Le Bonheur Children's Hospital
Memphis, Tennessee

Pediatric Pulmonology

Winter 2015

CF researcher to study CFTR-related protein complex

$1.8 million NIH grant to fund study

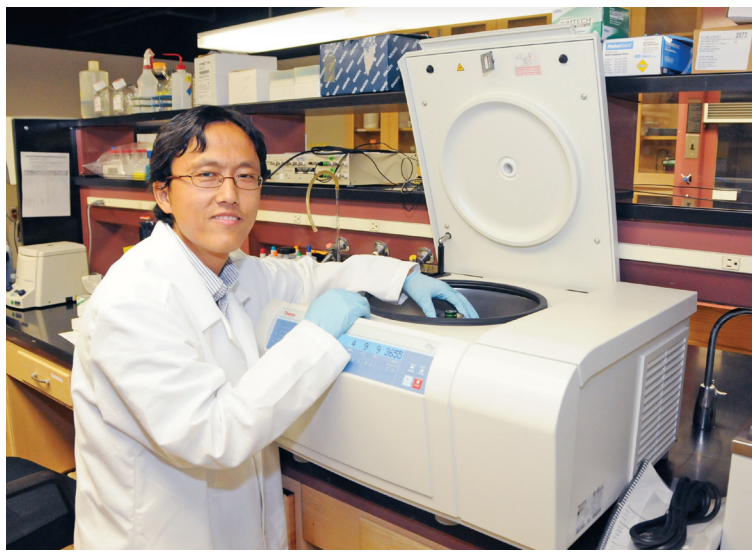
Researchers at Le Bonheur Children's Hospital and the University of Tennessee Health Science Center are studying the formation and regulation of a protein complex at the cell surface that inhibits CF transmembrane conductance regulator (CFTR).

A team led by Weiqiang Zhang, PhD, will use a $1.8 million grant from the National Heart, Lung and Blood Institute, a subsidiary of the National Institutes of Health, to study the protein complex.

CF is caused by the loss or dysfunction of CFTR, and F508del is the most common mutation in CF patients and associates with a severe form of CF disease.

"We know the formation of the complex protein can inhibit CFTR channel function and contributes to the disease severity," Zhang said.

Zhang's team will also identify novel reagents to target this complex to increase the channel function of the faulty F508del-CFTR protein, which have direct clinical relevance in mitigating or curing CF.



Weiqiang Zhang, PhD

The study is expected to help gain better understanding of the molecular mechanism underlying CF, expand knowledge of the CFTR protein network and pave the way to novel CF therapies. Researchers hope it might offer clinical relevance in combating other obstructive and inflammatory airway diseases such as asthma and chronic obstructive pulmonary disease (COPD).

"I am very excited about this award because it will enable us to continue our research on finding an optimal therapy, or even better, a cure for cystic fibrosis," Zhang said. "We also anticipate that the research will have clinical relevance in other obstructive airway diseases."

Cystic Fibrosis quality recognized

The Cystic Fibrosis Foundation recognized Le Bonheur Children's Hospital and the University of Tennessee Health Science Center with its Quality Care Award at the October North American Cystic Fibrosis meeting held in Atlanta.

The pediatric CF care team received the Quality Care Award for outstanding quality improvement processes after a site visit performed last year and specifically recognized the care team's accomplishment in reducing insufficient sweat test collection rates. Sweat testing is the standard way that a diagnosis of cystic fibrosis is made, and inadequate sweat collection for analysis can delay diagnosis and increase anxiety for families.

The multidisciplinary team's goal was to reduce quantity not sufficient (QNS) rates to less than 5 percent for children older than 3 months. The baseline rate was 6.15. The team improved rates by 84 percent for children older than 3 months and by 88 percent for those younger than 3 months, by tracking key measures, evaluating cause and effect and documenting the process. The team also developed a reporting mechanism to follow rates and identify when rates begin to deviate from the 5 percent goal.

Currently, the overall rate for the past 12 months is 3.68, and the rate for children older than 3 months is 2.17.

"We have a great CF care team here at Le Bonheur, with outstanding nurses, social work, PT, RT, and dietitians. This project also involved a team from the Clinical Laboratory, headed by Gina Guasco, working together with the CF care team," said Chief of Pulmonology Dennis Stokes, MD, MPH.

