

## New breakthroughs in childhood leukemia

**Siteman Kids at St. Louis Children's Hospital is among the first to offer breakthrough cancer treatment that turns a child's immune system into a cancer fighter.**



*Shalini Shenoy, MD; Robert Fulton;  
John F. DiPersio, MD, PhD*

Siteman Kids at St. Louis Children's Hospital is one of the first U.S. centers to offer a breakthrough pediatric cancer treatment in recent months. CAR-T immunotherapy harnesses a child's own immune system to fight cancer. The FDA approved the therapy in August 2017 as a defense against an aggressive form of acute lymphoblastic leukemia (ALL) in children who have not responded to standard therapies or whose cancer has relapsed.

A person's immune system normally fights disease and infection. However, in cancer patients, specialized immune cells called T-cells lose the ability to

recognize and attack cancer cells. With CAR-T therapy, a patient's own T-cells are isolated from the blood. Those cells then are genetically altered—or supercharged—enabling them to home in on cancer cells and destroy them. During this process, specialized receptors, called chimeric antigen receptors, are put onto patients' T-cells. When the immune cells are infused back into patients, these receptors allow the cells to recognize and attack tumor cells, thus turning the T-cells into cancer-fighting machines. These supercharged cells also stay alive and in circulation in the patient's body, lending added protection for years.

Washington University pediatric oncologists with extensive experience in treating leukemia will administer the CAR-T immunotherapy through the Siteman Kids program at St. Louis Children's Hospital.

"If it looks like the leukemia is not responding to treatment or relapsing, the CAR-T cells can attack it all over again using a different mechanism than chemotherapy," explains Shalini Shenoy, MD, a Washington University pediatric hematologist/oncologist and director of Siteman Kids at St. Louis Children's Hospital. "We think this is just the beginning for this kind of therapy. If we can make a patient's own cells smart enough in more cancers, and we think we can, we believe we'll be able

to tackle even more types of cancer with immunotherapies in the future."

Clinical trials have shown that in children with aggressive B-cell ALL who have not responded to standard therapies or have relapsed, CAR-T therapy has achieved more than an 80 percent remission rate. Some patients have remained in remission for more than five years. While the treatment is considered a major advance in cancer treatment, CAR-T therapy induces a heightened immune response that can lead to a range of side effects, some of which can be severe.

"Because of the potential side effects, it's important that patients undergoing CAR-T therapy are watched closely by physicians and care teams with extensive experience in blood cancer therapy and bone marrow transplantation," Shenoy says.

Research into the potential of CAR-T therapy continues. The Children's Discovery Institute (CDI)—a research partnership between St. Louis Children's Hospital and Washington University School of Medicine—has invested \$360,000 toward further investigation into these life-saving therapies. For this effort Dr. Shenoy has joined John DiPersio, MD, PhD, the Virginia E. and Sam J. Golman Professor of Medicine in Oncology and deputy director of

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# The CDI approves nearly \$3.5 million in new funding

## Studies spanning an array of childhood diseases launched in February 2018.

The CDI board of managers recently voted to fund 10 new pediatric research studies, which launched in early February.

**Ana Maria Arbelaez, MD**, pediatrics; and **Christopher Smyser, MD**, neurology, seek to understand the neurodevelopmental consequences of malnutrition in children. The researchers and their collaborators will use their funding to expand a previous CDI-funded pilot study in Cali, Colombia.

New funding from the CDI will pave the way for **Jacco Boon, PhD**, medicine, and **Daisy Leung, PhD**, pathology and immunology, to use advanced sequencing techniques to develop a much-needed RSV vaccine. In a previous CDI-funded study, Dr. Leung played a key role in mapping the molecular structure of an RSV protein that interferes with the body's ability to fight off the virus.

Leveraging her understanding of the molecular mechanisms of immunodeficiency, **Megan Cooper, MD, PhD**, pediatrics and pathology and immunology, will use whole exome sequencing to uncover personalized precision therapies based on the specific mutations causing a child's immune disorder.

Could an inexpensive and readily available nutritional supplement, known as CoQ10, be the secret to preventing severe bacterial pneumonia in some children? CDI investigator **Celeste Morley, MD, PhD**, pediatrics,

will seek to answer that question using a mouse model with a variant in a gene known to activate the enzymes the body needs to produce CoQ10, an antioxidant.

