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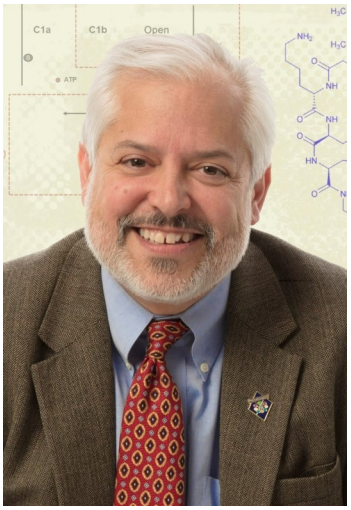
Academic partners advancing pediatric research

CF@LANTA

The Emory+Children's Cystic Fibrosis Center of Excellence

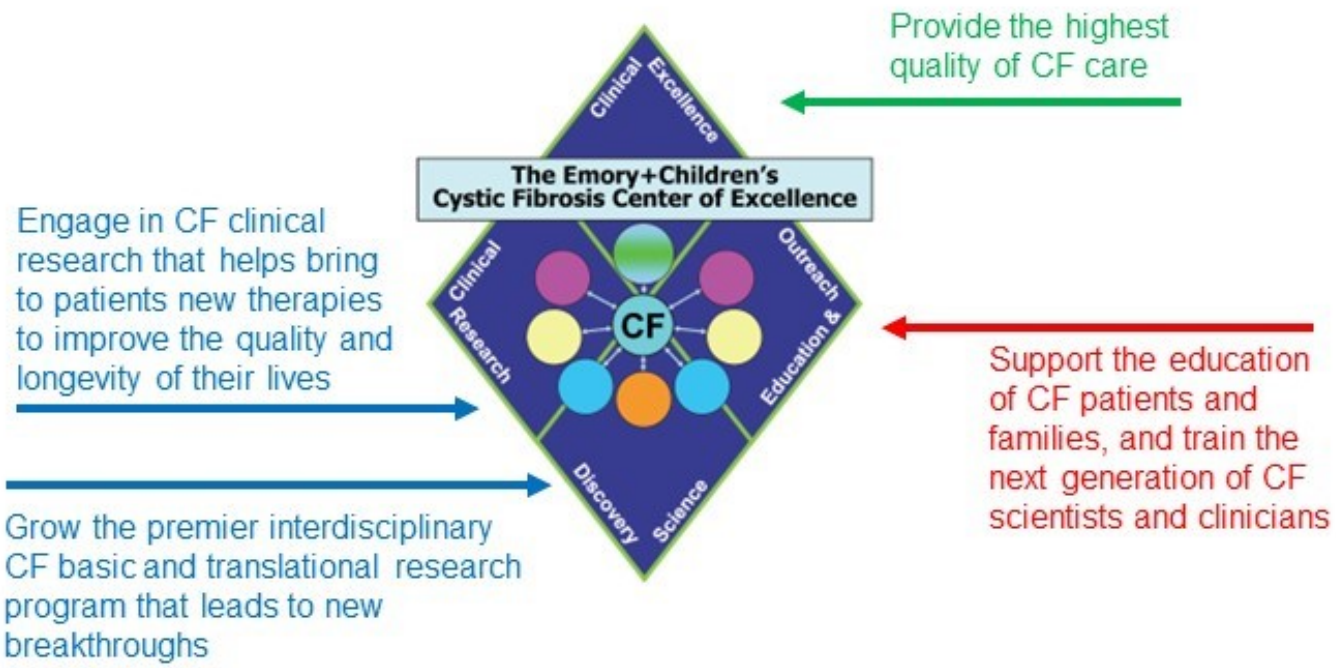
Message from the Director



Nael A. McCarty, PhD
Marcus Professor of Cystic Fibrosis
Emory University School of Medicine
Director, CF@LANTA

