



Uncovering basal ganglia changes in TSC with DTI

Self-injurious behavior (SIB) occurs in 10-41% of individuals with tuberous sclerosis complex (TSC). SIB can result in tissue damage or loss and has no cure. Although the pathophysiology of SIB is unknown, abnormalities in the basal ganglia are associated with features of TSC. Given this association, Tanjala Gipson, MD, and colleagues used magnetic resonance imaging and diffusion tensor imaging



(DTI) to identify a relationship between basal ganglia changes and SIB. The authors compared DTI findings between children with TSC and SIB and those with TSC without SIB.

Children with TSC and SIB exhibited significant volume reductions in the bilateral globus pallidus and caudate nucleus. Moreover, fractional anisotropy was significantly lower in the bilateral globus pallidus and left caudate in these children. Based on these findings, DTI is a potential biomarker for SIB in TSC. In the future, treatments targeting the basal ganglia may provide relief from SIB.

T.T. Gipson, A. Poretti, S.A. Kelley, K.A. Carson, M.V. Johnston, and T.A.G.M. Huisman. Characterization of the basal ganglia using diffusion tensor imaging in children with self-injurious behavior and tuberous sclerosis complex, Journal of Neuroimaging, Volume 29, May 2019, Pages 506-511, <https://doi.org/10.1111/jon.12628>

Bagga receives award for RSV research



Bindiya Bagga, MD, received the Caroline B. Hall Clinically Innovative Research Award for the manuscript "Unrecognized prolonged viral replication in the pathogenesis of human RSV infection" in *Journal of Clinical Virology*. This award is presented annually to a junior researcher who is a first author on a manuscript that best illustrates Dr. Caroline B. Hall's innovative approach to clinical research.

RSV respiratory symptoms continue long after the virus is no longer detected in culture. Bagga, DeVincenzo, and colleagues hypothesized that prolonged undetected RSV replication is responsible for these symptoms. Thus, the authors examined RSV replication in healthy adult volunteers inoculated with the Memphis 37 strain of RSV-A. RSV was absent in culture 5-6 days after infection. However, qPCR detected RSV an average of 8.9 days after infection. These findings provide a potential explanation for the extended manifestation of RSV respiratory symptoms. The results also indicate a wider window of opportunity for amelioration of clinical disease.

B. Bagga, L. Harrison, P. Roddam, and J.P. DeVincenzo. Unrecognized Prolonged Viral Replication in the Pathogenesis of Human RSV Infection, Journal of Clinical Virology, Volume 106, September 2018, Pages 1-6, <https://doi.org/10.1016/j.jcv.2018.06.014>

New faces in the CFRI



Courtney Bricker-Anthony, PhD, joins the CFRI as scientific editor. During her graduate education at Vanderbilt University, she had experience in scientific editing and writing in neuroscience, ophthalmology and biomedical research. Prior to joining the CFRI, she was an academic editor, editing scientific manuscripts, abstracts, presentations and grants in the areas of basic research and clinical medicine.



Cem Akkus, PhD, MS, MPH, joins the CFRI as biomedical informatics research specialist. He has more than 10 years of experience in geographical information systems (GIS). Recent work includes spatial analyses for childhood lead poisoning in Shelby County and GIS-based website development for Memphis FitKids, which focuses on reducing childhood obesity. In 2018, he served as a think tank member at the American Journal of Public Health to improve the journal's social media outreach.



Victoria Vance, BSN, RN, joins the CFRI as clinical research nurse coordinator. Previously, she was a nurse on Le Bonheur's pulmonology floor. During her undergraduate education, she worked in a toxicology lab and published work in scientific journals. She has a bachelor's in psychology from Mississippi State University and a bachelor's in nursing from Union University.



Manasa Mallampaty, MS, joins the CFRI as biomedical informatics research specialist. She has a master's in computer science from the University of Central Missouri, is an SAS certified base programmer for SAS9 and an expert in software, data storage and translational science technologies. Prior to joining the CFRI, she was a data scientist at the University of Mississippi Medical Center responsible for complex data analysis, management and reporting support for several NHLBI-funded projects.



