision Medicine to Children's

A multidisciplinary team works toward a day when a child's own tissue can be used to rebuild their heart

Michael Mitchell, MD, a Children's Wisconsin cardiothoracic surgeon, shares his screen during a Zoom call. And there it is: beating cardiomyocytes, the cells responsible for ensuring the heart contracts and relaxes with each beat.

Only these cells aren't from someone's heart. They're grown from pluripotent stem cells coaxed into differentiating towards heart muscle cells and bioengineered into a patch that could be used to fix a child's heart — the same child whose tissue provided the stem cells.

This is the hallmark of precision medicine. At HHI, it means taking a multidisciplinary approach to understanding the etiology and pathogenesis of individual kids with congenital heart disease to select the most effective treatment strategy for them. This includes innovative approaches related to genetics, genomics, discovery science, clinical management, outcomes, imaging and much more.

INDIVIDUALIZED APPROACH

HHI's cord blood repository allows for the clinical-grade storage of umbilical cord tissue and blood that serves as a rich source of progenitor, or stem cells. Those cells, under the right conditions, have the capacity to give rise to many different cell types, including those that make up the heart and other cardiovascular structures.

"Using these autologous cells from healthy and congenital heart disease patients, we have the potential to generate biocompatible cardiovascular cell populations or tissues that can be transplanted back into the patient during reconstructive surgery to correct for life-threatening congenital malformations," said Aoy Tomita-Mitchell, PhD, Medical College of Wisconsin professor and HHI investigator.

Personalized medicine stands in contrast to the classic one-size-fits-all approach, in which everyone with the same disease gets the same treatment. Today, the genetics of a tumor can determine the treatment, and drugs that target gene variants are transforming diseases like cystic fibrosis and neuromuscular conditions. The team at Children's is applying the same principles to treating congenital heart disease.

TAILORED TO THE HEART

"One in every 100 kids is born with a congenital heart malformation," said Medical College of Wisconsin professor and HHI investigator Joy Lincoln, PhD. "That includes kids from all walks of life, from every ZIP code, every ethnic and genetic background. We've begun to understand that there isn't one pill or one approach to treating them because every child is unique, and the reason that each is born with a malformed heart is different. That's why we're trying to take an individualized approach for each child."

Dr. Mitchell and Dr. Tomita-Mitchell work closely with Dr. Lincoln, who focuses on heart valves, with the goal of being able to "grow" a new heart valve for a child from the child's own cells.

Together, they are building "toolboxes" for all children born with congenital heart disease, banking their cord blood and tissue, testing the parents' blood for genetic abnormalities and trying to understand the role of genetics coupled with environmental influences on that child's disease. The child's own tissue allows the researchers to better understand the molecular dysfunction contributing to the disease.

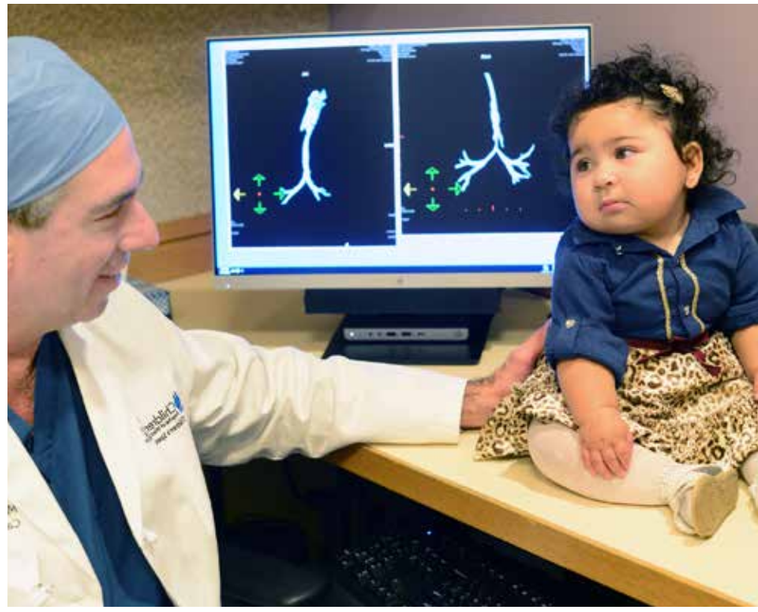
The ultimate goal is to then use the patient's own tissue or cord blood to grow the stem cells into whatever type of cardiovascular cell is required, be it cardiomyocytes that keep the heart beating, or new heart valves that keep the blood flowing. Using the child's own tissue to rebuild a heart negates the need for lifelong anticoagulation to prevent clots, which is required when devices like pacemakers, stents, and animal or artificial valves are used.

