



# PATHWAYS >

AN UPDATE FOR PARTNERS OF THE CHILDREN'S DISCOVERY INSTITUTE

FALL 2011

*Faces of the Children's Discovery Institute >*

## A QUEST TO BREATHE EASIER

*Institute-funded research is helping to understand one young boy's disease >*

As an active 3-year-old boy, Rylee Eastvold loves riding on his dad's shoulders and playing with his toy trucks. You would never know he spent the first two years of his life tethered to an oxygen tank.

Soon after he was born in 2008, Rylee's parents, Tori and Ryan, noticed their son's breathing wasn't normal. He was whisked to the newborn intensive care unit (NICU) at their local hospital in Forest, Iowa. This began a long journey that included another hospital to try to find what was causing Rylee's breathing problems. He was tested for pneumonia, cystic fibrosis, interstitial lung disease and other problems, yet doctors still couldn't offer a firm diagnosis. Finally, Rylee was sent home with oxygen and an apnea monitor.

Rylee continued to struggle as mucus filled his nose and lungs. An oxygen tank was his ever-present companion. More tests still didn't lead to a diagnosis. "I just wanted them to give me the right answer so we could move forward," Tori says.

Rylee was evaluated at a Chicago hospital, where he was diagnosed with a surfactant protein deficiency and interstitial lung disease. For the next year, he was treated for interstitial lung disease with round-the-clock oxygen.

In 2010, the Eastvolds had an insurance change that meant Rylee's care in Chicago would no longer be covered. However, it did cover visits to pulmonologists at St. Louis Children's Hospital, nearly seven hours from the Eastvold's Iowa home. The insurance change also changed Rylee's future.

At the first Children's Hospital appointment in January 2010, physicians re-evaluated Rylee's condition and determined he did not have interstitial lung disease.

Instead, doctors diagnosed Rylee with a different genetic disorder called primary ciliary dyskinesia, or PCD. PCD is a progressive airway disease that causes



**Diagnosed with a progressive airway disease, Rylee is participating in a research study funded by the Children's Discovery Institute in hopes to someday find a cure.**

recurrent infections of the lungs, middle ear and sinuses.

"The diagnosis left us with mixed emotions," Tori says. "We were relieved to have a diagnosis but sad that right now, there's no cure for PCD."

Rylee now comes to St. Louis four times a year to visit Thomas Ferkol, MD, a Washington University

pediatric pulmonologist at St. Louis Children's Hospital. "Dr. Ferkol is so knowledgeable about PCD," Tori says. "I always have lots of questions at each visit and he takes time to answer all of them. It's hard to be far away from your specialist but Dr. Ferkol and his nurse, Jane, feel like they're close by. All I have to do is call."

*(Continued on next page)*



## Symposium highlights Institute's investment in innovation

The theme of our 4th Annual Investor Symposium held October 5 was "Building on Discovery," and there were many vivid examples of this concept presented during the talks and poster presentations. During the welcoming remarks, **Todd Druley, MD, PhD**, an Institute-funded young investigator who is using next-generation DNA sequencing to study leukemia and other diseases, described how the Institute's four centers are dynamic and interactive, allowing discoveries made in one research group to support those in another.

Perhaps the most striking illustration of this cross-fertilization is the partnership between neurosurgeon **Eric Leuthardt, MD**, and computer scientist **William Smart, PhD**, who work on brain-computer interfaces. While **Dr. Leuthardt** places electrode arrays on the surface of the brains of patients who have lost motor control, **Dr. Smart** carries out mathematical computations to translate complicated neural signals into movements of computer cursors or a robotic hand.

Together, these two investigators have shown that the brain signals of children can be "de-coded" and used to operate prosthetic devices. As **Jeffrey Leonard, MD**, said after their talk, "They capitalize on each other's strengths to come up with a better product." This exciting research would not have happened if it weren't for their collaborative efforts and the support of the Children's Discovery Institute.

The Institute fosters innovation not only through its encouragement of interdisciplinary research, but also through its support of completely new approaches, as illustrated by the work of **Patrick Jay, MD, PhD**, who studies congenital heart disease. The traditional way of framing questions about this condition has been, "Which genes cause heart defects?" Unfortunately, this approach has not resulted in viable treatment options. Instead, **Dr. Jay** is asking, "Which genes contribute to a healthy heart?" So far, he has identified many possible factors that he is now further investigating, in hopes that these could be targeted by existing drugs to prevent, rather than simply treat, heart disease in infants.

