

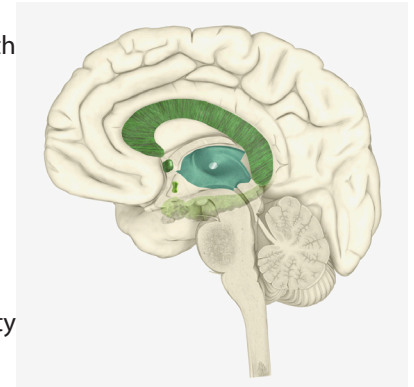


Epigenetic Editing Repairs Connections in a Developing Brain Model

Endocrinologist Joan C. Han, MD, and researchers at several universities and the National Institutes of Health (NIH) explored whether genetic tools could be used to repair the corpus callosum, the structure connecting the two hemispheres of the brain. When development of the corpus callosum is abnormal, results include disorders such as schizophrenia, intellectual disability and autism spectrum disorder.

Since genetic mutations may contribute to abnormal development of the corpus callosum, the researchers focused on a gene associated with intellectual disability (C11orf46) to see if mutations in this gene were also associated with changes in the corpus callosum.

Examined by MRI, the corpus callosum was significantly smaller in patients with only one normal copy of C11orf46 than in those with two normal copies.



The researchers blocked C11orf46 expression in developing mice to determine if it would change the developing corpus callosum. Following knockdown of C11orf46, axons, which enable communication between neurons and form the corpus callosum, failed to make connections between the two hemispheres of the brain. These changes also reduced the size of the corpus callosum in mice, similar to the MRI findings in humans.

Loss of C11orf46 increased the expression of Sema6a, a gene that regulates axon development. When Han and colleagues used epigenetic editing (a tool that adjusts gene expression without mutating DNA) to lower Sema6a expression to normal levels, the ability of axons to form the corpus callosum and connect the two hemispheres was restored, despite the absence of C11orf46. These findings indicate the possibility for early intervention in neurodevelopmental disorders.

Peter CJ, Saito A, Hasegawa Y, et al. In vivo epigenetic editing of Sema6a promoter reverses transcallosal dysconnectivity caused by C11orf46/Arl14ep risk gene. Nat Commun. 2019;10(1):4112. Published 2019 Sep 11. doi:10.1038/s41467-019-12013-y

CFRI Spotlight: Regulatory and Compliance



Kerry Moore

CFRI staff specializing in the IRB and compliance in research are available to help with the process of applying for IRB approval and maintaining compliance. Research Regulatory and Compliance Manager Kerry Moore answered questions about the typical situations investigators encounter and how to successfully establish a study.

What should researchers know about regulatory and compliance?

We provide resources to help all researchers. Ask questions – none of our investigators know all of the regulations when they start, and CFRI regulatory staff can walk you through it. Submitting a study to the IRB can appear very complicated, but we break it down and walk you through the IRB submission process.

What resources are available to investigators?

When starting a new study, we have two IRB research coordinators, Ashley Thompson and Celine Wu, who can assist with your IRB submission including iMedRIS (IRB submission software) and various forms decreasing your approval study start time.

What specific processes do you assist with?

We focus on the IRB including consent issues, protocol deviations, significant adverse

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Recent Awards and Honors



Gastroenterologist Dennis Black, MD, received the 2020 American Gastroenterological Association Institute Council Obesity, Metabolism & Nutrition Section Research Mentor Award for outstanding contributions to the mentoring and training of new investigators.



Pediatric Surgeon **Ankush Gosain, MD, PhD, FACS, FAAP**, won the 2019-2020 Mid-Career Award from the Society of University Surgeons.



Pediatric Surgeon **Eunice Huang, MD**, was recently awarded the 2020 American Surgical Association (ASA) Surgical Leaders Fellowship Grant in partnership with the Association of Women Surgeons (AWS).



Neurosurgeon **Paul Klimo Jr, MD, MPH**, won Pediatrics Paper of the Year, awarded by the Congress of Neurological Surgeons, for "The Preventable Shunt Revision Rate: A Multicenter Evaluation," published in *Neurosurgery* in March 2019.



Neonatologist **Ajay Talati, MD**, received the 2020 Founders Award from the Southern Society for Pediatric Research (SSPR) during the Society's annual meeting for his significant contributions to the health care of children and the activities of the SSPR.



Neonatologist **Kent Willis, MD**, published an article titled "Perinatal Maternal Antibiotic Exposure Augments Lung Injury in Offspring in Experimental Bronchopulmonary Dysplasia" in *American Journal of Physiology Lung Cellular and Molecular Physiology*. This article was chosen as the American Physiological Society's Select Article for December 2019 and was the subject of two editorials.