Does adversity become "biologically embedded" in a child, leading to disparities in health outcomes? A new study by **Barbara Warner, MD**, pediatrics, and **Joan Luby, MD**, psychiatry, will investigate the degree to which psychosocial stress, such as poverty, of a mother during the prenatal period or early infancy alters the microbial makeup of the baby's gut and, in turn, his or her immune system health and inflammatory response.

With his funding, **Timothy Wencewicz, PhD**, chemistry, will take on mycobacteria and short circuit their ability to resist antibiotics used to fight Mycobacterium tuberculosis (Mtb), which infects more than a million children annually. In children with cystic fibrosis, the inability to clear another type of mycobacteria from the lungs renders them unable to receive lung transplants. Dr. Wencewicz is taking an innovative approach to improve treatment results.

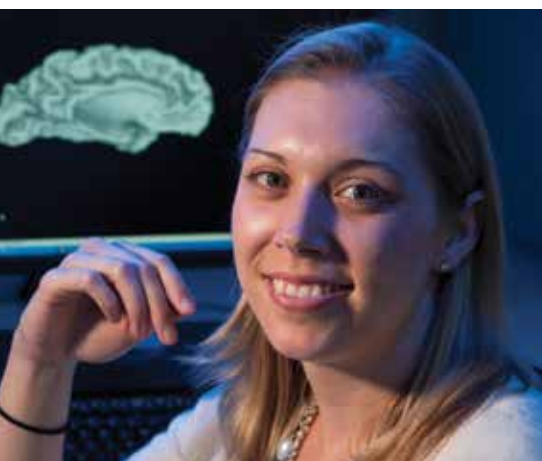
**Xunjun Xiao, PhD, MS**, pediatrics, and **Stephen Pak, PhD**, pediatrics, will study how inherited mutations in a pancreatic

digestive enzyme cause a cellular response that leads to chronic pancreatitis. Greater understanding of this disease, which can result in diabetes, chronic pain and the inability to digest food, could lead to effective therapies, which are currently lacking.

In this round of funding, infectious disease specialist **David Rosen, MD, PhD**, pediatrics, received a CDI Faculty Scholar award to lead a study of Klebsiella pneumonia to uncover its vulnerabilities for vaccine development.

Two post-doctoral fellowship awards were also given this round. **Harshad Ingle, PhD**, medicine, will study how malnutrition affects the microbial makeup of a child's gut and leads to severe virus-induced diarrhea. The second award was granted to **Kel Vin Woo, MD, PhD**, pediatrics, to find ways to protect vulnerable pre-term infants from pulmonary hypertension using mouse models.

"This robust list of newly funded projects builds upon the success of previous or ongoing investigations conducted by CDI investigators," says CDI scientific director **Mary Dinauer, MD, PhD**, the Fred M. Saigh Distinguished Chair of Pediatric Research at St. Louis Children's Hospital. "Each has the potential of being transformational for pediatric medicine."



Dr. Cynthia Ortinau

## The head-heart connection

**In search of the best way to protect the brain development of children with congenital heart disease.**

St. Louis Children's Hospital neonatologist Cynthia Ortinau, MD, has seen the pain expectant parents go through in learning their baby has a serious heart defect. It's a difficult conversation that gets even harder when telling parents about the link between congenital heart defects and developmental delays.

"Right now, we can tell parents what to expect in terms of the surgical and medical interventions available for their newborn's heart condition. Unfortunately, we can't do the same for their long-term brain development," Dr. Ortinau says. "That uncertainty is what drives us to learn more about how and why brain development is different in these babies."

The ultimate goal of Dr. Ortinau's CDI research that began in February of 2013 was to one day be able to change that conversation. Her hope is to be able to say: "yes, your baby has a heart defect that we'll begin treating, and here's what we are going to do to protect your baby's brain development along the way."

For her CDI pilot study, Dr. Ortinau's research team recruited 39 patients who had an MRI of their baby's brain before birth. Follow-up imaging and developmental testing took place after the children were born. This study was groundbreaking because it showed the feasibility of using MRI technology on babies before they are born.

"The study required us to come up with special protocols to capture pictures of a baby's brain while the baby was moving around inside of the mother," Dr. Ortinau says. "We are one of a select few centers around the country doing this type of work to advance fetal brain imaging, especially in babies with congenital heart disease."