"It adds function and energy to the heart and would grow with the patient to avoid having to intervene again," said Dr. Mitchell. "It could avoid the need for a heart transplant and make for a more normal, if not completely normal, quality of life for these children."

Dr. Lincoln acknowledged that the potential benefits of precision medicine go well beyond treating congenital heart disease. "While we're doing this for the heart right now, there are obviously infinite uses of the stem cells to benefit other children affected by other diseases in the future," she said. "But you know, our heart is really in the heart."

"It adds function and energy to the heart and would grow with the patient to avoid having to intervene again."

— Michael Mitchell, MD



HHI patient Julissa, pictured with Michael Mitchell, MD, was born with two tracheas. Dr. Mitchell successfully performed a surgical repair.

Improving Inclusion, Diversity and Equity

We're working to foster an inclusive culture within HHI and beyond

Improving inclusion, diversity and equity has been a key goal for the HHI. The Office for Inclusion, Diversity and Equity (IDE) at Children's has put together varying inclusion resource groups (IRGs) to assist the organization in fostering a diverse and inclusive culture that aligns with its values. A few examples of the current IRGs include Asian/Pacific Islander Allies, Black Professionals & Allies, Children's Pride (LGBTQ+) and Hispanic/LatinX Allies.

David Saudek, MD, Children's Wisconsin pediatric and fetal cardiologist; Regina Cole, BS, MT(ASCP), CCRP, clinical research coordinator; and Deborah Walbergh, have represented HHI as IDE ambassadors. Together, they have collaborated to host educational conversation circles within HHI. Cole and the other ambassadors said these educational opportunities have helped providers gain insights about their patients, including "understanding why they may be asking a certain question or be apprehensive about something."

At the HHI Vascular Research Core Laboratory, doctors have the ability to non-invasively measure endothelial dysfunction and identify which pediatric populations are at higher risk for cardiovascular disease later in life.

In an effort to provide more informed care, Salil Ginde, MD, a pediatric and adult congenital cardiologist at HHI, is starting a research project looking to clarify racial and socioeconomic disparities among children at risk for cardiovascular disease who live in southeast Wisconsin.

Dr. Ginde explained that Black adults have a higher prevalence of cardiovascular disease, including heart attacks and stroke, compared to white adults in Wisconsin. Many of the blood vessel changes that ultimately lead to heart attacks and stroke are present as early as childhood in the form of "endothelial dysfunction." At the HHI Vascular Research Core Laboratory, doctors have the ability to non-invasively measure endothelial dysfunction and identify which pediatric populations are at higher risk for cardiovascular disease later in life.

The goal of the study is to measure endothelial function in a diverse group of 300 children ages 8 to 18 and identify racial and socioeconomic factors that are associated with a higher prevalence of endothelial dysfunction. The hope is that the results of this project will lead to increased awareness, funding and resource allocation to higher-risk pediatric communities of southeast Wisconsin, including efforts to improve access to a healthy food environment and recreational physical activities that may reduce the risk for cardiovascular disease in adulthood. His research is being funded through the Greater Milwaukee Foundation and is expected to be completed in June 2024.

Manny, a longtime HHI patient, received a heart transplant in 2017.

Manny and his nurse celebrated his successful heart transplant.

Mending Broken Hearts

Spotlight on Lu Han, PhD

How to heal a broken heart? It's not just a rhetorical question, but one Lu Han, PhD, and her team at the Herma Heart Institute are trying to answer.