Lauren Davis, BS, joins the CFRI as clinical research coordinator. She has a bachelor's in biology from Southeastern Louisiana University. As a research associate at Louisiana State University Health Sciences Center, she managed a biorepository for patients with nontuberculous mycobacteria (NTM) pulmonary disease and developed a support group for patients and families.

139 abstracts presented at Pediatric Research Day 2019



The theme of this year's Pediatric Research Day was gastroenterology. Richard Weinberg, MD, began the day with a lecture on individuals who made groundbreaking discoveries by challenging previous assumptions and persevering despite criticism. The day's sessions were comprised of talks by faculty, clinical fellows, research staff members, postdoctoral fellows, clinical residents and graduate students.

Topics ranged from potential therapeutic targets in Hirschsprung's disease to the influence of the microbiome on health and disease. 139 abstracts were submitted, with a record-breaking 37 abstracts submitted by medical students. The day concluded with awards given to the best poster presentations. Pediatric Research Day displayed a wide variety of studies from our researchers working to make breakthroughs in pediatric diseases.



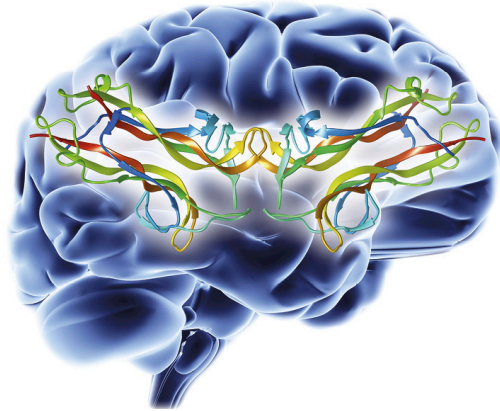
Publicize your research, grants and awards

We are always interested in highlighting the work of our researchers. If you have recently published a manuscript, obtained grant funding or received an award, please contact Haley Overcast at haley.overcast@lebonheur.org. Not only can we feature your work in Research Matters, but Le Bonheur's PR and Marketing departments can help spread your accomplishments and research to a wider audience.

BDNF: A potential target for pain relief

Brain-derived neurotrophic factor (BDNF) plays a critical role in pain sensitivity and may provide novel approaches to pain management. In collaboration with colleagues at the NIH, Joan Han, MD, and Jack Tsao, MD, PhD, examined the role of BDNF in pain sensitivity in individuals with Wilms tumor, aniridia, genitourinary anomaly, range of intellectual disabilities (WAGR) with or without heterozygous deletion of the *Bdnf* gene as well as heterozygous *Bdnf* knockout rats. Given BDNF's known role in pain, the authors hypothesized that *Bdnf* haploinsufficiency would alter pain sensitivity in rats and human subjects with WAGR.

Among participants with WAGR, those with BDNF haploinsufficiency were more likely to exhibit pain insensitivity than those without haploinsufficiency, as indicated by parental reports and quantitative sensory testing. Among the subset of genes that differentiates subjects with WAGR with BDNF haploinsufficiency from those without,



BDNF was more highly enriched in pain circuit regions than in other regions of the human body. Consistent with findings in human subjects, heterozygous *Bdnf* knockout rats exhibited reduced thermal nociception. Both WAGR subjects with BDNF haploinsufficiency and heterozygous *Bdnf* knockout rats responded to markedly strong stimulation, indicating a blunted response to aversive stimuli. Overall, these findings suggest that the complex trait of pain sensitivity is modulated by a large gene network that may encompass BDNF, which has broad implications for novel analgesic approaches.

M.R. Sapio, M.J. Iadarola, D.M. LaPaglia, T. Lehky, A.E. Thurm, K.M. Danley, S.R. Fuhr, M.D. Lee, A.E. Huey, S.J. Sharp, J.W. Tsao,

J.A. Yanovski, A.J. Mannes, and J.C. Han. Haploinsufficiency of the brain-derived neurotrophic factor (BDNF) gene is associated with reduced pain sensitivity, Pain, Volume 160(5), May 2019, Pages 1070-1081, <https://doi.org/10.1097/j.pain.0000000000001485>

IN BRIEF

Department of Pediatrics receives high marks on UTHSC lab safety report



As required by the National Institutes of Health and governmental regulatory agencies, the UTHSC Office of Research Safety Affairs conducts an annual risk-based laboratory inspection consistent with *RS003 – Laboratory Safety Inspections*. The senior laboratory safety specialist and the institutional biosafety officer perform this inspection. Higher inspection scores indicate the overall commitment to research safety and compliance on campus.

