Megan Cooper, MD, PhD, pediatric rheumatologist and immunologist, treats children with immune system problems. Either their immune systems are too active, causing auto-immune diseases such as arthritis, or not active enough, leaving them susceptible to infections. Using funding from the CDI, Dr. Cooper and her colleagues have been pursuing a keen interest in uncovering the genetic origins of these problems. Her work turned out to be a lucky break for a sick little boy, named Kory, whose first five years of life had been a struggle.

“How a little boy helped researchers gain a greater understanding of our immune system.”

– Dr. Megan Cooper
Accelerating Discovery Through a Forum of Support

The 2006 creation of the Children’s Discovery Institute (CDI) and the 2007 launch of the National Institutes of Health-supported Institute for Clinical and Translational Sciences (ICTS) have made for exciting times for medical researchers throughout the Washington University School of Medicine campus. Through their shared goal of accelerating the development of high-impact research and its clinical translation from the bench to the bedside, the CDI and the ICTS have invigorated researchers. The result has been new ideas, synergistic collaborations and, with the 2013 formation of the ICTS Research Forum-Child Health (RF-CH), unparalleled support for investigators.

The RF-CH comprises a multi-disciplinary team tasked with examining new research proposals and helping investigators identify key roadblocks, milestones, collaborations and funding strategies. Since its creation, the RF-CH team has met with 23 investigators – 13 from the department of pediatrics; and 10 from medicine, microbiology, OB/GYN, radiology, neurosurgery, orthopedics, neurology and psychiatry.

To date, the RF-CH has provided research personnel support to four projects and approximately $86,700 in seed funds to six projects. It also has helped secure one new CDI grant and one Gerber Foundation grant. Best of all, the investigators have come out of the process with valuable direction regarding the collection of more data and suggestions for broadening collaborations and refining their research focus.

What has been the most gratifying to the RF-CH team are the comments received from the investigators after analyzing their research design and making recommendations.

“Overall, the RF-CH saved me considerable time and forced me to collect additional data that made the grant submitted much more competitive,” wrote one pediatric researcher.

Another wrote: “The RF-CH was a fantastic experience. I was very pleased with the process and the mentoring I received. The process could not have been any better, and I plan to revisit the team following additional project design discussions.”

So what’s next for the RF-CH? Through its continued partnership with the CDI, the team will continue giving researchers the advice needed to move their ideas forward for the health of children worldwide.

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, professor of pediatrics, and of pathology and immunology at Washington University School of Medicine.

FROM THE SCIENTIFIC DIRECTOR

PERSONALIZED MEDICINE – continued from page 1

“Before we came to St. Louis Children’s Hospital, no one could tell us why Kory had so many health problems,” explains his mom, Donna. “He suffered from liver disease and skin problems. Arthritis gave him so much pain in his hips and knees, we would go through a bottle of children’s Motrin a week to get him through school.”

Meanwhile, medical tests were inconclusive, until analysis of his and his parents’ DNA swabs were submitted to Dr. Cooper’s lab. Using the sophisticated gene sequencing technology of the Genome Technologies Access Center at Washington University, Dr. Cooper found in Kory a previously unreported mutation in STAT3, a gene assigned to signal the immune system to activate.

“We knew that other mutations in STAT3 caused immune deficiencies, resulting in frequent infections,” Dr. Cooper says. “But, in our patient’s case, testing seemed to point to STAT3 as the cause of a gain in immune system function.”

Kory demonstrates his new active lifestyle at the gym with his friends, who took these pictures.
While attending a conference, Dr. Cooper told a colleague from the National Institutes of Health (NIH), who also studied STAT3, about the curious findings. That conversation led to collaborations between Dr. Cooper’s lab and researchers in the United States and across the Atlantic. These researchers identified 13 patients worldwide with nine different mutations in their STAT3 genes that led to a gain in immune system function. Back in St. Louis, Dr. Cooper’s lab modeled all nine mutations in tissue culture and was able to verify that STAT3 was a big player in the development of immune system dysfunction.

“The future for treating diseases where the immune system is overactive is to move away from global suppression and toward isolating the part that is causing that problem and targeting it.”

– Dr. Megan Cooper

“What this told us was that we should be thinking about creating therapies that are more targeted toward shutting down the ability of STAT3 to lead to disease,” Dr. Cooper says. “This is the realization of personalized medicine: being able to find the patient’s exact problem and treating that exact problem.”

It turns out that what gives Kory the greatest relief from his symptoms is anti-interleukin 6 therapy, an FDA-approved biologic agent prescribed to treat juvenile arthritis. The drug keeps STAT3 from signaling the over-activation of the immune system. It has done wonders for Kory, who has been receiving infusions the past couple of years to receive infusions.

“After just a few treatments, Kory’s physical therapist noticed a remarkable change in the flexion of his joints,” Donna says. “His fingers have straightened out. He has more energy. He can actually climb a flight of stairs.”

Kory, now 11 years old, was chosen to be an extra in his community high school’s play. “He was cast to be just a kid walking through the park. How ironic is that?” Donna says.

