Children's Foundation Research Institute

Research Matters

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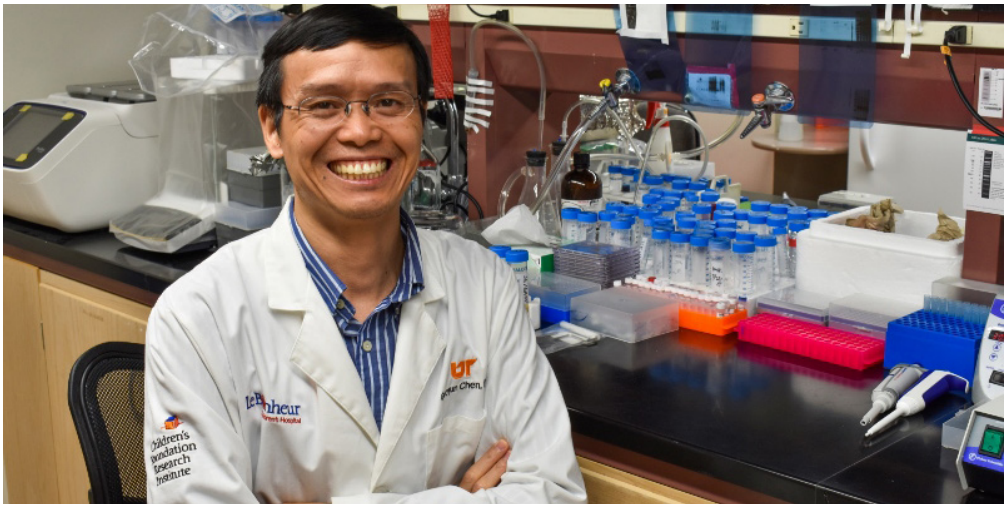
Chen receives R01 grant for sepsis treatment research



Guoyun Chen, PhD, MD

Guoyun Chen, PhD, MD, a basic scientist at the Children's Foundation Research Institute at Le Bonheur Children's Hospital and an associate professor of Pediatric Research at the University of Tennessee Health Science Center (UTHSC), has been awarded a $2.26 million R01 grant from the National Institute of Allergy and Infectious Diseases to continue researching new ways to treat sepsis, a potentially deadly immune response to infection.

In his project titled "The molecular mechanism of Siglec-E in bacterial clearance," Chen is building on prior work investigating key interactions at the molecular level that may help inhibit bacterial sepsis progression.

"Sepsis is still one of the leading causes of death worldwide," said Chen. "Effective therapies for sepsis could help to reduce its associated mortality and improve outcomes of patients with severe sepsis."

Most cases of septic shock are caused by a type of bacteria known as Gram-negative bacteria, the most common being E. coli. In other research studies, Chen and his research team previously discovered that special immune system receptors called Siglecs played a key role in the progression of sepsis. They found lack of Siglec-E increased mortality in organisms infected with Gram-negative bacteria. This heightened susceptibility correlated with impaired bacterial clearance, suggesting Siglec-E helps control the immune response against Gram-negative bacteria.

In this newly funded study, the Chen lab will now work to discover how Siglec-E helps in clearing bacterial infections. His team will investigate how Siglec-E differently regulates the immune response during infections by Gram-positive and Gram-negative bacteria.

By achieving these goals, the team hopes to uncover new ways to treat sepsis and improve outcomes for patients affected by this life-threatening condition.

THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

Le Bonheur Children's Hospital

Le Bonheur enrolls first patient in US for VALOR clinical trial

Principal Investigator Jeffrey A. Towbin, MD, co-executive director of Le Bonheur's Heart Institute, and Kathryn Sherman, BSN, RN, clinical research coordinator, enrolled the first patient in the United States in the VALOR clinical trial.

Jeffrey A. Towbin, MD, principal investigator for the VALOR clinical trial

This trial is a phase 2/3, randomized, placebo-controlled, double-blind, clinical study to evaluate the efficacy, safety and pharmacokinetics of vericiguat in pediatric participants with heart failure due to systemic left ventricular systolic dysfunction. This condition is a specific cause of heart failure where the function of the pumping action of the left ventricle of the heart is reduced.

Vericiguat is approved by the U.S. Food and Drug Administration (FDA) for heart failure in adults. This study will help determine if vericiguat can be safely given to infants, children and teenagers with systemic left ventricular systolic dysfunction and see if it will improve their heart failure.

"The Heart Institute continues to be on the forefront of clinical, genetic and basic cardiovascular research and clinical trials focusing on heart failure in children," said Towbin. "We are proud to have been the first site to enroll a patient in this trial and look forward to what the results could mean for kids."

