Joining Forces to Help Kids Breathe Easier

Unique Team Investigates the Role of Cilia in Lung Disease and Ear Infections

In children, respiratory, sinus, and ear disease can result from dysfunction of the cilia—tiny, hairlike structures in the lungs, nose, sinuses, and ears. Now, with help from the Children’s Discovery Institute, a unique team composed of a physician, a geneticist, and a mechanical engineer is tackling the problem.

Every year, a small number of children are born with primary ciliary dyskinesia (PCD). This hereditary disease prevents the movement of mucus in the lungs, causing pneumonia, bronchitis, and sinus and ear infections.

Every year, tens of thousands of children receive treatment for chronic ear infections. These two groups of children may have something in common. A research team is homing in on genetic defects affecting the cilia. These tiny structures keep infections at bay by sweeping mucus, fluids, pollutants, and bacteria from the lungs, sinuses, and ears. Some genetic defects may be shared by children with rare PCD or relatively common ear infections.

One fascinating aspect of the research is that cilia can be studied by looking at a single-celled organism called *Chlamydomonas*, which swims with a tail (flagellum). The flagellum is structurally identical to a human cilium. It offers a sophisticated, cost-effective way to test new ideas.

The team conducting this research is among the most innovative ever supported by the Children’s Discovery Institute—a wide-ranging collaboration of medicine, genetics, and engineering:

**Thomas Ferkol, MD**—Professor of Pediatrics, Cell Biology, and Physiology and Director, Division of Allergy, Immunology, and Pulmonary Medicine at Washington University School of Medicine. Working with Dr. Ferkol and the entire team are Associate Professor **Steven Brody, MD**, from the Department of Medicine, and research technician **Brian Lewis**.

**Susan Dutcher, PhD**—Professor of Genetics/Cell Biology and Physiology at Washington University School of Medicine.

**Philip Bayly, PhD**—Lilyan and E. Lisle Hughes Professor of Mechanical Engineering and Chair of the Department of Mechanical, Aerospace, and Structural Engineering at Washington University.

A continuum of children’s diseases

Dr. Thomas Ferkol suspects that we under-recognize respiratory diseases caused by dysfunctional cilia. At one end of the continuum, said Dr. Ferkol, “is classic PCD. Occurring in approximately 1 in 12,000 to 20,000 births, PCD is a genetic disorder resulting from abnormal cilia structure and function.”

Children with PCD suffer from persistent lung, sinus, and ear infections, because their cilia cannot sweep away bacteria-laden mucus. Their internal organs may be on the wrong sides of their bodies, called *situs inversus* or heterotaxy, because cilia are necessary to position organs within the developing fetus. As they grow to adulthood, patients with PCD, especially boys, are usually infertile—the flagella of their sperm, like their cilia, don’t work.

“At the other end of the continuum,” noted Dr. Ferkol, “are children who have ear infections year after year.” These children don’t outgrow their ear infections, and require repeated treatment with antibiotics and ear tube surgeries. “We think,” Dr. Ferkol said, “that these children may have genetic and functional defects of their cilia, much like those in children with PCD, but less severe.”

(Continued on page 8)
Remembering Philip Dodge

In 1967, pediatricians at St. Louis Children’s Hospital did not have CT scans or cardiac catheterization. They did not have cell phones or email. But they did have the remarkable talent of Philip R. Dodge, MD, the pediatric neurologist who, in 1967, began his 19-year tenure as the Head of the Department of Pediatrics and Physician-in-Chief at Children’s Hospital.

Dr. Dodge passed away in 2009 at the age of 86. He is considered a founder of modern pediatric neurology, and was honored as professor emeritus in the Departments of Pediatrics and Neurology at Washington University School of Medicine.

Dr. Dodge had impeccable academic credentials, including the creation of the Division of Pediatric Neurology at Massachusetts General Hospital. His expansive neurologic research interests included bacterial meningitis, pediatric cerebrovascular disease, and the neurologic complications of fluid abnormalities.

Clinicians who knew him, however, are quick to describe his compassion and clinical skills. Colleagues expressed their awe of Dr. Dodge as a master diagnostician, remembering how he could conduct a complete neurologic examination of a toddler simply by using toys.

Dr. Dodge arrived at a critical juncture in the history of Children’s Hospital. Construction had been completed on the 10-story Tower Building. The new building infused a new energy to expand services. When Dr. Dodge arrived, he fervently took up this challenge. During his tenure, faculty in the Department of Pediatrics increased from 12 to 100. St. Louis Children’s Hospital grew from a local facility to a world-renowned institution.