Meanwhile, Dr. Cooper published her lab’s findings in the journal Blood.

“The future for treating diseases where the immune system is overactive is to move away from global suppression and toward isolating the part that is causing that problem and targeting it. That leaves the rest of the immune system to do the things the body needs it to do,” Dr. Cooper says.

If you are lucky enough to have known him, you’d agree that there will be no other guy like Fred Saigh.

Born in 1905, the son of Lebanese immigrants, this successful attorney, real estate investor and former owner of the St. Louis Cardinals was known to be a visionary who was passionate about giving back to the people and the institutions of the city he loved.

Maybe that’s why he sold the Cardinals in 1953 to Anheuser-Busch for $750,000 less than he would have received from out-of-state interests. Maybe that’s why he never passed up the opportunity to assist those less fortunate and helped people he barely knew at critical times in their lives through random acts of kindness. Maybe that’s why the foundation he began to establish in 1953 to Anheuser-Busch for $750,000 less than he would have received from out-of-state interests. Maybe that’s why he never passed up the opportunity to assist those less fortunate and helped people he barely knew at critical times in their lives through random acts of kindness.

JoAnn Hejna, Saigh Foundation executive director, Mary Kemp, Saigh Foundation associate executive director; Franklin Wallis, Saigh Foundation co-trustee.

“We are so amazed at the progress made by the CDI researchers in understanding diseases that affect children, and we are sure Fred would be, too.”

– JoAnn Hejna, executive director, Saigh Foundation
Adult cardiologist, **Kory Lavine, MD, PhD**, completed his advanced heart failure transplant fellowship at Washington University School of Medicine with more questions than answers. He had been researching dilated cardiomyopathy, a chronic disease that renders the heart muscle too weak to work efficiently. Eventually, the heart begins to fail, making a transplant necessary. This can happen in adults or children.

Pediatric dilated cardiomyopathy can either be acquired, such as through a virus or cancer chemotherapy, or inherited through a gene mutation of one or both parents. However, according to the Children’s Cardiomyopathy Foundation (CCF), 75 percent of cases do not have a known cause. Families faced with the diagnosis today are forced to come to terms with an ominous prognosis. The CCF says the five-year survival rate for children with dilated cardiomyopathy is just 40 to 50 percent. For those who can survive until a heart transplant can be performed, the peril continues. In fact, throughout his career, Dr. Lavine has treated patients who had transplants as children. In many cases, those patients grow up to once again develop heart failure as young adults. Dr. Lavine’s desire to find a way to more effectively treat children in heart failure became a CDI-funded project.

Inside the human heart are white blood cells called macrophages. Some, known as embryonic-derived macrophages, are seeded there during fetal development. Others are derived from another type of white blood cell known as monocytes. Originating in bone marrow, monocytes become macrophages once they leave the blood stream and enter a tissue.

Before applying for a CDI grant, Dr. Lavine’s lab had been modeling human dilated cardiomyopathy in mice. What he and his colleagues noticed from that work was that, in a neonatal mouse heart, very few monocytes are attracted into the heart from the blood stream. Dr. Lavine will use his CDI funding to study outcomes in the mouse model when those monocyte cells are selectively removed. With them out of the way, the question becomes will the embryonic-derived macrophages take over to repair the heart or slow the progression of heart failure.

“We hope to identify a mechanism that will disable the harmful immune cells and activate the reparative immune cells,” Dr. Lavine says. Cheering him on are Colleen and Mike Miller. In 2010, just two days before Christmas, at 6 months of age, their daughter Layla Rose was diagnosed with dilated cardiomyopathy. As a registered nurse with cardiac care experience, Colleen knew her family’s life would never be the same from that day forward. “When the diagnosis was cardiomyopathy, we felt like we were given a death sentence,” Colleen says. “More than half of all children diagnosed don’t live past age 5. If they do survive, it is a fluke or due to a heart transplant, and that is not a cure, since the life span of a new heart is only around 10 to 15 years.”

“We hope to identify a mechanism we can tap into that will disable the harmful immune cells and activate the reparative immune cells.”

– Dr. Kory Lavine
Layla spent her first Christmas in the Maxine Clark and Bob Fox Cardiac Intensive Care Unit at St. Louis Children’s Hospital, and had many more hospitalizations, tests, medical and surgical procedures after that. The Miller’s lives became filled with doctors’ appointments, medication schedules and worry, knowing the whole time that a transplant loomed in their future. That time came in August of 2014.

“We always had an idea of where the dilated cardiomyopathy road would lead,” Colleen wrote in her Caring Bridge blog after learning they were out of options. “We prayed and worked and gave meds, faithfully went to doctors’ appointments and spent many nights in the hospital and cardiac ICU. All of this was done to keep the worst at bay… knowing full well it was out of our control.”

Unfortunately, Layla passed away after going into cardiac arrest during a cardiac catheterization that was meant to determine the readiness of her lungs to handle a new heart. Since that devastating day, the Millers have channeled their grief into acts of kindness, such as installing a buddy bench at Layla’s school or purchasing a rocking chair for the cardiac ICU, where they spent so much time. The chair has a plaque with Layla’s name and a quote that has sustained the Millers through it all. It reads: “There is no foot too small that it can’t leave an imprint on this world.”