The Department of Pediatrics received a high average inspection score of 98 and a rating of “guarded” (general risk) with only one repeat finding originally identified in the 2017-18 inspection. Pediatrics had the highest number of principal investigators with outstanding performance on their annual inspections.

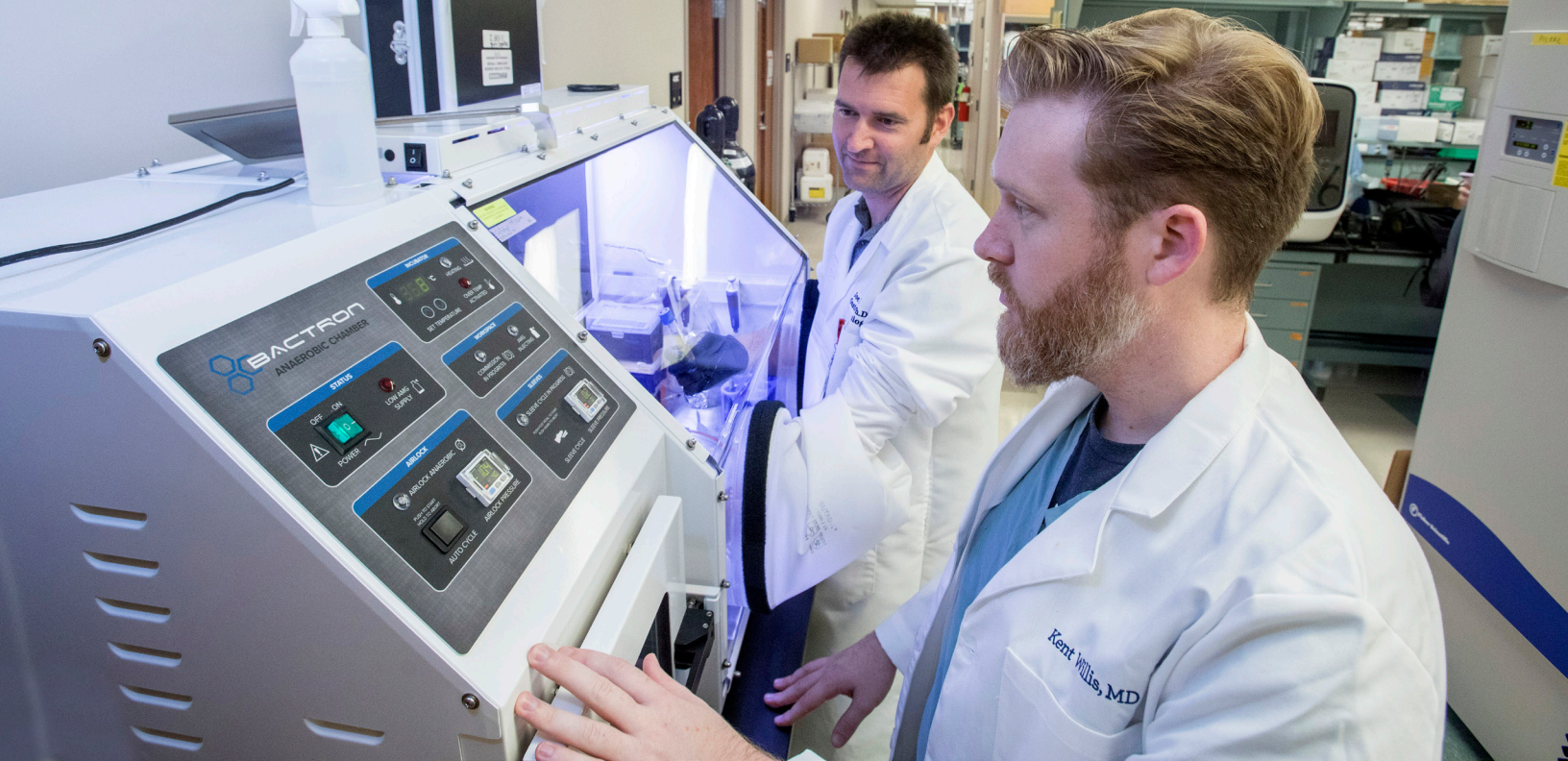
CFRI acknowledgments reminder

Please remember to include the Children's Foundation Research Institute (CFRI) in your acknowledgments when you publish a manuscript or give a presentation. This helps raise the profile of our institution in national and international research communities. Additionally, mentioning CFRI in your acknowledgments will help us promote your work to a wider audience, including donors who support research. Please see the list of accepted spelling and corresponding abbreviations for all associated organizations below:

- Le Bonheur Children's Hospital: LBCH
- Le Bonheur Children's Hospital Foundation: LBCHF
- Children's Foundation Research Center: CFRC

Scientific editing available in the CFRI

The scientific editor, Courtney Bricker-Anthony, assists in all stages of manuscript development, including drafts, figures, editing and proofing. During the submission process, she will aid in obtaining co-author permissions and meeting publication requirements. Once manuscripts return from review, she can help address reviewer comments and participate in the preparation and submission of revised manuscripts. Editing services are also available for abstracts, presentations, posters and grants. In addition, the scientific editor serves as a resource on scientific writing through lectures and written materials. To take advantage of these services, please contact Courtney Bricker-Anthony at courtney.bricker-anthony@lebonheur.org.



Early answers

Study analyzes how gestational age influences gut microbiome

Microbial DNA is present in the gut of developing fetuses and differs by gestational age at birth, according to a study published in the November print issue of *The FASEB Journal*. Using advanced culture and DNA sequencing techniques, researchers at Le Bonheur Children's Hospital/University of Tennessee Health Science Center analyzed samples of meconium to explore neonatal gut microbial communities.

"For the last hundred years, scientists have believed that the human fetus developed, protected from the outside world, in a womb that – unless something went terribly wrong – remained sterile and completely isolated from the host of bacteria, fungi and viruses that waited to make us sick when we emerged into the outside world," said lead author Kent Willis, MD. "This belief was largely based on the fact that it was very difficult to grow cultures of live microorganisms from this part of the body."