Unlike the liver, skin and most other organ systems, the adult human heart cannot heal itself. That's because heart muscle cells — cardiomyocytes — barely proliferate, or divide, after birth. So damage from a heart attack, for instance, remains, eventually weakening the heart and often leading to heart failure.

Dr. Han wants to change that. She entered cardiology research from the cancer world, where she studied how cancer cells divide during her doctoral training. "The heart is the most complicated organ nature ever designed," she said. "Yet it's amazing that there's no cancer in the heart."

From a cell biology standpoint, the basic mechanism underlying cell division is shared in all types of cells — cancer and heart cells.

"The difference is that in cancer cells, quite opposite from heart muscle cells, uncontrolled growth becomes a problem," she said. Activating heart cells to divide — albeit in a controlled manner — is the key to heart regeneration.

So why doesn't the heart regenerate? "The heart has this meticulous structure it needs to maintain," said Dr. Han. "It needs to beat in a particular rhythm with all the cells synchronized."

She and others hypothesize that to maintain its function, the heart has sacrificed the ability to regenerate. In other words, it's too busy doing its job to worry about making new cells.

Today, Dr. Han's research focuses on the process and molecules that regulate heart muscle cell proliferation and maturation. She uses engineered mouse models and human-induced pluripotent stem cells (cells that have been reprogrammed into an embryonic-like state enabling them to differentiate into nearly any other type of cell), together with single-cell sequencing and genome editing to decipher the cellular and molecular mechanisms of cell cycle dynamics in heart muscle cells.

One of her major discoveries is that a protein called Lamin B2 is critical for cardiomyocyte regeneration. In mammals, Lamin B2 decreases after birth, blocking cell division and leading to "polyploid" cardiomyocytes, in which the entire genome is duplicated, and the cells go from two copies of the chromosomes to four and sometimes more.

"The heart is the most complicated organ nature ever designed. Yet it's amazing that there's no cancer in the heart."

—Lu Han, PhD

If you can find a way to make Lamin B2 overexpress itself in heart muscle cells through gene transfer, she believes, the cells can begin dividing, and the injured muscle will regenerate.

Dr. Han's next step is to understand the role of naturally developed polyploid cardiomyocytes and the mechanism that blocks adult heart regeneration. Eventually, she'd like to find a cocktail to trigger that cell proliferation in a meticulously controlled manner that maintains the heart's function. This could quite literally fix a broken heart. ■

Taking an Engineering Approach

Spotlight on John LaDisa Jr., PhD

By the time he interviewed for his post-doctoral fellowship, John LaDisa Jr., PhD, had authored 16 journal articles. But hidden within one paper on a computational model of a stent was a line that would send him into the world of congenital heart disease: "Thus, the present results may be clinically relevant for congenital heart disease interventions that require stenting."

"Well," said the pediatric cardiologist who was interviewing him. "I can clearly see you're interested in pediatric cardiology from what you've written in your paper here." And so Dr. LaDisa began researching hemodynamics in congenital heart disease and completing his post-doctoral fellowship in pediatric cardiology.

Today, Dr. LaDisa directs the Computational Engineering and Visualization Program at the Herma Heart Institute, where he and his team are trying to understand the impact of mechanical-based stimuli on cardiovascular disease onset and progression. To do that, they build computer models that mimic the stresses and strains blood vessels experience. That detailed spatial and temporal information helps pinpoint areas of potential concern within the vessel.

Dr. LaDisa's lab is focused on coarctation of the aorta (CoA), or narrowing of the aorta. It accounts for 8–11 percent of all congenital heart defects, affecting between 3,000 and 5,000 infants each year.[1] The condition is treated with surgery or inserting a catheter, both of which are generally successful. However, many children with CoA later develop hypertension as well as a heightened chance for early-onset coronary artery disease, stroke and aneurysms.

"The burning question is why these children develop hypertension despite the fact that they're treated very, very early."