These two projects may ultimately have a profound impact on children's lives, and they highlight the ways in which the Children's Discovery Institute serves as the engine that drives future patient care.

### Mary Dinauer, MD, PhD

*Mary Dinauer, MD, PhD, is the Scientific Director of the Children's Discovery Institute. She is also the Fred M. Saigh Distinguished Chair in Pediatric Research at St. Louis Children's Hospital, and professor in pediatrics, pathology and immunology at Washington University School of Medicine.*

## BETH KOZEL, MD, PHD

Large blood vessels are composed of connective tissue, and this elastic tissue allows vessels to repetitively stretch and recoil in response to blood flow. Genetic mutations that alter one of this tissue's proteins, elastin, are at the root of several cardiovascular diseases, including Williams syndrome, a condition in which the blood vessels narrow and blood isn't adequately pumped from the heart to the rest of the body.

Individuals with elastic fiber disorders show a remarkable range in the severity of their vascular disease, a phenomenon that for many years has intrigued **Beth Kozel, MD, PhD**, a new recipient of a Faculty Scholar Award from the Children's Discovery Institute. Dr. Kozel began researching how elastic fibers form, as well as seeing patients with these conditions in clinic, while she was a medical and graduate student at Washington University.

"Most individuals with Williams syndrome have the same missing piece of DNA that causes their condition. However, about 30 percent of patients have life-threatening vascular disease, while 20 percent have normal blood vessels. The remaining individuals are more mildly affected," Dr. Kozel said. These subgroups may require different interventions, medications, and follow-up monitoring, she added. "Currently, we can't predict where a baby with Williams syndrome will fall on this spectrum. While it's very important to make a diagnosis, being able to tell parents what to expect going forward is even more important."

To investigate the genes that cause the severity of vascular disease to vary, Dr. Kozel is using mouse models of cardiovascular disease, and will apply the findings from these studies to individuals with Williams syndrome. The mice she uses have mutations in the elastin gene that cause abnormalities in blood vessels, similar to those in human patients. After breeding these mice with mice from other families with different genetic backgrounds, Dr. Kozel and her team look for genes that determine the severity of vascular disease.

So far, the team has identified one important factor: genes that regulate the build-up of toxic oxygen-containing molecules that damage cells. If these molecules also contribute to disease severity in humans, high-risk patients could possibly be given medications to prevent further blood vessel narrowing, Dr. Kozel said. "Understanding what genes and pathways influence vascular disease in patients with elastin defects may contribute to the discovery of new targets to provide personalized treatments to these patients."

*(Continued from front page)*

## A QUEST TO BREATHE EASIER

Rylee's treatment, while not curative, is aimed at preventing lung infections and delaying the progression of lung disease. For 20 minutes each day, Rylee wears a vest device that provides high-frequency chest wall oscillation (HFCWO) therapy to keep his airways clear.

"Once Rylee started on this therapy, we saw a big difference in him," Tori says. "His health is much more stable and he doesn't get sick or need antibiotics as often. Having the answer and knowing what we are fighting makes it easier for us to plan for Rylee's future health needs."

Dr. Ferkol is part of a clinical research network to study rare diseases of the airways, concentrating on PCD and atypical forms of cystic fibrosis. Rylee is participating in the PCD study. Dr. Ferkol also has created a multidisciplinary research collaborative, funded by the Children's Discovery Institute, which is developing better standards for diagnosis, clinical care and identification of novel therapeutic approaches for PCD and other airway diseases.

"By being part of the study, we hope Rylee and other children with PCD will have a cure one day," Tori says. "It's so important to support research to help doctors understand PCD better. PCD is considered a rare disease, but considering how difficult it was to get a diagnosis, you have to wonder how many other children have suffered and never got a diagnosis."



Rylee, with parents, Tori and Ryan.

# NEW CORE FUNDING SUPPORTS RESEARCH ON LUNG AND CARDIOVASCULAR DISEASES

*One core receives renewal funding; another is newly established >*

In June 2011, the Children's Discovery Institute approved funding for two large core initiatives: the Airway Epithelial Cell Core and a new Translational Cardiovascular Tissue Core.