In the book, *Hope and Healing*, which chronicles our hospital’s history, William Danforth is quoted as saying that “Philip Dodge is one of the heroes of St. Louis Children’s Hospital. He worked day and night, taking stints in the emergency room. He rebuilt morale and sense of direction.”

Sadly, Philip Dodge is gone, but his legacy lives on in our research and in the care we give to children every day.

Alan L. Schwartz

Alan L. Schwartz, MD, PhD is the Executive Director and Interim Scientific Director of the Children’s Discovery Institute. He is Harriet B. Spoehrer Professor and Chairman of the Department of Pediatrics, Professor of Developmental Biology, and Pediatrician-in-Chief, St. Louis Children’s Hospital.

Erratic heart rhythms, or arrhythmias, claim more than 400,000 lives each year in the US. George Van Hare, MD, the Louis Larrick Ward Chair in Pediatric Cardiology at St. Louis Children’s Hospital and Washington University School of Medicine, studies arrhythmias in children. Recently, Dr. Van Hare received a $200,000 Children’s Discovery Institute grant to bring a novel heart imaging technology to bear on serious pediatric heart problems. The technology, called electrocardiographic imaging (ECGI), was developed by Yoram Rudy, PhD, the Fred Saigh Distinguished Professor of Engineering at Washington University.

Want to learn more about how this important technology can help children? Visit our website at [childrensdiscovery.org](http://childrensdiscovery.org) and click on the Pathways icon.
St. Louis native Joe Schlafly is an investment banker and venture capitalist who donates to the Children’s Discovery Institute. In the 1980s, Mr. Schlafly was a member of the St. Louis Children’s Hospital Development Board, but his relationship with the hospital dates back to his childhood. Today, as a specialist in life-sciences investing, he remains actively involved with our region’s scientific and medical communities.

Pathways sat down for a talk with Mr. Schlafly to learn what inspires his commitment to children’s health.

Question: What motivates you to give to the Children's Discovery Institute?

JS: The most basic reason is that St. Louis Children’s Hospital saved my life. In the early 1950s, when I was 4 years old, I developed a very serious nephritis. My kidney problem was life threatening.

I was in and out of the hospital for two or three years, staying in for up to three months at a time. Fortunately, the physicians who treated me really valued research, and had conducted investigations here and in Europe. They gave me what was then a new therapy—cortisone—which had just been synthesized and introduced. One of my doctors was Dr. Hulda Wultmann, the chief resident and a pioneering woman physician who mentored a generation of great pediatricians.

I am here today because of the care I received at Children’s Hospital. The hospital, with its tradition of research, is profoundly important to me. I wouldn’t be alive without it.

Question: Is there something special about the Children’s Discovery Institute that influences your decision to donate?

JS: Absolutely. The Children’s Discovery Institute is unique. Encouraging scientific collaborations between Children’s Hospital and Washington University will only help boost the national and international prestige of our facilities. Ultimately, that will improve the business climate and quality of life in St. Louis.

Question: Does giving to the Institute dovetail with your economic vision for St. Louis?

JS: I am passionate about St. Louis and the intellectual assets we have here. What our scientists discover can and should be commercialized—starting with early stage venture capital and eventually leading to new products, services, and therapies.

I am hopeful that St. Louis will focus more on the commercialization of its great research. We should be as open to private funding as we are to grants from the National Institutes of Health. Commercialization is a dynamic process that links us with cities around the nation and around the world. That means more good jobs and more economic activity throughout St. Louis.

Question: What would you say to people who may want to donate, but who are concerned about the recession?

JS: My short answer is “go ahead and give.” I’m a firm believer that one should never waste a good recession—there’s no better time to invest in and support your community. The Children’s Discovery Institute has a chance to propel Children’s Hospital to become an extraordinary global institution located right here in St. Louis. The Institute has a real head start, through its ability to fund the important work necessary for breakthroughs in children’s health.

Through tough times like these, while other institutions are struggling, St. Louis Children’s Hospital and Washington University should prosper. Giving now to the Children’s Discovery Institute advances two noble causes: a better St. Louis and a better life for kids.

“...the most basic reason why I donate? St. Louis Children’s Hospital saved my life...”

— Joe Schlafly

Do you have a personal story or a deeply held belief that inspires you to give?

Pathways would like to publish a WHY I GIVE profile about you. Please contact Rebecca Bergson, rbergson@bjc.org.
“The NIH won’t support research until the idea is proven valid—the Children’s Discovery Institute funds the studies that provide the proof.”

— Dr. Patrick Jay

HONORING DISCOVERY

At our Second Annual Symposium, researchers shared new ideas on heart failure, genetics, and cell biology in children.