Shortly after launching this project, Dr. Ortinau decided to move her work to Brigham and Women's Hospital in order to continue her mentoring relationship with Terrie Inder, MD, a pioneer in the use of MRI scans of premature infants to predict future delays in development. In Boston, Dr. Ortinau worked with a large team studying cardiac neurodevelopment, and together with a pediatric neurologist at Boston Children's Hospital, Dr. Ortinau began another fetal MRI study. Preliminary results from both her CDI pilot study and the Boston project have shown that differences in brain development begin early in pregnancy for babies with heart defects. These include differences in brain size and how the outer part of the brain folds.

After gaining valuable experience working with experts in cardiac neurodevelopment and fetal imaging, Dr. Ortinau returned to St. Louis, where the work she began in 2012 has continued with funding from a new CDI study launched last July. "The initial CDI-funded pilot study was key to designing the project in Boston. Then, what I learned from my work there was used as a platform to build on my new research here. It has come full circle," Dr. Ortinau says.

"We were thrilled to welcome Cynthia back into our fold," says F. Sessions Cole, the Park J. White, MD, Professor of Pediatrics at the Washington University School of Medicine and director of newborn medicine at St. Louis Children's Hospital. "Her

“We were one of a select few centers around the country doing this type of work to advance fetal brain imaging, especially in babies with congenital heart disease.”

Dr. Cynthia Ortinau

# The science and the stories

The 2017 CDI symposium struck the right balance of both.



CDI investigator Todd Fehniger, MD, PhD, explains research that promises to give children with a recurrence of leukemia a better chance.

An evening of science and stories captivated the nearly 200 guests at the 10th annual CDI Investor Symposium on Nov. 2, 2017. The photos tell the tale of inspired engagement between the CDI investors, the researchers they support and the families of those they impact.

"What made this year's symposium so meaningful was the full incorporation of patient stories to help highlight the importance of the important research we fund," says Malcolm Berry, chief development officer, St. Louis Children's Hospital Foundation.

Save the Date for the 2018 CDI Symposium:  
Thursday, November 1 DETAILS TO COME

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Siteman Cancer Center; Matthew Cooper, PhD, an instructor in medicine; and Robert Fulton, an assistant professor of genetics and a scientist at the McDonnell Genome Institute. The team members will use their CDI funding to develop several new treatments. They hope to produce an "off-the-shelf" CAR-T therapy product that prevents CAR-T cells from attacking each other or non-cancer cells in the patient. They will also innovate new strategies to overcome a life-threatening side effect of CAR-T therapy called cytokine release syndrome (CRS), and create a novel "suicide gene" that will track and eliminate CAR-T cells in the body, if needed, using a unique form of positron emission tomography (PET) scanning. "Siteman Kids is equipped to manage the therapy, which is why our center is among the first to offer it," Dr. Shenoy says.

## The head-heart connection

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passion for ensuring our newborns have a fighting chance for healthy, happy, productive lives coupled with her intellectual curiosity will help improve the way we care for these babies and the understanding of the science behind it."

One of the differences in the two CDI studies is that Dr. Ortinau is now trying to focus more on why brain development is different in babies with heart defects. There are two potential mechanisms she believes are important. The first is that the heart defect likely affects how blood flow and oxygen are delivered to the brain. The second is

that different genetic makeups may lead to abnormal development of both the heart and brain. In the first CDI study, Dr. Ortinau's team recruited only patients with isolated heart defects, meaning they had no other diagnosis. The second study will involve collecting data on all patients with heart defects, even those with other types of birth defects, and will include genetic testing.

"A broader cohort, with the incorporation of genetic testing, will help us begin to understand the role different genetic variants play in both heart and brain development," Dr. Ortinau says. "We will be able

to see what the brains of different patients with different genetic variants look like in the hopes that we will begin to find patterns. At the same time, measurements taken on blood flow and oxygen to the brain will help us narrow in on the physiological differences in the brains of these children."

Dr. Ortinau hopes all this testing will lead to a day when expectant parents can leave their prenatal counseling session with peace of mind, knowing that no matter what must be done to repair their baby's heart defect, their ability to learn, communicate, play and live their best life will be protected.