A TALE OF TWO LEUKEMIAS

Two stories of struggle and survival, two CDI researchers looking for answers

Brendan was just 11 weeks old in 2005 when his mom, Jayne, felt a small lump on the right side of his head. That and a slight fever triggered her professional instincts as a nurse in the St. Louis Children’s Hospital newborn intensive care unit (NICU). She brought him to the hospital, where an MRI revealed the worst possible news: Brendan had infant leukemia.

Todd Druley, MD, PhD, assistant professor of pediatrics and of genetics, and a CDI faculty scholar, was a Washington University School of Medicine hematology/oncology fellow at Children’s Hospital when he had to deliver the bad news to Jayne. Infant leukemia is rare and extremely deadly. More than half of all babies who are diagnosed with it will die.

“I knew when Dr. Druley walked into the room that it wasn’t good,” Jayne says.

The next few months were filled with fear as tiny Brendan struggled through his treatment. At one point, during a long stay in intensive care, doctors told Jayne to prepare herself for the worst.

Jayne wondered why her child developed leukemia at such a young age. Dr. Druley, who had heard that question too many times, wondered the same thing.

In 2009, with CDI funding, Dr. Todd Druley (right) and Dr. Robi Mitra developed a quick, cost-effective method for detecting rare genetic changes in DNA that is widely used today.
New Discoveries Can Happen When Collaborations and Infrastructure Are Strong

In the Spring of 2009, we announced the creation of the St. Louis Neonatal Gut Microbiome Initiative. Barbara Warner, MD, professor of pediatrics, and her co-investigator Phillip Tarr, MD, the Melvin E. Carnahan Professor of Pediatrics at Washington University School of Medicine, were awarded a CDI grant to learn more about the biology of the human gut’s bacterial population and the role it plays in human diseases, including obesity, diabetes, asthma and autoimmune disorders.

Intestinal microbial colonization begins during the first year of life and may have lifelong consequences. Using sets of twin volunteers, the investigators and their colleagues proposed not only to determine the nature and concentration of microbes in the gut, but also to provide revolutionary data about the effects of human genes on bacterial content. These activities, they predicted, would form the basis for additional studies examining the role of early microbial colonization and health.

Just four years later, that prediction has been realized in the form of a published study in the March 19 issue of Clinical Infectious Diseases. The initial CDI grant allowed Dr. Warner, Dr. Tarr and their colleagues to create the infrastructure necessary for scientific discovery. The investigators were able to parlay the collaborations, infrastructure and data that emerged from the original initiative into additional funding from the National Institutes of Health and other sources to show that preterm babies’ guts harbor infectious microbes that can cause late-onset sepsis.

These investigators did not know what they would find when they embarked on the St. Louis Neonatal Gut Microbiome Initiative. But then, scientific discovery is never entirely predictable. By allowing the process to unfold, researchers made important discoveries that suggest new strategies to detect and prevent severe bloodstream infections in newborn intensive care units (NICUs), insight made possible by the ripple effect of CDI seed funding.


Mary Dinauer, MD, PhD

Mary Dinauer, MD, PhD, is the scientific director of the Children’s Discovery Institute. She also is 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.
WHEN LEUKEMIA STRIKES A TEEN

It was 106 degrees outside and a 16-year-old pitcher named Michael struggled on the mound. He attributed his weakness and shortness of breath to understandable, but uncharacteristic, heat exhaustion. Tests a few days later told a different tale.

Michael also was diagnosed with leukemia.

When Robert Hayashi, MD, professor of pediatrics at the School of Medicine, started treating Michael at Children’s Hospital, he was looking at a boy who presented with an extremely high white blood count, an indication of the severity of his disease. As a teenager, his age also put him into a higher risk group. The good news for Michael and his family was that the type of leukemia his age group develops responds well to aggressive therapies 80 to 90 percent of the time. The bad news was that the side effects can really pack a punch.