Cores are resources that support interdisciplinary research through large grants, with the goal of speeding discoveries. The services provided through these cores are an ideal mechanism to make highly sophisticated resources accessible to primary investigators within the Institute and across the Washington University campus in a more cost-effective manner. The newly-funded cores will accelerate research discoveries relevant to a range of respiratory and cardiovascular disorders.

Since 2007, the **Airway Epithelial Cell Core** has helped scientists study lung biology and develop therapeutic strategies for diseases such as asthma, respiratory virus infection and cystic fibrosis. This resource provides investigators with complex preparations of cells taken from the respiratory tracts of mice and humans, a repository of normal and diseased lung tissue, and technical training in methods for generating, maintaining and analyzing these high-quality cell preparations.

Renewal funding was requested by project leader **Steven Brody, MD**, because of increased demands for cultured lung cells and for instruction in the methods required for using them. To meet these growing needs, **Dr. Brody** and his team have developed efficient, cost-saving protocols to maximize the use of these limited cells. "Using our experience and skills, our goal is to help researchers



**Project leader Steven Brody, MD, uses additional funding to meet increased demands by Institute investigators for cultured lung cells.**

overcome barriers and expand their capacity for studying lung disease," he said.

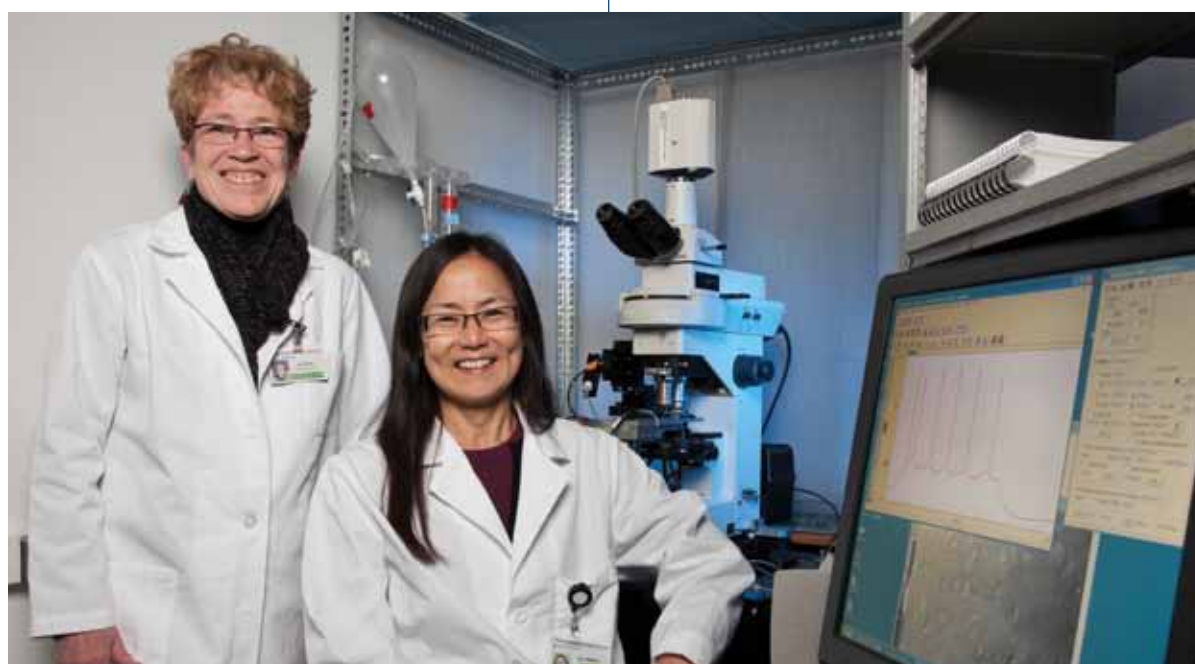
The **Translational Cardiovascular Tissue Core** will serve as a centralized system for acquiring, storing, using and distributing pediatric cardiovascular tissue samples. These samples will be used for studies of various heart and vascular conditions, such as congenital heart disease, hypertrophic cardiomyopathy and cardiac arrhythmias. The resulting data will be integrated into databases with patient information to foster collaborations among

scientists and to accelerate the application of research findings to clinical practice.