Referrals: 866-870-5570
www.lebonheur.org/pulmonology

A pediatric partner with The University of Tennessee Health Science Center/College of Medicine and St. Jude Children's Research Hospital

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High-risk asthma program leads to decreased hospital visits, health care costs

Avoidable asthma-related hospitalizations and Emergency Department visits are down for children enrolled in a Le Bonheur program aimed at improving quality of life and lowering health care costs. In 2013, Le Bonheur launched CHAMP, or Changing High-Risk Asthma in Memphis through Partnership, with a $2.9 million Health Care Innovation Award from the Centers for Medicare and Medicaid (CMS).

Asthma-related symptoms is the hospital's No. 1 diagnosis and accounts for 3,500 visits each year. Shelby County has the highest Emergency Department utilization and hospitalization for asthma in the state of Tennessee.

CHAMP is designed for children with asthma at greatest risk: those between ages 2-18 who had two or more hospital admissions, one Intensive Care Unit admission or two Emergency Department/Urgent Care visits in the past year. All must be enrolled in TennCare, Tennessee's Medicaid program.

In addition to a medical team, families work with a team of community health workers, asthma care educators and social workers who support families in their homes and communities. The team provides environmental interventions, reinforces asthma education and helps navigate psycho-social issues.

More than 400 children are enrolled in the program. Emergency Department and inpatient visits have significantly reduced, and the program estimates a cost saving of more than $4 million by June 2015.

Read more about CHAMP at lebonheur.org/promise.

Dennis Stokes, MD, MPH

Dennis Stokes, MD, MPH, is chief of Pulmonology and St. Jude Professor at The University of Tennessee Health Science Center (UTHSC). He is also center director of the UT CF Care and Research Center and director of pulmonology services at St. Jude Children's Research Hospital.

Stokes graduated from the University of Kentucky, completed a pediatrics residency at the Johns Hopkins Hospital, and a pulmonology fellowship at Boston Children's Hospital/ Harvard University School of Medicine. He holds a Masters of Public Health degree from Indiana University and is board certified in pediatrics and pediatric pulmonology. Stokes' patient care emphases include asthma, cystic fibrosis, and pulmonary infections in the immunocompromised host.

Tonia Gardner, MD, MS

Tonia Gardner, MD, MS, is an assistant professor at UTHSC. She is board certified in pediatrics with a subspecialty in pediatric pulmonology and internal medicince. Gardner graduated from Medical College of Wisconsin and received a Masters of Science in Clinical Research from Indiana Purdue University. She completed fellowships in pediatric pulmonology and pediatric clinical pharmacology. Her clinical interests are Cystic Fibrosis patient care and improving the transition of those patients to the adult world. Her research interest is personalized medicine for pulmonary patients – using genetics to predict benefit vs. toxicity of medications in individual patients.

Brent Haberman, MD

Pulmonologist Brent Haberman, MD, is an assistant professor at UTHSC. He is board certified in pediatrics with a subspecialty in pediatric pulmonology and is board eligible in sleep medicine. Haberman graduated from Saint Louis University College of Medicine. He completed a pediatrics residency at Le Bonheur and a fellowship in pediatric pulmonology at Baylor College of Medicine. His clinical interests include pulmonary complications of neuromuscular disorders, cystic fibrosis and pediatric sleep disorders.

Robert Schoumacher, MD

Robert Schoumacher, MD, is a professor at UTHSC and director of Le Bonheur's Pediatric and Adolescent Sleep Center. He is board certified in sleep medicine and in pediatrics with a pediatric pulmonology subspecialty. Schoumacher attended Vanderbilt University School of Medicine, pediatrics residency at the University of Virginia, and fellowship training at the University of Alabama at Birmingham. He has special interests in pediatric sleep medicine, home ventilation and cystic fibrosis.

Saumini Srinivasan, MD, MS

Saumini Srinivasan, MD, MS, is an assistant professor at UTHSC and associate director of the UT CF Care and Research Center. She completed her medical degree at the University of Delhi in India and completed her pediatric residency at UCLA Children's Hospital. She earned her fellowship in pediatric pulmonology at the Children's Hospital of Los Angeles/University of Southern California. She is board certified in pediatrics with a subspecialty in pediatric pulmonology. Her clinical interests include cystic fibrosis, exercise physiology and clinical exercise testing and pediatric sleep disorders.