An Allergy Treatment



Allergist/Immunologist Jay Lieberman, MD, right

A first-of-its-kind peanut oral immunotherapy, Palforzia (AR101), was recently approved by the Food and Drug Administration (FDA). Le Bonheur was one site in the trial that brought this drug to market, providing a viable treatment for children who have lived years with a peanut allergy.

In this study, peanut allergic patients were given small amounts of peanut protein in the form of a powder. The powder was increased every two weeks until they were eating approximately one peanut's worth. Participants with an allergic response were randomly assigned to receive AR 101, the investigational biologic oral immunotherapy drug (up to 300 mg of peanut protein), or a placebo.

Other therapies being investigated beyond oral immunotherapy include patch immunotherapy, modified allergen therapies and adding a biologic medicine to one of the immunotherapies to improve efficacy or safety.

"There's a lot on the horizon, and it's a good time to be a part of the food allergy community. For so long we haven't had anything to treat these patients, and hopefully soon we'll have more than one option," notes Le Bonheur Allergist/Immunologist Jay Lieberman, MD.

Previously, the only recommended treatment was avoidance first and emergency therapy second, specifically in the form of epinephrine, if a reaction occurred.

It is estimated that 1-2 percent of the population in the United States is peanut allergic with higher numbers in children and adolescents. No known root cause has been identified for peanut allergies, but Lieberman explains there is no single cause — it is a multifactorial disease.

"There's a genetic component, an environmental component and possibly a component of when these foods are introduced into the diet that can play a role into why some kids get peanut allergy and others don't," he explains.

One theory is the hygiene hypothesis. As society becomes more hygienic and has less infectious disease, whether parasitic or bacterial, immune systems may shift to develop more allergies in general, not just peanut allergy. Delayed introduction of peanuts into a child's diet may also play a part.

"Studies have shown that allergic disease in general, meaning developing allergic antibodies to things like dust mites or peanuts, may be more apt to happen in patients who are not exposed to certain infectious agents early on," adds Lieberman.

Thanks to Palforzia, allergists/immunologists like Lieberman now have a proven treatment that they can provide to their peanut allergic patients.

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events or significant medical events during a study. Contact us so we can help you document these events appropriately. We're also here to help make sure everyone is audit ready as the IRB can audit a study at any time.

If I'm a new investigator and I want to start a study at Le Bonheur, what's the first thing I need to do?

Once you have met with your advisor(s) and have a proposal, we can meet to start the new study application. We develop questions and give you what we need to accomplish, including meeting with your advisor(s) or our business manager to look at the study budget. Then, we can meet again and finish the submission and route it to everyone on the protocol for signatures.

What happens if I want to do a full-board study?

You will present the study to the Clinical Trials Advisory Committee (CTAC) at Le Bonheur and then to the IRB at UTHSC. CTAC is led by Dr. Black and includes physicians who are experienced researchers who help with all aspects of study design. CFRI Finance Director Chris Smith and Biostatistics Core Director Tamekia Jones, PhD, and myself are brought in for regulatory support. We try to help you look at the study from all perspectives and give you feedback to help you prepare before going to the IRB. We can see pitfalls that you may not have thought about as a new researcher.

How do I ensure a smooth study?

Investigators who take the time to meet with a regulatory specialist who will answer the initial questions begin a smooth study process. If we're contacted by an investigator who has a new study idea, we will send out a very short survey with questions that go on an IRB application. If we can get some information and help with the application, we can help

prevent inconsistencies, which are common errors we see. If investigators will sit down with us, fill out the form, and let us help guide the process, studies often get approved faster.

What pitfalls do you commonly see?

We see studies automatically deferred by the IRB when the data collection forms are not submitted. People often forget to attach these forms, and this means they have to start over and go back through the review process. Unfortunately, we see this error fairly frequently. We could catch it really easily because it's one of the first things we look for.

Once a study is up and running, how are you involved?

Our department gets all of the outcome letters from the IRB for every open study at Le Bonheur. If it's time for the annual continuing review, you get automatic notices via email. Once you get to 20 days, we will step in and send reminders. If we see you're making changes to your study, we will go into the database and check for discrepancies and email you to offer our help. We are always behind the scenes watching communication from the IRB.

What happens when a researcher is ready to end a study?

When everything is done, you have to complete a closeout report with the IRB. We can help you with the closeout report and make sure it's done appropriately. One of the big mistakes I see is that investigators don't do the annual continuing review, and the IRB will change the study to an expired status. Ideally, that's not the way you want to close a study. You want to do a true closeout report because it will show as a completed study.

Is there anything else you would like researchers to know?

Call us. We are here to help. If investigators are too busy to come here, we can go to you. We're happy to do what we can to use your time effectively.