The development of this new core builds on experience acquired from the existing core of adult cardiovascular tissues at Washington University. "There was a strong need to establish a new core for pediatric tissue," said **Jeanne Nerbonne, PhD**, a professor of developmental biology who is spearheading the initiative. "We're very interested in taking this to the pediatric arena because it's clear that pediatric cardiac disease is really different from adult cardiac disease, and we need to explore the underlying mechanisms in pediatric tissues directly," she said.

The core is unique because it will allow scientists to record the electrical activity of heart tissue and study its contractile properties to directly learn about the functioning of the heart, in addition to heart structure and molecular attributes. "That's what makes this core so different from a pathology core," Nerbonne said. "We will collect tissues and do functional studies; this core is the first of its kind."

The long-term goal of this initiative is to link genetics to the structural and functional properties of the heart and cardiovascular disease presentation at a patient-specific level. This approach will enhance the understanding of disease causes, the prediction of disease severity, and the development of individualized therapies. "We think that we will be able to identify disease mechanisms in a way that just hasn't been possible with animal models of human disease," said Nerbonne.



**Jeanne Nerbonne, PhD, and Kathryn Yamada, PhD, are developing a centralized system for pediatric cardiovascular tissue samples to be used for heart and vascular studies.**

# BUILDING ON DISCOVERY

Symposium highlights research advances and lessons learned >



Doug and Kathy Pope with Lee Fetter, President, St. Louis Children's Hospital.

The Children's Discovery Institute's Fourth Annual Investor Symposium, held October 5 at the Charles Knight Conference Center at Washington University, gave donors the opportunity to learn about research advances from a selection of Institute-funded projects.

During the poster session, **Josh Rubin, MD, PhD**, associate professor of pediatrics, and **Jeff Leonard, MD**, associate professor of neurosurgery, presented key accomplishments from the Brain Tumor Bank. The development of innovative strategies to improve the effectiveness of vaccines in young children was the focus of a poster presented by **Deepti Bhattacharya, PhD**, assistant professor of pathology and immunology. **Kyunghee Choi, PhD**, associate professor of pathology and immunology, explained how her team has turned embryonic stem cells from mice into cardiac progenitor cells, an approach that could pave the way for using stem cells to repair damaged heart tissue in children with heart disease.

After the poster session, **Todd Druley, MD, PhD**, assistant professor of pediatrics and of genetics and Children's Discovery Institute Faculty Scholar, described the impact of Institute funding on biomedical research. He noted the impact that the diminishing budget of the National Institutes of Health will likely have on the number of biomedical research grants, especially those for young investigators who are unproven but have the potential to make innovative discoveries. "This void is being filled by the Children's Discovery Institute, and while its role is big now, it's going to become much bigger in the coming years," he said.

**Barbara Warner, MD**, associate professor of pediatrics, both in a poster and a talk, described progress in the St. Louis Neonatal Gut Microbiome Initiative, in which her team analyzes the microbial makeup of infant stool. So far, the researchers have discovered that a breast milk diet promotes the growth of "good" bacteria in the gut, and in the future, their collaborators will use the samples to answer questions about malnutrition, the development of antibiotic resistance, and the development of life-threatening gut inflammation in premature infants.

Equipped with a robotic hand as a prop, **Eric Leuthardt, MD**, assistant professor of neurological surgery and of biomedical engineering, and **William Smart, PhD**, associate professor of computer science and engineering, reviewed their work on brain computer interfaces, in which neural signals recorded from the surface of the brain are used to control machines. They have developed a method that allows children who have experienced stroke, cerebral palsy, or other debilitating neurological conditions to quickly learn to move a computer cursor or robotic hand with great skill.

Finally, **Patrick Jay, MD, PhD**, assistant professor of pediatrics, discussed advanced genetic strategies to move the field of congenital heart disease beyond simply describing and surgically repairing heart defects. To date, there has been no way to target genes known to cause congenital heart disease. Through sophisticated genetic studies in mice, Dr. Jay has discovered factors that contribute to a healthy heart. In the future, he hopes to look at how similar factors affect the risk of congenital heart disease in children. He hopes that one day a pill given to expectant mothers could correct some of these risk factors and help prevent heart defects.

Visit [ChildrensDiscovery.org](http://ChildrensDiscovery.org) for more photos and video presentations from the Symposium.



Left to right: John and Anita O'Connell, and Alan Schwartz, MD, PhD. John O'Connell is a board member of St. Louis Children's Hospital and chairman of the St. Louis Children's Hospital Foundation Board.