—John LaDisa Jr., PhD

"The burning question is why these children develop hypertension despite the fact that they're treated very, very early," said Dr. LaDisa. Because he trained as a biomedical engineer, he views the body through an engineer's eyes, and hypertension is a mechanical issue as much as a medical one. Perhaps, he hypothesizes, stimuli experienced by the arteries before surgery have lasting ramifications on vascular mechanics.

To that end, his lab is creating complex computational models using imaging data to better understand the mechanisms contributing to hypertension under clinical conditions. The models allow his team to evaluate treatment outcomes and disease severity in ways that are not possible with existing imaging alone.

With these and similar tools, Dr. LaDisa said in his paper reporting on the study, "We are optimistic that applying these computational techniques to CoA will ultimately help to reduce the long-term morbidity currently observed in these patients by identifying associated processes before they are clinically apparent." In other words: This will help these kids live longer, healthier lives. ■

1 LaDisa JF Jr, Alberto Figueroa C, Vignon-Clementel IE, et al. Computational simulations for aortic coarctation: representative results from a sampling of patients. J Biomech Eng. 2011;133(9):091008. doi:10.1115/1.4004996

Bioengineering Heart Cells

Spotlight on Aoy Tomita-Mitchell, PhD, and Michael Mitchell, MD

Medical College of Wisconsin professor Aoy Tomita-Mitchell, PhD, and her husband, Children's Wisconsin pediatric cardiothoracic surgeon Michael Mitchell, MD, are on a mission to find a better way to repair one of the most complex congenital heart conditions: hypoplastic left heart syndrome (HLHS). Babies born with the disease have an underdeveloped left side of the heart. The condition affects about 1 in every 4,000 births.[1] While several genetic contributors to the disease have been identified, the underlying mechanisms remain unclear.

"It's a nice cost-efficient platform that allows us to get a mechanistic handle on the pathophysiology of the disease."

—Aoy Tomita-Mitchell, PhD

The primary treatment is a three-stage surgical strategy involving the Norwood, Glenn and Fontan procedures. While survival and outcomes have improved in recent years, the Mitchells want to know why some children do better than others. To do this, they turned to the tissue bank they began when they were at the University of Louisville in the early 2000s, an endeavor that expanded greatly when they moved to Children's in 2006. Now, they and their team have thousands of carefully prepared and characterized samples from hundreds of patients and their families. "Many of the families of the patients we operate on have generously participated in these studies," said Dr. Mitchell.

The Mitchells employed next-generation sequencing for nearly 200 patients with HLHS and found rare, often novel genetic variants in the MYH6 gene in about 10% of cases. To determine if the variants were responsible for the disease, they used CRISPR gene editing

technology to add the abnormal variant to cardiomyocyte cells that didn't carry it and removed the variant in cells that did carry it. Removing the variant "rescued," or cured, the cellular dysfunction; adding it to normal cells caused abnormal development. These results were published in an original research article last summer.[2]

"It's a nice cost-efficient platform that allows us to get a mechanistic handle on the pathophysiology of the disease," said Dr. Tomita-Mitchell. Even more importantly, it enables them to test drugs in the grown cardiomyocytes to see if they're effective or if a patient might be more responsive to one drug over another. Eventually, they might even be able to treat infants prenatally.

"This is a huge endeavor made possible by the enthusiastic collaboration of patients, clinicians and researchers at Children's Wisconsin, the Herma Heart Institute, Marquette University and the Medical College of Wisconsin," said Dr. Mitchell. "We are confident that this teamwork will lead to improved understanding and, eventually, to expanded treatment options for patients with this critical lesion." ■

1 Mai CT, Isenburg JL, Canfield MA, et al. for the National Birth Defects Prevention Network. National population-based estimates for major birth defects, 2010-2014. Birth Defects Res 2019; 1–16. https://doi.org/10.1002/bdr2.1589.