Treatment for leukemia requires highly complex therapy. Leukemia cells can find sanctuary in cerebral spinal fluid, the liquid that surrounds the brain and spinal cord. To cure Michael, chemotherapy has to be injected into his spine to bathe his brain with these drugs. While it helps prevent relapse, the treatment has been known to cause side effects that can include weakness, paralysis, seizures and poor school performance. According to Dr. Hayashi, Michael suffered side effects only experienced by about 5 percent of patients who receive the same treatment.

But Michael doesn't dwell on his side effects, even prefers not to discuss them. He’s a positive, confident young man, whose perfect ACT score caught the eye of the University of Alabama. He's headed there this fall, and along with the things he needs for his dorm room, he’ll take along a big dose of gratitude.

“Maybe it’s my faith, but I always knew I would get through this,” he says. Looking down at a bracelet he wears in memory of a friend he met on the ninth floor hematology/oncology unit who wasn’t so lucky, he adds that the experience has helped him understand that there is very little in life that’s in our control.

Brendan’s and Michael’s lives have been deeply affected by their leukemia. But, just as kids are not little adults biologically, the biology of teenage Michael’s leukemia varied greatly from infant Brendan’s. Jeff Magee, MD, PhD, assistant professor of pediatrics and a CDI faculty scholar, studies how leukemia can differ with age. The goal is to understand not just the mutations that cause leukemia but also how contextual factors, such as the age of a blood cell, can determine the consequences of each mutation.

"We know that age has an impact on the kind of leukemia a patient develops, but we don’t really know why," Dr. Magee says. "What is it about a mutated leukemia cell that makes it susceptible to develop a cancer? Why does a mutation that causes leukemia at one age not cause leukemia at another? Or more plainly, what’s different between Brendan and Michael? If we can answer these questions, maybe we can develop drugs to give the leukemia cells an identity crisis — somehow make them think that they are older or younger than they really are. If mutations need to occur at a specific age to cause leukemia, then we do not necessarily have to fix the mutations to blunt their effects. We just have to change how the leukemia cells interpret the mutations. It’s a conceptually different approach to cancer treatment."

In the short term, Dr. Magee sees this kind of insight potentially leading to better diagnostic tools or to the repurposing of drugs already in use for other diseases. Long term, he joins Dr. Hayashi, Dr. Druley and other pediatric oncologists in the pursuit of better, safer treatments and possible preventive therapies for childhood leukemia.

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Featured Research

RARE DISORDER SHEDS LIGHT ON TREATING COMMON CONDITIONS

A CDI faculty scholar identifies genetic factors that increase the risk for vascular problems in patients with Williams syndrome, paving the way for better diagnostics and treatments for a range of diseases.

Nicole Fuehne was experiencing poor weight gain during her pregnancy. Ultrasound tests revealed why. Her unborn daughter, Gracie, wasn’t growing and was much smaller than normal, so doctors decided to perform genetic tests.

“Gracie was diagnosed with Williams syndrome before her parents had a chance to meet her,” says Beth Kozel, MD, PhD, an assistant professor of pediatrics and of genetics at Washington University School of Medicine and Gracie’s physician at St. Louis Children’s Hospital. “Being able to give good information about what to expect is important to families, and that is what we are looking to provide through research funded by the Children’s Discovery Institute (CDI).”

Children with Williams syndrome tend to be very social and cute. They often are described as having pixie-like facial features. But the disorder also can cause serious conditions, such as intellectual disabilities and cardiovascular problems. The severity of vascular problems in Williams syndrome patients varies. While some patients, like Gracie, have only mild symptoms, up to 30 percent of patients need vascular surgery to stay alive. Very little is known about the genetic factors that influence the severity of symptoms in Williams syndrome.

“The goal of our research is to find out which genes increase the risk of blood vessel disease in these patients so that we provide better information about what to expect in terms of cardiovascular problems,” says Dr. Kozel. “This research will help us identify new medications that could protect the cardiovascular health of these children and help them live longer.”

To do so, Dr. Kozel uses mice with a mutation in the elastin gene, which is one of the 26 to 28 genes that are missing in patients with Williams syndrome. Elastin is a protein that allows blood vessels to stretch and recoil. When levels of this protein are low due to a genetic mutation or deletion, blood vessels become stiff and narrow, increasing the risk of stroke, heart attack and death.