Left to right: Barbara Warner, MD, describes her work with the St. Louis Neonatal Gut Microbiome Initiative with Young Friends Board Members Retta Leritz and Dana Borchert.

# WHY I GIVE

Through personal challenges and experiences, Don and JoAnn Shaw have learned the importance of helping others and a never-give-up attitude. Their experiences and big hearts also led to a devotion to children—and a passion for the Children's Discovery Institute.

**Question: Both of you have had personal experience with cancer. How has that influenced your commitment to children and the Children's Discovery Institute?**

**JoAnn:** I am a cancer survivor and cancer is a part of our lives. I was very close to my grandfather and lost him to brain cancer. In addition my mother and aunt died of pancreatic cancer. Finally, our son-in-law's mother died of brain cancer. We knew we had to do something. So we started a foundation for brain cancer research. At the time, the Children's Discovery Institute didn't exist. But once it was created, we rolled our foundation into it. So many children are diagnosed with brain cancer so it was a natural fit. It's hard to lose an adult to cancer but I've seen what it does to children and their families and it's devastating. I'm thankful to be in a place now where I can give back.

**Don:** I had prostate cancer three years ago. Just before my diagnosis, two of my brothers had died from prostate cancer. So cancer has been part of our lives for a long time. Yet JoAnn and I have been blessed with a healthy daughter. We've seen other families struggle with sick children so we have a shared passion about cancer in children.

**Question: JoAnn, as a BJC HealthCare leader, you developed something brand new: the BJC Center for LifeLong Learning. The Children's Discovery Institute is a fairly new endeavor, too. Do you have a special affinity for the entrepreneurial spirit?**

**JoAnn:** I love people willing to accept risk and who don't accept the status quo. The Children's Discovery Institute does not accept the status



quo either. The Children's Discovery Institute was created to find cures for the most devastating childhood diseases. It's not an organization in maintenance mode. Instead it asks how can we do even better. We see what has happened using our funds and are so pleased to know it always goes back to help kids.

**Question: Why do you have such confidence in the Children's Discovery Institute?**

**JoAnn:** There is a group of true visionaries at St. Louis Children's Hospital. They had a vision and took a risk. And I love the idea of discovery—finding something new. The progress we've seen is fascinating. Like the Center for LifeLong Learning, the Children's Discovery Institute offers a continuum of learning with no start or end. The potential is so great.

I was in a clinical trial when I had cancer at 19 in 1965. Treatment is so much better now than it was then because of ongoing research. The Children's Discovery Institute is doing breakthrough research now. Where better to start than with kids? They are our future and our most vulnerable. We don't have to live to see a big "a-ha" moment. We just want to help them get to the "a-ha" a little faster. I want

**After personal battles with cancer, Don and JoAnn Shaw are sharing their passion for pediatric cancer research by supporting the Children's Discovery Institute.**

the scientists at the Children's Discovery Institute to cure more kids, learn and go change the world. That's the best way to pay it forward.

**Don:** We have a profound faith in the people in the Children's Discovery Institute. We may not have a cure for brain cancer in our lifetime, but we have strong faith that they will make important progress. We don't expect an early return. It doesn't matter. If we contribute to the end goal, then that's what matters.

*JoAnn Shaw is vice president and chief learning officer at BJC HealthCare. She volunteers to speak to newly diagnosed cancer patients, is president of the Leukemia and Lymphoma Society, is co-coordinator of the St. Louis chapter of ConKerr Cancer, an organization that makes decorative pillowcases for children in hospitals, and serves on several other boards.*

*Don is a retired engineer and also volunteers for ConKerr Cancer, where he delivers hundreds of pillowcases to children each month. Don also volunteers with the USO at St. Louis Lambert International Airport, and tutors children through the OASIS program.*

## Why do you give?

Share your personal story with us. Contact Julie Simmons at [jburkemper@bjc.org](mailto:jburkemper@bjc.org).

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## FOURTH ANNUAL INVESTOR SYMPOSIUM *(more on page 4)*



Investors and investigators listen to Patrick Jay, MD, PhD discuss his work with congenital heart disease.



Todd Druley, MD, PhD, shares opening remarks.

This newsletter exists to share the accomplishments of the Children's Discovery Institute with our stakeholders, particularly those whose generosity supports the research carried out by Institute investigators.

If you have comments or questions about Pathways, please contact:

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