2 Kim M-S, Fleres B, Lovett J, et al. Front. Cell Dev. Biol., 2020 Jun 23;8:440. https://doi.org/10.3389/fcell.2020.00440

Fixing Bicuspid Valve Disease

Spotlight on Joy Lincoln, PhD

You could attribute the work Joy Lincoln, PhD, does to her younger brother, Paul. She was five when he was born with a congenital heart condition, and she recalls spending many hours at Great Ormond Street Hospital for Children in London while he received surgeries and treatment. So when Lincoln, now director of cardiovascular research at the Herma Heart Institute, did her post-doctoral training at Cincinnati Children's hospital, it made sense that she would focus her research on congenital conditions.

"The realization that 1 in every 100 kids is born with a congenital heart malformation was just mind blowing for me," she said.

Today, she runs her own lab at Children's Research Institute devoted to understanding the molecular mechanisms that regulate normal heart formation in the embryo and how disturbances in the process lead to congenital malformations present at birth. Most recently her focus has been on heart valves, including bicuspid aortic valve disease, which affects 1–2 percent of the overall population and is the most common congenital cardiovascular manifestation.

"The Mitchell team has the most outstanding approach to science and medicine; they have no fears, and no challenge is too big when kids are involved."

—Joy Lincoln, PhD

Her goal is to understand how cells communicate to ensure they get to the right place at the right time to form fully functioning heart valves during the fetal stage. She also wants to understand why some infants born with what look like normal heart valve structures develop valve disease later in life, including calcification or degeneration, both of which impair blood flow and can lead to heart failure and even death if left untreated.

Dr. Lincoln's work at Children's began with her collaboration with Michael Mitchell, MD, and Aoy Tomita-Mitchell, PhD, who are bioengineering heart cells that can be used to treat hypoplastic left heart syndrome, another congenital heart disease.

"The Mitchell team has the most outstanding approach to science and medicine; they have no fears, and no challenge is too big when kids are involved," said Dr. Lincoln. The Mitchells mesmerized her with their vision of using patients' own progenitor cells, found in cord blood, to engineer heart tissue to repair their own structural defects. Soon, she was working with them to create a cord blood and tissue repository from children born with congenital heart disease. "They were so passionate they got me believing in it," she said.

Now, Dr. Lincoln's lab has partnered with external national registries to collect and store clinical-grade umbilical tissue. The lab then works with the Children's Research Institute to isolate progenitor cells and differentiate them into heart valve cells. The team is also working with patient families who want to participate in the program.

While it's still early in the process, Dr. Lincoln and her team have already learned some interesting things. For instance, they are using patient cells to understand how and why heart valve cells undergo calcification, commonly found in young adults with congenital bicuspid aortic valve disease, and they are working toward therapeutic strategies to prevent this process. In addition, the team has been successful in generating functional heart cell types from patients' own progenitor cells. It's gratifying to see what seemed like an impossible dream becoming a reality. ■

Top right: Joy Lincoln, PhD, works with cord blood samples in the lab.

Right: Daniel McLennan, MD, monitors a patient born with tetralogy of Fallot and pulmonary vein stenosis.

Providing Advanced Echocardiographic Data for Researchers

Spotlight on Benjamin Goot, MD

The Echocardiography Lab is not what you think of when you hear the word "lab." There's no basic or translational research, no petri dishes or microscopes. Instead, components of the lab function as a clinical entity as well as the core lab, providing advanced echocardiography and other imaging services for researchers around the country.

"They can be multi-institution or single-institution studies where we interpret imaging data based on research protocols," said Benjamin Goot, MD, the lab director and an associate professor of Pediatric Cardiology at Medical College of Wisconsin. That includes work for the Pediatric Heart Network, a National Institutes of Health-funded initiative designed to accelerate the discovery of new treatments for congenital and pediatric-acquired heart disease. "The data for studies we are involved with comes to us for processing, analyzing and reporting," Dr. Goot said.

"There's a ton of 3DE data in the adult world regarding ventricular volumes, but not much data in terms of what's normal for infants or young children."