To help make that imprint, the Millers also never shy away from opportunities to raise awareness of pediatric cardiomyopathy.

“We are thrilled to do anything we can do to keep Layla’s story going,” Colleen says. “Promoting awareness for a condition that has no cure, limited treatment, high mortality and needs more funding to find a cure is a goal of ours.”

“There is no foot too small that it can’t leave an imprint on this world.

– Colleen Miller

Layla Rose Miller 2010–2014

Promoting awareness for a condition that has no cure, limited treatment, high mortality and needs more funding to find a cure is a goal of ours.”

– Colleen Miller

Layla Rose Miller 2010–2014

There is no foot too small that it can’t leave an imprint on this world.
As any mother who must vigilantly protect her child from ingesting a peanut can attest, food allergies are frightening, isolating and disruptive. And, for the past decade, they have been on the rise. According to the Centers for Disease Control and Prevention (CDC), there has been a five-fold increase in hospital admissions due to food allergies. Not only is the problem getting more common, it’s getting more severe. Going back to 1993, the CDC shows a steady rise in the life-threatening reaction.

You also can judge the level of the problem by the rise of peanut-free tables at elementary school lunchrooms across the nation,” says Rodney Newberry, MD, medicine. “The significant thing is that it’s happening to younger and younger kids. Something is occurring between birth and age 5 that is increasing the risk of food allergy.”

That’s where Dr. Newberry and co-principal investigators, Avraham Beigelman, MD, pediatrics; Phillip Tarr, MD, the Melvin E. Carnahan Professor of Pediatrics; and Barbara Warner, MD, pediatrics, are focusing their CDI-funded study. Launched in February, the new study seeks to uncover the early environmental exposures that put children at risk for food allergies.

“It’s difficult to ignore that, in 2001, the World Health Organization (WHO) came out with the recommendation that mothers exclusively breastfeed for the first six months of the infant’s life. Over the next 10 years, food allergies have been rising,” Dr. Newberry says.

Around the same time, new mothers began to practice avoidance strategies, taking peanuts, shellfish and other known allergens out of their diets. Yet, even more kids developed an exaggerated immune response to these foods.

Dr. Newberry says if you put together all the data from animal and human studies done thus far, it begins to point to a timing issue. Could there be a window of time in early life that is optimal for inducing tolerance to food allergens, an exact period when the immune system is developed enough to discern when and when not to launch an offensive attack? To find out, the researchers are going to delve deeply into not just what goes in but what comes out of an infant’s body.

In 2009, with funding from the CDI, Drs. Tarr and Warner conducted a study involving the collection of fecal samples of 40 sets of infant twins over the course of a year in order to characterize and map the colonization of the bacterial contents of their intestinal tracts. The fecal samples they collected

“The significant thing is that it’s happening to younger and younger kids. Something is occurring between birth and age 5 that is increasing the risk of food allergy.”

– Dr. Rodney Newberry
have become a valuable resource for scientists studying the role bacteria plays in child health. They wonder how a baby’s gut goes from being sterile at birth to one that has a fully developed microbacterial community, known as the microbiome. Fast forward to 2015, and the St. Louis Neonatal Microbiome Initiative, as it has come to be called, lends those samples to the food allergy study in order to validate the window-of-time theory.

What the researchers already know is that the contents of breast milk changes over time. In very early life, an infant ingests breast milk with high concentrations of factors that suppress food antigens that might cause an allergic reaction from coming in contact with an immature immune system. As the immune system matures, the concentration of those breast milk factors decreases. At just the right time, when the immune system has matured enough to mount appropriate responses, food allergens are safely introduced to the immune system, along with tolerance-inducing bacteria that have colonized the gut. It’s a beautiful yet fragile balance that can be thrown off in a variety of ways, including avoidance of food known to cause allergies by new mothers and the early use of antibiotics. Dr. Newberry and his team are using mouse models, as well as the stool samples from the neonatal microbiome initiative, to piece together how that balance can be altered and how it can be restored.

“At the end of the study we hope to be able to make recommendations regarding when food allergens should be introduced, when to avoid antibiotics or which antibiotics to avoid,” Dr. Newberry says. “Meanwhile, what we learn about the immune system along the way might inform future studies looking into how to reprogram that system, essentially reset the clock, as a way to reintroduce food allergens safely and suppress the immune response. Maybe then, kids sitting at the peanut-free table can rejoin their friends.”

“…What we learn about the immune system along the way might inform future studies looking into how to reprogram that system, essentially reset the clock, as a way to reintroduce food allergens safely and suppress the immune response.”

– Dr. Rodney Newberry
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 $43 million in scientific grants for pediatric research projects aimed at some of the most devastating childhood diseases and disorders.

Visit our website for ongoing research updates.
ChildrensDiscovery.org

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Please Join Us!

Plan now to attend the Eighth Annual Children’s Discovery Institute Symposium

November 18, 2015 • 6:30-8:30 p.m.

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

Your invitation is coming this fall!

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:
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