“The Children’s Discovery Institute catalyzes ideas among scientists, who might never have been able to work together without this funding.”

So said Patrick Jay, MD, PhD, an Institute investigator and cardiologist at St. Louis Children’s Hospital and Washington University School of Medicine. Dr. Jay echoed a sentiment heard over and over at the Institute’s Second Annual Symposium. As noted by Lee Fetter, President of Children’s Hospital, speaking at the symposium, “many applications of basic research to childhood illness just wouldn’t be happening without funding from the Children’s Discovery Institute.”

The annual symposium showcases cutting-edge research and its implications for children’s health. The symposium brings together investors, investigators, and friends of the Institute—a diverse group of people who, in the words of the Institute’s Executive Director, Alan Schwartz, MD, PhD, “are united in their dedication to children who suffer from serious, sometimes deadly diseases.”

“From bench to bedside” in children with heart failure

All of the Institute’s research projects ultimately aim to improve pediatric diagnosis and treatment—to translate findings at the laboratory “bench” to better care at the patient’s bedside. So when investigators begin to study potential therapies for young patients, it’s a cause for celebration.

One research team presenting its work at the symposium—Dr. Jay and his fellow cardiologist, Charles Canter, MD—has embarked on studies to show how abnormalities of insulin and glucose (blood sugar) metabolism develop in children with heart failure. Today, medical advances allow many children born with congenital heart defects to survive, but these survivors often face the threat of heart failure. By understanding the nature of insulin resistance in their patients, Drs. Jay and Canter hope that its treatment could improve their quality of life and outcomes.

The research began at the laboratory bench, when Dr. Jay teamed up with Paul Hruz, MD, PhD, a pediatric endocrinologist also at Washington University. By conducting research in mice, Dr. Jay and Dr. Hruz learned that heart failure is associated with systemic resistance to insulin and abnormal uptake of glucose in the heart muscle (the myocardium). They wondered whether correcting these abnormalities with a drug prescribed for diabetes would help. In fact, when insulin sensitivity and myocardial glucose uptake improves, so does the function of the heart and survival in the animals.

As a result of this basic research, Drs. Jay and Canter are now studying insulin sensitivity and myocardial glucose uptake in children with heart failure. Their preliminary findings suggest that the abnormalities discovered in the lab likely occur in their patients as well. “I’m encouraged by what we see,” said Dr. Canter. “If there is a relationship
NIH won’t support research until a scientist has been aided in their work by nuclear medicine expertise. He added that “a large organization like the Children’s Discovery Institute.” He added that “a large organization like NIH won’t support research until a scientist has strong data to prove an idea is valid. That’s where the Institute comes in—it funds the studies that provide the proof.”

Genetic and cellular research presentations
Several other investigators presented important findings at the symposium.

Genetics of respiratory distress. Many of the serious diseases of children have a basis in genetics. At the symposium, Rob Mitra, PhD, an assistant professor of genetics at Washington University, presented genetic research on one of the most devastating events a family can endure—respiratory distress syndrome (RDS) in a newborn.

The lungs of babies with RDS do not produce enough of a substance called pulmonary surfactant, so they cannot get enough oxygen when they breathe. Dr. Mitra’s goal is to find out which genes, when mutated, cause or predispose to RDS. To achieve his goal, Dr. Mitra is using cost-efficient, next-generation technology to conduct gene sequencing—a method to determine the order of the components in a DNA molecule. Collaborating with Dr. Mitra is a team of physicians from the Department of Pediatrics: F. Sessions Cole, MD, Aaron Hamvas, MD and Todd Druley, MD, PhD.

Neuromuscular diseases. Genetics also determine another group of serious illnesses that begin in childhood—the inherited neuromuscular diseases (NMDs). NMDs include muscular dystrophy, spinal muscular atrophy, and a host of other syndromes that progressively weaken muscles and nerves.

During his symposium presentation, Robert Baloh, MD, PhD—a neurologist at St. Louis Children’s Hospital and Washington University School of Medicine and one of the Institute’s Faculty Scholars—noted that NMDs “lead to severe disability and premature death. And unfortunately, there are no effective, disease-altering therapies we can give to patients with most of these diseases.”

Dr. Baloh is leading two major projects. The Neuromuscular Genetic Project will maintain a centralized database of DNA samples from patients with NMDs. Since 2006, over 750 DNA samples have been collected for use in research. The project will also examine how to use next-generation gene sequencing technology to make genetic diagnoses of NMDs. Simultaneously, the Fibroblast and Induced Stem-Cell Project will use adult stem cells—which are derived from a small piece of each patient’s own skin—to study the pathways of NMD and the treatments that might alter those pathways.