—Benjamin Goot, MD

When the lab started in 2005, it was one of only a few in the country, and it focused on basic two-dimensional echocardiographic measures. Today, it provides more advanced echo services, including ventricular deformation and three-dimensional echo (3DE). While not a new technology, 3DE use in pediatrics for clinical imaging is relatively recent, given advancing technology. "Most 3D platforms are built for adult imaging, not congenital imaging, which is what we do," said Dr. Goot. "So, while the technological growth has been really slow, we have worked hard to make use of this technology for our patients."

Today, 3DE provides a valuable tool for surgical planning. For instance, surgeons planning a valve repair can use it to examine the entire valve. "You can gain a lot of anatomic details that you can't see from regular echocardiograms, including relationships with other structures near it," said Dr. Goot. While 3DE currently is used primarily as a clinical tool, he is pushing to find more uses in research.

Recently, Dr. Goot and other directors of 3DE labs in North America and Europe formed a consortium to focus on research in the area. "We started meeting regularly at some of the national meetings and decided we wanted to start using 3DE to answer some of our specialties' unanswered questions," he said. The first question was defining the "normal" volume of a left ventricle across the range of pediatric patients.

"There's a ton of 3DE data in the adult world regarding ventricular volumes, but not much data in terms of what's normal for infants or young children," said Dr. Goot. The group pooled its data to develop standardized values. "That's the value of having a multi-institutional group like this," he said.

Above: Edward (Ted) Kirkpatrick, DO, reviews echocardiography images.

Right: HHI patient BrentLee with Ronald Woods, MD, PhD.

The lab is also expanding, with a new vascular function lab in development and new technology and software to automate standard echocardiographic and cross-sectional imaging measurements based on machine learning technology. The vascular function lab is particularly groundbreaking because most patients with congenital heart disease have presumed vascular dysfunction, yet this has not been investigated. "There is a great deal of adult research into atherosclerosis and peripheral vascular disease. Yet we are just scratching the surface in understanding how it may affect our patients," Dr. Goot said. ■

Diagnosing Fetal Arrhythmias, Saving Lives

Spotlight on Janette F. Strasburger, MD

Janette F. Strasburger, MD, a pediatric cardiologist at Children's Wisconsin and researcher and professor of Pediatric Cardiology at the Medical College of Wisconsin, has pioneered fetal magnetocardiography (fMCG). This groundbreaking technology can identify fatal arrhythmias in the fetus, allowing for early intervention. Although the recording technology was FDA-approved in 2016, its use has been limited by the significant capital investment required for the shielded room that houses the machine as well as the fMCG itself.

That's changing, however, thanks to a strong clinical and research collaboration between Dr. Strasburger's lab, the UW Madison Biomagnetism Laboratory and Advanced Physics Solutions, Inc., a Silicon Valley company that develops new technological advances in fetal heart rhythm recording.

"In our experience, 7 of 9 cases of torsades were missed by echo because echo and ultrasound cannot see repolarization."

—Janette F. Strasbrger, MD

"We're working to build a commercial optically pumped fetal magnetometer and shield for much higher-resolution fetal heart recordings at one-tenth the cost of current systems," said Dr. Strasburger. The team anticipates partial funding from a $1.7 million National Institutes of Health business grant next year.

Making fMCG more accessible to pediatric cardiologists and maternal fetal medicine physicians could, one day, enable it to be used as a screening tool for fetal arrhythmias and conduction diseases, which are thought to be a common cause of unexplained miscarriages and stillbirths. "I think we're going to get to the point where every fetal care center can utilize this technology," said Dr. Strasburger.

That's important given that stillbirths account for about 25,000 fetal deaths each year in the United States, with arrhythmia suspected as a cause in a significant percentage.[1, 2]

A study out of Dr. Strasburger's lab could make a big difference in diagnosis and treatment, potentially preventing fetal deaths.

Dr. Strasburger and her co-authors reviewed fMCG tracings and the medical records of 215 women undergoing fMCG for fetal arrhythmia or risk of arrhythmia over the past decade. They found that fMCG led to critical changes in diagnosis, leading to major management changes in 28 percent of patients. The largest changes occurred in pregnancies complicated by fetal bradycardia (slow heart rate), mainly alterations in prognosis and medications.