Recent studies have challenged that theory, and scientists are learning more about the early colonization of microorganisms inside the womb.

Willis's team collected meconium samples from both very low birth weight preterm and term-born infants to study how gestational age affects a newborn's microbial DNA. Factors considered in data collection included prenatal and postnatal antibiotic exposure, prenatal steroid exposure, delivery mode and illness severity. Researchers characterized microbial findings using both culture-independent and culture-dependent techniques.

"We found that the largest determinant of the amount and type of fungi detected is the infant's gestational age at birth," said senior author Joseph F. Pierre, PhD. "This suggests that the fungal DNA we detected is not the result of random

contamination of the uterus or colonization following birth, but rather is highly associated with the age at which the infant leaves the womb."

Understanding the order and timing in which microorganisms colonize the intestines is important, the researchers say, because therapeutic interventions, like perinatal antibiotics, may affect the gut's mature microbiome at birth and play a crucial role in disease development.

For instance, findings showed that preterm birth was highly correlated to the presence of *Candida*, a potentially pathogenic type of fungi.

"This suggests that, unlike the majority of the fungi we studied, these fungi might contribute to the disease process of preterm birth," said Willis.

In recent years, the gut's microbiome has received substantial attention as scientists discover more about the role it plays in an individual's health. Studies have linked diversity of gut bacteria and fungi to everything from food allergies and obesity to cancer and mental health.

The UTHSC team is continuing to follow study participants to determine whether the meconium samples, or additional samples collected in the weeks following, are correlated with later disease risk and growth parameters.

K.A. Willis, J.H. Purvis, E.D. Myers, M.M. Aziz, I. Karabayir, C.K. Gomes, B.M. Peters, O. Akbilgic, A.J. Talati, and J.F. Pierre. Fungi form interkingdom microbial communities in the primordial human gut that develop with gestational age, The FASEB Journal, In Press, August 2019, <https://doi.org/10.1096/fj.201802655RR>