Cancer and circadian rhythms. Erik Herzog, PhD, an associate professor of biology at Washington University, presented findings on the link between brain cancer and circadian rhythms—the biological clocks that control our bodies. “There are certain times of day” Dr. Herzog said, “when children’s cancers may be more susceptible to treatment and when side effects of anticancer drugs could be minimized.”

Winning NIH sponsorship
In the short-term, Drs. Canter and Jay plan to collect additional data at St. Louis Children’s Hospital as well as with other pediatric heart failure centers, in a study sponsored by the National Institutes of Health (NIH). They have been aided in their work by nuclear medicine expert Robert Gropler, MD. Dr. Gropler conducts imaging studies that measure the uptake of glucose by a child’s heart.

In the long-term, these investigators hope their work will lead to clinical trials that answer a question posed by Dr. Jay: “Can diabetes drugs, which affect the uptake of glucose, improve the lives of children with heart failure?”

Dr. Canter stressed that Institute-funded research has led to “a real opportunity in children with heart failure. It’s possible that therapy targeting blood sugar or insulin metabolism might help these children.”

Dr. Jay agreed, and noted that today, “our team wouldn’t be involved in the NIH study without the initial funding of the Children’s Discovery Institute.” He added that “a large organization like NIH won’t support research until a scientist has...
Investor Sally Johnston asks:
“How long does it take to bring basic discoveries to the kids who need help?”

Investigator Kelle Moley, MD answers:
“All biomedical research takes time. If you look at pharmaceutical research, it can take anywhere from 8 to 15 years—and that’s after the basic research is done.

“The basic research funded by the Children’s Discovery Institute generates and verifies new scientific ideas. In my experience, it can take 5 to 7 years from the time a scientist has an idea to the time he or she amasses data to support the idea. Then, it might take another 5 to 10 years to determine how the idea might be harnessed to help sick children. That’s a timeline of about 10 to 20 years, just to get to the point where a new treatment might be tested.

“There are no shortcuts in research. A mentor of mine used to say, ‘They call it ‘research’—not just ‘search’—because you have to repeat it again and again.

“An inescapable part of the process is that for every idea that proves valid, several fail. The risk of failure is part of science—you can’t have discovery without risk. But there can also be a beautiful serendipity: An experiment might fail to prove your idea, but it might reveal a whole new line of investigation.

“Really, it’s best for patients that we take our time. Our long-term goal is always a healthier, longer life for children with serious diseases. We can’t risk treating these children with drugs or procedures unsupported by basic science. We have to conduct extensive studies in cells or in mice, because we cannot use children or pregnant women as the subjects of exploratory research.

“In the end, this lengthy, cautious process yields treatments we can confidently use in children.”

Sally Johnston is a passionate supporter of the Institute’s Center for Pediatric Pulmonary Disease.

Dr. Moley is the James P. Crane Professor and Vice Chair of Basic Science Research in Obstetrics and Gynecology at Washington University School of Medicine.

Do you have a question?
If so, send it to Rebecca Bergson, rbergson@bjc.org.
For as long as he can remember, Dr. Robert Mecham wanted to become a scientist. Hometown teachers nurtured his talent during middle school and high school. An undergraduate work-study job at the University of Utah started Dr. Mecham on a path he still travels—research on the connective-tissue proteins that structure blood vessels, bones, skin, and organs of the body. Today, Dr. Mecham is a leading expert on these proteins, with over 200 scientific papers, nine books, and dozens of professional honors and chairmanships to his credit.

Insights of a seasoned scientist
Dr. Mecham brings his experience as a scientist to the Scientific Advisory Board of the Children’s Discovery Institute. He knows that pediatric health research can be a long road, needing the kind of support the Institute provides.

“Just look at my career,” said Dr. Mecham. “When I was an undergraduate in the early 1970s, we were just beginning to characterize the protein, elastin, which is a very complex, connective-tissue protein responsible for the elasticity of blood vessels and the lung. After years of work, we had enough information to begin to delve into how the protein forms the functional polymer—the way the molecules line up together to form the elastic structures in the body. Now, 30 years later, we are still working to understand elastin, using new findings in genetics to describe elastin’s role in health and disease.”

Likewise, it can take years for a discovery in biology to lead to new treatments for children. Fortunately, the Children’s Discovery Institute can help accelerate the process.