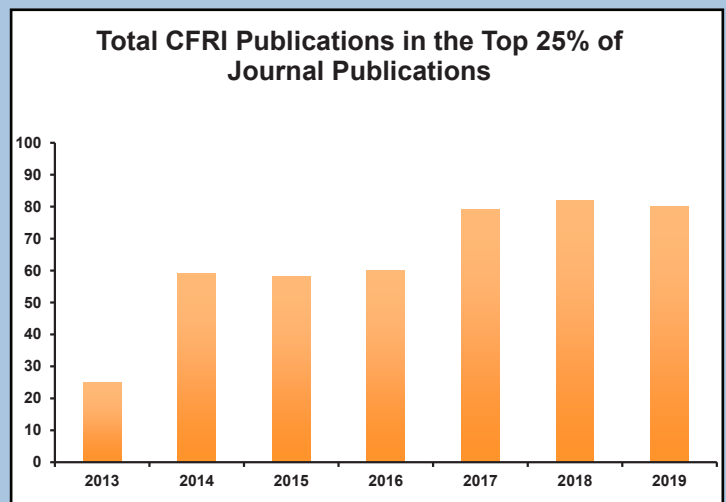
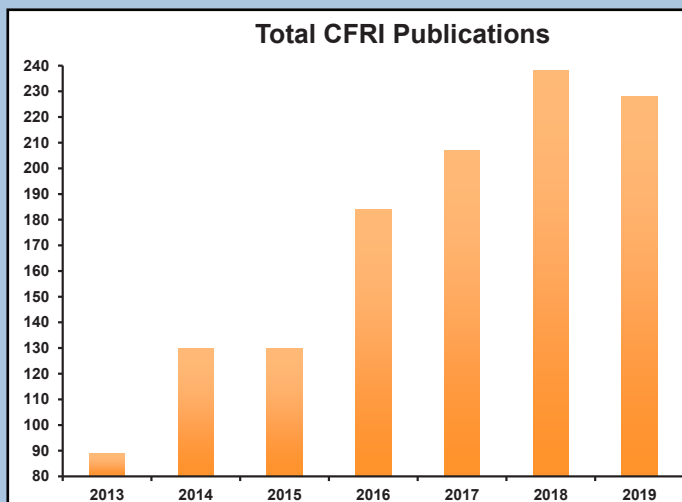
Register Your Clinical Trial