The fMCG scan can also alert clinicians to a potential genetic cause for the arrhythmia that, together with genetic testing, could lead to a lifesaving diagnosis for the mother and other family members. That's what happened with one patient referred for fMCG evaluation.

"The fetus had a very guarded prognosis," said Gretchen Eckstein, RN, an obstetrical nurse and research coordinator for Dr. Strasburger's study. The fMCG showed a type of ventricular tachycardia called torsades de pointes, which is associated with QTc prolongation, in which it takes the heart longer to recharge, or repolarize, between beats. It can result in sudden death but had not been found with the echocardiogram. The fetus had two types of Long QT Syndrome. Testing in the mother identified one form.

HHI patient Ezekiel was born with ventricular tachycardia.

The fetus received medication treatment transplacentally, or across the placenta when the mother was given magnesium and beta blocker orally, and this improved the fetal heart failure and arrhythmia. Mom delivered at 37 weeks, and a cardiac surgeon immediately implanted a pacemaker to keep the infant's rhythm steady. Both mother and baby were then started on beta blockers that they will take throughout their lives. "The long-term results of treated Long QT Syndrome are actually quite good," said Eckstein. "The risk comes when you don't know it's there."

"In our experience, 7 of 9 cases of torsades were missed by echo because echo and ultrasound cannot see repolarization," said Dr. Strasburger. "This demonstrates the potential for this new fMCG technology to change medical practice and potentially save lives." ■

1 Strand S, Strasburger JF, Cuneo BF, Wakai RT. Complex and Novel Arrhythmias Precede Stillbirth in Fetuses With De Novo Long QT Syndrome. Circ: Arrhythm Electrophysiol. 2020:427-434

2 Donofrio MT, Moon-Grady AJ, Hornberger LK, et al. Diagnosis and Treatment of Fetal Cardiac Disease. A Scientific Statement From the American Heart Association. Circulation. 2014;:129(21):2183-242.

Addressing Unintended Consequences of Lifesaving Surgery

Spotlight on Andrew D. Spearman, MD

Over the past 30 years, pediatric cardiology has made tremendous strides in surgical approaches for babies born with the most complex form of congenital heart disease: single ventricle congenital heart disease. This includes hypoplastic left heart syndrome, where the left side of the heart is underdeveloped.

"It's pretty amazing what the field has done," said Andrew D. Spearman, MD, a Children's Wisconsin pediatric cardiologist. The surgeries, which are considered palliative, not curative, reroute blood to the lungs by bypassing the heart. However, although kids with these conditions are now surviving into adulthood, the surgeries they require lead to dramatic changes in pulmonary circulation, including the development of pulmonary arteriovenous malformations (PAVMs), or abnormal connections between the arteries and veins in the lung. This can cause hypoxia, dramatically impacting the child's overall quality of life.

"We've uncovered really different and new problems, and some of them can be pretty dramatic complications that we really don't understand very well."

Andrew D. Spearman, MD

"Now we've uncovered really different and new problems," said Dr. Spearman, "and some of them can be pretty dramatic complications that we really don't understand very well."

This is where Dr. Spearman and his team have focused their research. "We want to understand exactly what's going on," he said. "It's the necessary first step before we can develop medical therapies to prevent or treat the condition."

To do that, the team is investigating the molecular pathways involved in the development of PAVMs. In other words, which genes and proteins are responsible for the vascular remodeling? Their preliminary data identified an important pathway in the process: vascular endothelial growth factor (VEGF), a signaling pathway that plays a key role in developing and maintaining normal blood vessels. High levels of VEGF signaling are found in other types of AVMs, and anti-VEGF drugs, many of them used to treat cancer, can decrease symptoms for some patients.

A key area of focus for Dr. Spearman's lab has to do with the connection between the liver and the lungs. "There's this idea that some kind of hepatic factor is protective in the lungs, helping prevent PAVMs," he said. But the surgeries these kids undergo change the pulmonary circulation so that blood from the liver does not go into the lungs. To test the hypothesis that the lack of the hepatic factor is at least partially to blame for the PAVMs, Dr. Spearman and his team are using blood samples from patients seen at Children's, which is much more relevant than starting with an animal model.