Heart failure in children is thought to have an incidence ranging from 0.87 to 7.4 children per 100,000 globally and, in the United States, heart failure-related hospitalizations occur in 11,000 to 14,000 children each year with an in-hospital rate of death as high as 7.4%. Pediatric cardiomyopathy patients have one- and five-year rates of death or transplantation of 31% and 46%, respectively.

Due to differences between children and adults, very few heart failure medications have been tested and approved for use in children. As a result, children have typically received the same treatments and medications that have been tested and approved by the FDA for adults without knowing if the risks and benefits are similar for children.

The majority of cardiovascular medications prescribed to children, in fact, have never been tested specifically for children. Studies like the VALOR clinical trial are important to add to the body of evidence to show which medications work best for children with heart failure.

The Le Bonheur Heart Institute, under Towbin's leadership, is on the forefront of understanding and treating children with heart failure and this trial is one of the many studies on heart failure and heart muscle disease with which the Heart Institute is involved.

Gipson initiates K23 study for early language in TSC

Tanjala Gipson, MD

Le Bonheur Pediatric Neurologist and Neurodevelopmental Disabilities Specialist Tanjala Gipson, MD, recently received a K23 grant from the National Institutes of Health (NIH) for her project "Early Communication in Tuberous Sclerosis Complex (TSC) and Its Prediction of Autism."

The objective of this project is to examine potential predictors of language outcome and autism spectrum disorder (ASD) severity in infants with TSC. Currently, despite the high risk of language difficulties and ASD in TSC, very little to no data are available about the origin and trajectory of language in TSC and how this might predict outcome. This project builds on previous research from Gipson that found deficits in early vocal development in most infants with TSC regardless of the diagnosis of ASD.

Gipson is now seeking participants for the "Baby Talk in Tuberous Sclerosis Complex" study, funded by the K23 grant. This study will examine the vocalizations (sounds) and early language of infants with TSC. Gipson's ultimate goal is to examine if early baby speech can help predict ASD severity or language problems.

Le Bonheur neonatologist awarded $2.5 million to study neonatal cerebral vascular disease pathology

Massroor Pourcyrous, MD

The National Institute of Neurological Disorders and Stroke has awarded $2.5 million to a research duo at Le Bonheur Children's Hospital and the University of Tennessee Health Science Center (UTHSC) for a project aimed at finding new ways to treat brain damage caused by lack of oxygen at birth. Le Bonheur Neonatologist Massroor Pourcyrous, MD, is co-investigator alongside principal investigator Helena Parfenova, PhD, professor in the Department of Physiology at UTHSC.

For more than 25 years, productive collaboration between Parfenova, a basic scientist, and Pourcyrous, a clinical scientist, has centered on prevention and treatment of cerebrovascular disease that occurs due to devastating neonatal brain disorders, including epilepsy and asphyxia. With this new award, the team will focus on novel mechanisms that could keep the brain and its blood vessels working properly in newborns when they experience prolonged asphyxiation.

Neonatal asphyxia is a leading cause of neurodevelopment issues. Early research suggests an enzyme called Nox4 is the main producer of harmful oxygen particles in the brain's blood vessels when a newborn does not get enough oxygen. On the other hand, H2S, a gas enzymatically produced by astrocytes, acts as an antioxidant, protecting cells from damage. Building on this knowledge, Parfenova and Pourcyrous are proposing a new form of neurovascular cell-directed therapy that combines selectively blocking the Nox4 enzyme while increasing the body's H2S-based antioxidant defenses.

"Nox4 selective inhibitor is available on market and is recognized as a clinically safe drug," said Pourcyrous. "The combination therapy may represent promising candidates for the development of a new drug for neonatal hypoxic ischemic encephalopathy."

Using a combination of complementary techniques, the team will seek answers to three specific questions: first, whether blocking Nox4 enzyme activity can protect the blood vessels in the brain from being damaged by asphyxia; second, whether boosting the body's natural H2S antioxidant system can protect astrocytes from damage resulting from asphyxia; and lastly, whether a combined neurovascular-targeted treatment using antioxidants that stop Nox4 and substances that increase H2S, supplemented by therapeutic hypothermia, can prevent cerebrovascular disease caused by prolonged neonatal asphyxia.

The research is unique in its combination of practical experiments on the whole brain's blood flow with an investigation of cellular and molecular details behind diseases of these blood vessels.

"Preventing neonatal cerebral vascular disease will help prevent neonatal encephalopathy and improve health of a new generation," Parfenova said. "This project may lead to the development of new relevant neurovascular-targeting treatments to fully protect the neonatal brain during asphyxia. Importantly, we collected sufficient preliminary data to support our hypothesis on neurovascular cell-directed combination therapy for neonatal cerebral vascular disease."