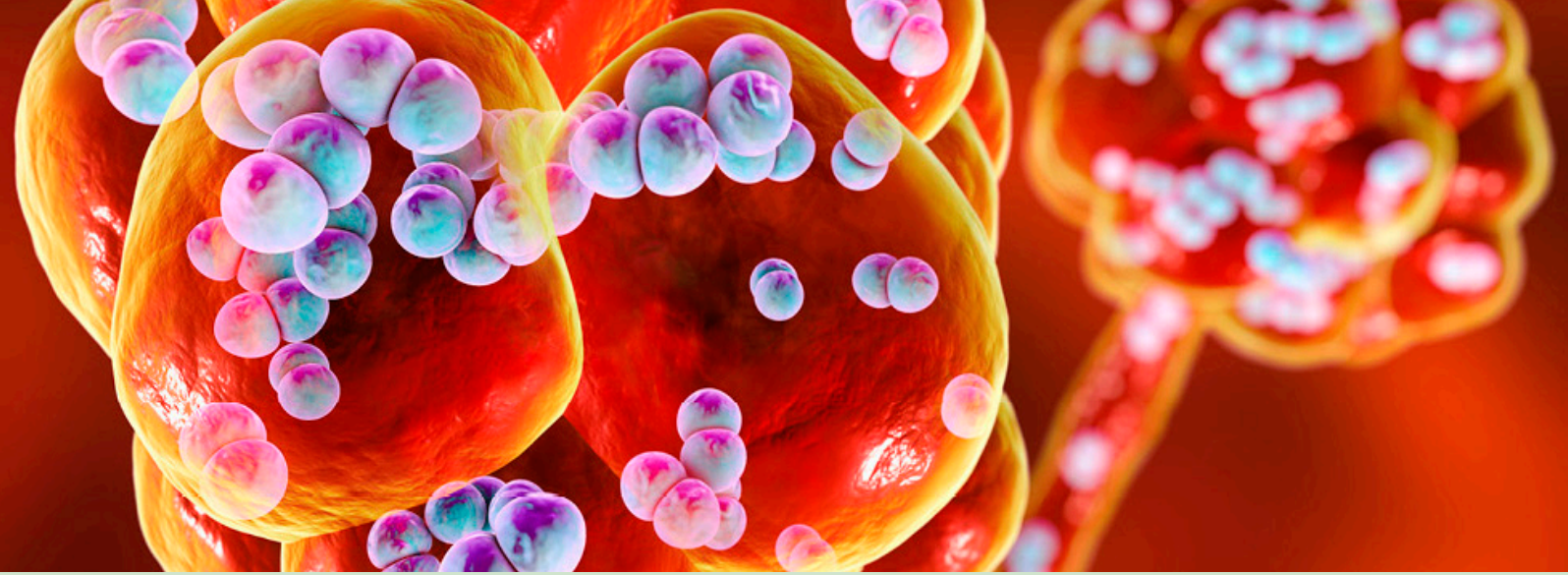
IN BRIEF

All clinical trials must be registered at clinicaltrials.gov BEFORE you collect any data in order to publish the results. Please remember to enter your results following the end of the study. Many patients and families search ClinicalTrials.gov in search of potential treatments.

CFRI Researchers Continue Publishing High-Quality Manuscripts in 2019

During 2019, CFRI researchers published 228 manuscripts in peer-reviewed journals, maintaining the trend of more than 200 published manuscripts per year since 2017. Among these manuscripts, 80 were published in the top 25 percent of journals. Topics ranged from a new treatment for respiratory syncytial virus to PDA closure in the smallest newborns.





Allergic Asthma Protects from H1N1 Influenza Virus and Streptococcus Pneumoniae

Pre-existing allergic asthma protects from severe morbidity from influenza A virus (IAV) and Streptococcus pneumoniae (Spn) co-infection because of extensive alterations in the respiratory tract including immunological and microbiological differences.

This Le Bonheur research, published in *Scientific Reports*, was prompted by the results from the 2009 swine flu pandemic during which asthmatics had less severe outcomes of influenza including reduced bacterial pneumonia and ICU admittance as compared to non-asthmatics.

“Asthma is a complicated syndrome that develops through intricate gene and environment interaction,” said Le Bonheur Researcher Amali Samarasinghe, PhD. “Our study aimed to understand the possible mechanisms at play in asthmatics during respiratory infections to determine how each asthmatic may respond.”

Researchers developed a mouse model of asthma, influenza and pneumococcal pneumonia in order to study host-pathogen interactions in live tissue, which is unable to be observed in humans.

The results of the study revealed several ways in which allergic airways differ from non-allergic during co-infection of IAV and Spn including:

1. The inflammation of allergic airways delayed or protected

against severe disease from co-infection.

2. Allergic airways had a more diverse immune cell signature during co-infection.
3. Antibiotic treatment impeded protection from infection-induced morbidity in allergic mice.
4. Lung mucosal microbiome was more diverse in allergic airways, and antibiotic-induced dysbiosis rendered the allergic mice susceptible to severe disease associated with co-infection.

“Underlying conditions present unique challenges and opportunities for invading pathogens,” said Samarasinghe. “The extensive alterations in the respiratory tract during allergic asthma encompass both immunological and microbiological differences that can have a profound impact on susceptibility to infection.”

The results show that asthmatics have a distinct microbial signature that may contribute to the protective capacity of asthma during IAV and Spn co-infection. Any antibiotics should be prescribed with caution especially in patients with underlying chronic conditions.

This study was conducted in collaboration with St. Jude Children’s Research Hospital researchers Jason Rosch, PhD, Ti-Cheng Chang, PhD, and Peter Vogel, DVM, PhD.

View the full text article at <https://www.nature.com/articles/s41598-019-55712-8#Abs1>.

Air Guns Pose Safety Hazard for Children



trauma centers from 2007 to 2016.

The researchers found 499 children with an average age of 9.5 were injured by air guns and treated at the participating trauma centers. Of the 499 children, 331 were admitted to

To assess the current rate and severity of air gun injury, Chief of Pediatric Surgery Trey Eubanks, MD, and colleagues from five other Level 1 pediatric trauma centers, part of the Arizona-Texas-Oklahoma-Memphis-Arkansas (ATOMAC) Consortium, performed a retrospective study of air gun injuries treated at their

the hospital, and 151 required surgery. It cost an average of \$24,000 to treat each injury.

In 2011, air guns caused 16,451 injuries, and more than half of these injuries (62.5 percent) affected children age 19 or younger. In 2018, air gun injuries totaled 12,660 for all ages, with 9,273 injuries among children.

Due to a trend toward increasing projectile velocities, the study predicted that air guns will cause more severe injuries in the future. As 80 percent of these injuries were accidental, greater awareness of the potential for injuries and stricter regulations may be needed to curb this health concern.

Apelt N, Greenwell C, Tweed J, et al. Air Guns: A Contemporary Review of Injuries at Six Pediatric Level I Trauma Centers [published online ahead of print, 2019 Dec 11]. J Surg Res. 2019;248:1–6. doi:10.1016/j.jss.2019.11.002