"We're really trying to focus on our patients, so we don't spend our time finding information that may not be relevant to them," said Dr. Spearman. ■

New Faculty Announcements

Children's welcomes the following faculty members to the Herma Heart Institute.

New research faculty

John LaDisa, PhD, is a researcher with a focus on the impact of mechanical-based stimuli on cardiovascular disease onset and progression and professor of Pediatric Cardiology and director of Computational Engineering and Visualization at the Medical College of Wisconsin.

Lu Han, PhD, is a researcher with a focus on the process and molecules that regulate heart muscle cell proliferation and maturation and assistant professor of Pediatric Cardiology at the Medical College of Wisconsin.

New clinical faculty

Kasey Chaszczewski, MD, is a pediatric cardiologist with expertise in transthoracic, transesophageal and fetal echocardiography and an assistant professor of Pediatric Cardiology at the Medical College of Wisconsin.

Nikki Singh, MD, is a pediatric cardiologist with expertise in cardiomyopathy, heart failure and transplantation and an assistant professor of Pediatric Cardiology at the Medical College of Wisconsin.

Matthew Amidon, DO, is a cardiac critical care physician with interests in mechanical circulatory support, anticoagulation and pediatric transport medicine. He is an assistant professor of Pediatric Critical Care at the Medical College of Wisconsin.

Cory McFall, MD, is a cardiac critical care physician with expertise in adults with congenital heart disease in the pediatric ICU and antimicrobial stewardship. She is an assistant professor of Pediatric Critical Care at the Medical College of Wisconsin.

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Graduated fellows

Children's congratulates our graduated fellows.

Matthew Amidon, DO, completed his advanced pediatric cardiac critical care fellowship and will continue with the Herma Heart Institute as an associate professor of Pediatric Critical Care at the Medical College of Wisconsin.

Dan Beacher, MD, completed his pediatric cardiology fellowship and will continue with the Herma Heart Institute, working primarily in the Fox Valley and Green Bay locations. He is an assistant professor of Pediatric Cardiology at the Medical College of Wisconsin.

- Academic product: "Impact of Valve Type (Ross vs. Mechanical Valve) on Health Related Quality of Life in Children and Young Adults who have Undergone Surgical Aortic Valve Replacement"

Kirsten Borsheim, MD, completed her pediatric cardiology fellowship and is currently working in an advanced imaging fellowship at Advocate Children's Medical Group.

- Academic product: "Septal Hypoplasia Allows for Novel Care Strategies in Tetralogy of Fallot And Double Outlet Right Ventricle with Normally Related Great Arteries"

Chalani Ellepola, MD, completed her pediatric cardiology fellowship and will continue with the Herma Heart Institute as an advanced imaging fellow at the Medical College of Wisconsin.

- Academic product: "Limitations of Predicting Postoperative Left Atrioventricular Valve Regurgitation by Intraoperative Transesophageal Echocardiography"

Brian Hughes, DO, completed his pediatric cardiology fellowship and returned to the U.S. Navy. He is working at Walter Reed National Military Medical Center.

- Academic product: "Predictors of Life-Threatening Arrhythmias and Mortality in Fetal Cases with Ventricular Ectopy Evaluated by Fetal Magnetocardiography"

Caitlyn Rood, MD, completed her advanced pediatric cardiac critical care fellowship and was hired by Boston Children's Hospital.

Rachel Sullivan, MD, completed advanced training in pulmonary hypertension and was hired by Vanderbilt University.

- Academic product: "Cardioprotective effect of nicorandil on isoproterenol induced cardiomyopathy in the Mdx mouse model"

Christopher Sumski, DO, completed his pediatric cardiology fellowship and was hired by Washington University to work at St. Louis Children's Hospital.

- Academic product: "Cardiac Physical Exam Skills & Auscultation Session for Pediatric Interns"