James Tutor, MD

James Tutor, MD, is a professor at UTHSC and medical director of the Infant Pulmonary Function Laboratory at Le Bonheur. He completed medical school and residency at the University of Mississippi and pulmonology fellowship at Tulane. He is board certified in pediatrics with a subspecialty in pediatric pulmonology. Tutor's clinical interests include infant pulmonary function testing, aspiration disorders, cystic fibrosis and sleep disorders.

Published research 2014

Oancea SC, Gurney JG, Ness KK, Ojha RP, Tyc VL, Klosky JL, Srivastava D, Stokes DC, Robison LL, Hudson MM, Green DM. Cigarette smoking and pulmonary function in adult survivors of childhood cancer exposed to pulmonary-toxic therapy: results from the St. Jude lifetime cohort study. *Cancer Epidemiol Biomarkers Prev*. 2014 Sep;23(9):1938-43. doi: 10.1158/1055-9965.EPI-14-0266. Epub 2014 Jun 17.

Denbo JW, Zhu L, Srivastava D, Stokes DC, Srinivasan S, Hudson MM, Ness KK, Robison LL, Neel M, Rao B, Navid F, Davidoff AM, Green DM. Long-term pulmonary function after metastasectomy for childhood osteosarcoma: a report from the St. Jude lifetime cohort study. *J Am Coll Surg*. 2014 Aug;219(2):265-71. doi: 10.1016/j.jamcollsurg.2013.12.064. Epub 2014 Mar 4.

Tutor JD. Chylothorax in infants and children. *Pediatrics*. 2014 Apr;133(4):722-33. doi: 10.1542/peds.2013-2072. Epub 2014 Mar 31.

Arora K, Moon C, Zhang W, Yarlagadda S, Penmatsa H, Ren A, Chandrima S, Naren AP. Stabilizing rescued surface-localized ΔF508 CFTR by potentiation of its interaction with Na+/H+ exchanger regulatory factor 1. *Biochemistry*. 2014; 53:4169-4179.

Current Research Grants

CF-Fibrosing Colonopathy: *A 10 year Prospective Observational Study of the Incidence of and Risk Factors for Fibrosing Colonopathy in US Patients with Cystic Fibrosis* – AbbVie/ Aptalis/Janssen, CF-TDNCC, 2012-present, Saumini Srinivasan

CAT-Gilead - *A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Aztreonam for Inhalation Solution (AZLI) in a Continuous Alternating Therapy (CAT) Regimen of Inhaled Antibiotics for the Treatment of Chronic Pulmonary Pseudomonas aeruginosa Infection in Subjects with Cystic Fibrosis [Protocol GS-US-205-0170]*, Gilead Sciences, Inc. - 2013 –2014 – Saumini Srinivasan

EPIC OBS years 11-15: The EPIC Observational Study: Longitudinal Assessment of Risk Factors For and Impact of *Pseudomonas aeruginosa* Acquisition and Early Anti-Pseudomonal Treatment in Children with CF, CFFT Therapeutics Development Network Coordinating Center, 2014 - Robert A. Schoumacher

KB001A-05 - *A Phase 2, Randomized, Double-blind, Placebo-controlled, Repeat-dose Study of KB001-A in Subjects with Cystic Fibrosis Infected with Pseudomonas aeruginosa [Protocol KB001A-05]*, KaloBios Pharmaceuticals, Inc., 2013 - Present, Dennis C. Stokes

Optimize/NIH -Pa 1st culture – OPTIMIZing Treatment for Early *Pseudomonas aeruginosa* Infection in Cystic Fibrosis: The OPTIMIZE Multicenter, Placebo-Controlled, Randomized Trial, NIH/NHLBI, 2013 –present – Saumini Srinivasan

Vertex 809-104 – *A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination with Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation* – Vertex Pharmaceutical Inc., 2013 – 2014 - Dennis C. Stokes

Vertex 809-105 – *A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation* – Vertex Pharmaceutical Inc., 2013 – present - Dennis C. Stokes

Vertex - VX13-661-103 - A Phase 2, Randomized, Multicenter, Double Blind, Placebo Controlled Study to Evaluate Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of VX661 in Combination with Ivacaftor for 12◦Weeks in Subjects with Cystic Fibrosis, Homozygous for the *F508delCFTR* Mutation, Vertex Pharmaceutical Inc., 2014 – Dennis C. Stokes