Dr. Kozel identified several other genetic factors in the elastin-deficient mice that determine the severity of vascular problems, and has established a large DNA and tissue bank to test whether...
these same genetic factors increase the risk of vascular problems in Williams syndrome patients. By revealing important genetic modifiers of vascular disease severity, Dr. Kozel will be able to identify and test new medications and develop early diagnostic screens for these genetic risk factors so patients get the medical care they need as soon as possible.

“I was lucky because I got a prenatal diagnosis and started having tests right away,” Nicole says. “But that’s not the case for so many families. They get too far along and too much has gone wrong, but there’s not enough time to fix the problem.” Beyond affecting blood vessels, vascular stiffness can cause kidney problems and may impair brain function. Moreover, vascular stiffness occurs in common conditions such as high blood pressure and diabetes.

“Rare diseases offer a window to understand more common medical problems,” Dr. Kozel says. “Investigation of these issues in our Williams syndrome patients also will benefit child health in general.” While 3-year-old Gracie remains relatively healthy, Nicole recognizes the importance of Dr. Kozel’s research. “Vascular problems tend to worsen with age, and we don’t really know now if this is something we’ll have to deal with in the future,” Nicole says. “Her research is incredibly valuable because parents are desperately trying to get any information they can after the first diagnosis. As parents, we want to give our children whatever medical help we can to make sure they will live as healthy and as long as possible.”

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Pneumococcal disease is an infection caused by the *Streptococcus pneumoniae* bacterium (pneumococcus). Infection can spread from the upper respiratory tract and cause pneumonia, middle-ear infections, bacterial meningitis and serious blood stream infections.

In the U.S., a pneumococcal vaccine was added to routine childhood immunizations in 2000, with a resulting dramatic reduction in hospitalization and mortality — particularly in the target (under age 2) population. In countries that lack vaccination, however, pneumococcal disease claims the lives of one million children under age 5 every year.

But even in this country, with access to vaccination, advanced critical care and new antibiotics, some youngsters will die from pneumococcal disease — many within the first 48 hours of infection.

Why do some vaccinated children become severely ill from pneumococcal infection and others don’t?

S. Celeste Morley, MD, PhD, assistant professor of pediatrics and of pathology and immunology at the School of Medicine, and her colleagues are investigating this very question. Their work has focused on the function of macrophage cells in clearing pneumococcus from the lungs.

“Macrophage cells are a first line of defense against pathogens that invade our bodies,” says Dr. Morley. “Macrophages exist within the alveoli (the small air sacks) of the lung and attack microbes by engulfing and digesting them.”

Dr. Morley notes, however, that it isn’t quite that straightforward. Pneumococcal bacteria have evolved a defense against macrophage destruction in the form of distinct and variable surrounding capsules that can prevent macrophages from doing their job. Pneumococcus has more than 90 distinct variations (called serotypes). Not all of the pneumococcal variations cause problems. In response, the body may call in the big guns of the immune system — antibodies. An antibody can bind to a pneumococcal cell surface and essentially give the macrophage a fork to aid its pathogen-eating job.

The hitch is that each serotype requires a specific antibody. That’s where vaccination comes in. Vaccination primes the immune system to have specific antibodies ready when a pathogen enters.

The first pneumococcal vaccine induced antibodies against seven of the 90-plus serotypes. The newest vaccine — in use since 2010 — protects against 13. The vaccine covers the worst offenders.

In light of that fact, the question of why vaccination fails to protect all children is even more perplexing.

“We are looking at the possibility that the macrophage cells in some people may not function properly, even though antibodies are present and doing their job,” says Dr. Morley.

In mouse models, Dr. Morley has identified a specific protein called L-plastin, which plays an important role in giving structure to macrophages — the structural scaffolding that enables them to change shape when activated. Mice that lack L-plastin are highly susceptible to pulmonary infection with pneumococcus and their ability to clear infection is drastically reduced.

What does this have to do with people?

“Children who are highly susceptible to pneumococcal infection may have changes in the genes that produce L-plastin and other proteins that impact macrophage activation,” says Dr. Morley.