“By supporting collaboration among researchers in different fields,” said Dr. Mecham, “the Institute allows scientists to exchange ideas that move their research along.” This enables investigators to “keep up with the many, many scientific developments that are happening across disciplines,” often leading to fruitful new avenues of study.

Choosing the projects to fund
Dr. Mecham’s experience helps him make informed decisions when it comes to the Advisory Board’s key responsibility—choosing the investigators who will be awarded funding from the Children’s Discovery Institute. The Board reviews proposals from investigators across the community of St. Louis Children’s Hospital and Washington University.

When considering a proposal, Dr. Mecham and all other board members are looking for the very best science. “You know it when you see it,” declared Dr. Mecham. “It’s a proposal that asks an interesting and important question. A study with a feasible design—something that will open up new vistas and inspire subsequent research.”

Dr. Mecham also looks for worthwhile projects in children’s health that might not be funded by more traditional sources like the NIH.

Ultimately, said Dr. Mecham, everyone on the Advisory Board shares a strategic vision. “In addition to funding the strongest science, we want the Children’s Discovery Institute to encourage and enable scientists who might not normally apply their ideas to pediatric disease.”

By doing that, “we facilitate discoveries that bear on children’s health, which might not have happened without our help.”
Deciphering the genetic code
In all these children, health problems appear to reside in the genes that code for the function of cilia. Cilia genetics are the province of Dr. Dutcher, borne of her intensive study of the Chlamydomonas organism.

“The similarity between the Chlamydomonas flagellum and a human cilium is amazing,” said Dr. Dutcher. “That means we can study Chlamydomonas to learn about human cilia.”

For instance, Dr. Dutcher observed, “we can produce genetic mutations that result in a poorly functioning flagellum. Then, we can see if similar mutations occur in children who have diseases caused by poor cilia function.” Conversely, she said, “we might identify a genetic mutation in kids with PCD or ear infections, then create a similar mutation in Chlamydomonas, and see what it does to the flagellum.”

So far, the team has identified a number of genetic mutations that may affect flagella and cilia. The mutations disrupt the biochemical pathways of motor proteins that ring each cilium and make it move. As a result of this research, explained Dr. Dutcher, “we may be able to test drugs that act upon or override these pathways, potentially leading to new treatments for PCD or chronic ear infections.”

The puzzle requires one more piece—a description of how cilia and flagella move in health and disease. That’s where Dr. Philip Bayly comes in.

Motors and microtubules
“When you know how cilia or flagella move,” declared Dr. Bayly, “you know when they function normally or abnormally.” This information helps determine whether a specific mutation leads to severely dysfunctional cilia, as in PCD, or to a milder problem. “By understanding cilia mechanics,” Dr. Bayly added, “you might be able to make a more accurate diagnosis, or devise treatments targeting specific mechanical abnormalities of the cilium.”

From an engineering point of view, a cilium or flagellum is a “mini-robot” that powers itself. Each is composed of small, flexible tubes (microtubules) encircled by motor proteins—“like drive shafts powered by engines,” in Dr. Bayly’s analogy. Genetic defects compromise the protein “engines,” altering the normal, waveform motion of the cilium.

So far, Dr. Bayly has analyzed motion of flagella on high-speed video, and developed mathematical models to compare the waveform of a normal flagellum with the abnormal waveforms of flagella with genetic mutations. “This modeling,” said Dr. Bayly, “gets us closer to linking particular abnormal waveforms with a specific set of mutations.”

Putting it all together for children
“Ultimately,” said Dr. Ferkol, “our goal is to connect specific abnormalities of cilia motion with a child’s genetic profile, then connect that with a child’s disease.” One day, “we could potentially personalize treatment to the genetics and cilia motion abnormalities present in the individual child.”

For example, in one group of children, a drug might interrupt a genetically encoded biochemical process that harms the motor proteins. In another group, a drug might improve the flexibility of microtubules—improving cilia function despite underlying problems with motor proteins.

To date, the team’s collaboration has resulted in scientific insights that, in the words of Dr. Ferkol, “we could never have achieved alone.” Dr. Bayly concurred, noting that he is “honored that mechanical engineering can make this contribution to children’s health.” The team started working together in anticipation of an Institute award, so their research paths converged thanks to this funding.

“Having different scientists from different disciplines takes you out of your comfort zone,” said Dr. Dutcher. “You look at things in new ways, and come up with new ideas.”

Want more details on this elegant research? Visit our website at childrensdiscovery.org and click on the Pathways icon.™

Photo: Cilia in the airways. The Children’s Discovery Institute funds research on cilia dysfunction, which leads to pediatric lung, sinus, or ear disease.

Photomicrograph by Dr. Steven Brody