Apply for the CFRI Early Career Physician Scientist Development Grant

The CFRI Early Career Physician Scientist Development Program supports clinical and basic research at Le Bonheur Children's Hospital. The award will provide physician scientist recipients with a maximum 20% salary support to allow protected time for research. The program prioritizes research proposals from junior faculty members.

Junior faculty members at Le Bonheur with UTHSC faculty appointments who are also fewer than five years out of training and interested in pursuing pediatric research are eligible to apply. The applicant must propose an independent research project with a pediatric focus that they will undertake after receiving the award. Principal investigators can submit only one project for review. Investigators are limited to funding for no more than three consecutive years. No adult studies will be considered.

Grants provide salary support for protected time for one year of funding with a maximum of $30,000. Additionally, a maximum of $30,000 with appropriate justification may also be requested to support personnel costs, supplies and approved equipment.

Grants may be renewed twice, for a total of three years of funding by submitting a renewal application with a progress report and a budget report at the end of the first and second years. Renewal applications will be judged for additional funding based on progress made in the past year.

Applicants should complete the online CFRI Early Career Physician Scientist Development Program Grant application and include a cover letter that outlines his/her research career development plans and how the funding will facilitate these plans. Applicants will need to identify a faculty mentor who will supply a letter of support, as well as an NIH-style biosketch. Applicants may use these grant funds to supplement other funding sources if there is no budgetary overlap and the budget is well justified.

The deadline for applications is Oct. 31, 2024 at 5 p.m. For more information and to apply, visit lebonheur.org/research/physician-scientist-grant.

Risk-based program changing health care use, outcomes for children with high-risk asthma

Le Bonheur's risk-based innovation program Changing High-Risk Asthma in Memphis through Partnership (CHAMP) significantly decreased health care use related to asthma by targeting barriers to asthma care, according to research published in the *Annals of Allergy, Asthma & Immunology*.

Christie Michael, MD, medical director of the CHAMP program

After one year of enrollment in the program, results analyzing 945 children included a 48% reduction in Emergency Department (ED) visits, 68% reduction in inpatient and observation visits, 42% reduction in urgent care visits and 53% reduction in asthma exacerbations. Asthma exacerbations per patient significantly decreased from 2.97 to 1.4.

"Children in Shelby County, which includes the Memphis metro area, have disproportionally high asthma-related health care resource use compared with other regions in Tennessee," said Christie Michael, MD, Le Bonheur allergist/immunologist and medical director for the CHAMP program. "Our results show that taking down the walls of the clinic and going to where kids live, play and go to school has been a success."

The study analyzed data for children who had completed one full year of the program between January 2013 and Dec. 31, 2022. Of 1,348 children enrolled, 945 completed a full year of the program. The demographics of the participants were 63% male and 90% Black with a mean age of 6.8 years old.

The CHAMP program was developed with a goal of improving asthma care and reducing risk of exacerbation for patients with high-risk asthma, who have significantly increased morbidity and mortality and, consequently, higher use and cost of health care. High-risk asthma can be defined in a few ways, including asthma that causes higher health care use, is poorly controlled despite appropriate medical management or is controlled but requires the maximum medications available. The areas around Le Bonheur have the highest rate of ED visits and hospitalizations for asthma in the state, which is twice as high for kids with Medicaid compared to those with private insurance.

The CHAMP program evolved over time, getting a jumpstart from a Centers for Medicare & Medicaid Services (CMS) grant in 2012. Patients with high-risk asthma are eligible for the program if they are residents of Shelby County, aged 2-18 years and enrolled in Medicaid or TennCare. For the program, high-risk asthma means the patient has had one of the following: three or more asthma-related ED or urgent care visits in the previous year; two or more asthma-related hospitalizations in the previous year; any admission to the intensive care unit (ICU).

Some of the unique aspects of the program include:

- 24/7 CHAMP call line for guidance on care at home or if escalation to urgent care or ED is needed
- Dedicated medical team and clinic to provide coordination of care and proper asthma education
- Home visits from community health educators
- Respiratory therapist who communicates a child's asthma action plan with school nurses and primary care providers
- Asthma repository where providers can download claims data for TennCare patients to see all medical encounters and if prescriptions are filled

Community Health Educator Tammy Lewis (above left) meets a patient in her home to provide education and support.

The CHAMP program represents an innovative way to care for children with chronic disease that not only improves their outcomes but also could lower the cost of health care for each child. After a third-party evaluation of the CHAMP program following the original three-year grant period with the CMS, health care costs were reduced by $545 per child per quarter with a total reduction of $2,180 per year.

CHAMP seeks to change the standard for caring for these kids by addressing key factors that lead to high health care use and exacerbation of asthma. A dedicated medical care team works to provide the best outcomes for these children by working outside of the traditional paradigms of health care.

Contact us

If you have any research news or announcements you would like to include in an upcoming issue of *Research Matters*, please email research@lebonheur.org.