Dr. Morley and her colleagues have begun collecting DNA samples from families with children who have severe pneumococcal pneumonia and are seen at St. Louis Children’s Hospital. Another colleague will be collecting DNA from families in Papua, New Guinea, where vaccination is rare.

CDI researcher Todd Druley, MD, PhD, will compare the gene sequences that produce the proteins linked to L-plastin for all of these families. Finding genetic differences may enable doctors to use rapid genetic testing to identify highly susceptible children for heightened surveillance.

The work eventually may lead to treatments for these children.

Data from Dr. Morley’s basic L-plastin protein research has been shared widely, most recently in the journal *Infection and Immunity,* and already has benefited investigators studying other diseases such as leukemia and autoimmunity.
WHY I GIVE

Investment executive and St. Louis Children’s Hospital Foundation Board of Trustees member, Jim Johnson III, explains why he believes investment in the Children's Discovery Institute (CDI) is worth making.

When did you first become involved with St. Louis Children’s Hospital?
When we moved back to St. Louis 21 years ago, I was looking to get involved in the community. My parents had always been philanthropically involved with Washington University and instilled in me a strong sense of responsibility to give back to the community. Because we were looking to start our own family, I was drawn to the mission of Children's Hospital. With encouragement from longtime hospital supporter Becky Hailand, I joined the Foundation’s Development Board and eventually found my way to the Foundation Board.

What sparked your imagination about the CDI?
When the Foundation launched its Care and Cures campaign to create the CDI in 2005, I knew I wanted to contribute. But I wasn’t interested in investing in buildings. What excited me was the timing of the CDI’s inception. Washington University had just sequenced the genome. Couple that with the fact that the National Institutes of Health (NIH) and other public sources were making cuts in their funding, and it just seemed like the right time to invest in some groundbreaking research.

But why pediatric research?
There just isn’t enough money spent on pediatric care relative to overall medical research dollars. The least amount of dollars is being spent in an area that could make the biggest impact. That just seems backward to me. When you invest in pediatric research, you create the opportunity to make a difference in the lives of millions of children for years to come. It is what Dr. William Danforth refers to as saving lives wholesale.

Has the CDI met your expectations so far?
I originally invested in the Congenital Heart Disease Center of the CDI. And there has been some noteworthy progress made in that area. But here’s the thing about research. There is no immediate payback, there is no instant gratification. I wasn’t looking for that. I was looking to provide some of these researchers investment dollars so that they could take some risks. With the NIH funding going down, some of the riskiest, most highly impactful research just doesn’t get done because they’re only looking for the safe bet, the single or the double. I think it would be great to just go for the home run.

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In addition to the St. Louis Children’s Hospital Foundation Board of Trustees, Jim serves on the Donald Danforth Plant Science Center Leadership Council.

Why do you give?
Share your personal story with us. Contact Janice Bailey at jbailey@bjc.org.
The Children’s Discovery Institute is a multidisciplinary, innovation-based research partnership between St. Louis Children’s Hospital and Washington University School of Medicine. Founded in 2006, the Institute has awarded more than $38 million in scientific grants for pediatric research projects aimed at some of the most devastating childhood diseases and disorders.

**Please Join Us!**

_Don’t miss this stand-out event. Mark your calendars now!_

**Seventh Annual Children’s Discovery Institute Symposium**

_Tuesday, November 18, 2014_  
6:30-8:30 p.m.

Charles F. Knight Executive Education & Conference Center at the Washington University Danforth Campus

Meet Children’s Discovery Institute researchers and experience this interactive, hands-on event. Learn more about how your investments are accelerating discoveries for children.

_Invitation coming this fall!_

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This newsletter shares the accomplishments of the Children’s Discovery Institute with our stakeholders, particularly those whose generosity supports the research carried on by Institute investigators.

**If you have comments or questions about Pathways, please contact:**  
Janice Bailey, Vice President, St. Louis Children’s Hospital Foundation  
314.286.0971 / 888.559.9699  |  jbailey@bjc.org