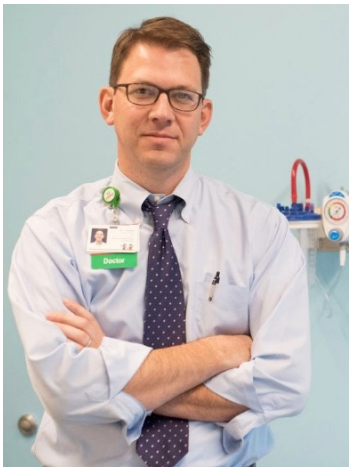
Greetings,

Great things are happening in Atlanta, home to several outstanding institutions engaged in high quality ***research, education, and clinical care*** including Emory University, Children's Healthcare of Atlanta, and the Georgia Institute of Technology (Georgia Tech). This includes the establishment of the Emory+Children's Cystic Fibrosis Center of Excellence, CF@LANTA, in 2009. CF@LANTA seeks to become the top CF Center in the country, with excellence in clinical care, education/outreach, and research. Research that ties together these institutions. Research that impacts our great city. Research that improves the lives of our patients.



Research

One of the most exciting programs, growing and developing over the past 14 years, is the ***Center for Cystic Fibrosis and Airways Disease Research*** (CF-AIR). We have three primary areas of research focus: cystic fibrosis, asthma, and food allergy.



Brian Vickery, MD

Food Allergy is a serious and potentially lethal condition that is the leading cause of pediatric anaphylaxis and now affects 1 in 13 children in metro Atlanta. Roughly 120,000 children in metro Atlanta are at risk of food anaphylaxis. Dr. Brian Vickery established The Food Allergy Center in March 2018 to transform the to transform the lives of food allergy patients and families in the Southeast and beyond through impactful research and high-quality, high-value, patient-centered care. With strategic focuson research, clinical care, and advocacy coupled with education and training, we work toward a worldwith a cure for severe food allergies and peace of mind for families everywhere.

Anne Fitzpatrick, PhD

Asthma, a disorder of reversible airway obstruction, is highly prevalent in Georgia, with incidence in Atlanta nearly twice that of the nation as a whole. Children's is the largest pediatric asthma provider in Georgia. Our asthma research program, led by Dr. Anne Fitzpatrick, seeks to identify the most innovative and effective treatment approaches for children with asthma, to reduce the burden of this disorder. Our personalized asthma research program includes basic science and clinical trials, along with an exciting new effort to develop cellular therapies for patients suffering from this impactful disease.

Research, continued

Cystic fibrosis is a genetic disease, which impacts many organ systems. Drs. Arlene Stecenko and Nael McCarty launched our CF research center in 2010. Since then, we have built a strong cadre of internationally recognized MD and PhD researchers with expertise in microbiology, epithelial biology, nutrition/diet, airway immunology, pulmonology, endocrinology, gastroenterology, exercise, bioinformatics, and drug discovery, who work together to develop new therapies. At the center of our work are the ~750 patients in the Children's+Emory CF Care Center, nearly all of whom are engaged in our research. Further information about our CF program can be found at: www.cfatl.org.

We are happy to present you with this window into some of the recent activities at CF-AIR. Over the past 14 years, CF@LANTA and CF-AIR have benefitted from very strong support from our three primary institutions, totaling over $46M. This has allowed us to recruit a number of stellar investigators who are leaders in these research foci. Taking advantage of the strengths in Immunology research at Emory, our team is holding an international search for young investigators with a focus on mucosal immunology, which ties together CF, asthma, and food allergy. If you are interested in learning more, we encourage you to send us a note at: CFatlanta@emory.edu.

Meet the Core CF Research Faculty

Arlene Stecenko, MD
EU - Pediatrics

James Gurney, PhD
GaState – Biol.

Rachel Linnemann, MD
EU - Pediatrics

Xiangming Ji, PhD
GaState – Nutr.

Rishi Kamaleswaran, PhD
EU - BioInformatics

Sam Brown, PhD
GT - Biology

Jessica Alvarez, PhD
EU - Medicine

Facundo Fernández, PhD
GT - Chemistry

Sheyda Azimi, PhD
GaState – Biol.

Kathryn Oliver, PhD
EU - Pediatrics

Dio Kavalieratos, PhD
EU - Palliative Med.

Rabin Tirouvanziam, PhD
EU - Pediatrics

Joshua Chandler, PhD
EU - Pediatrics

Vin Tangpricha, MD/PhD
EU - Medicine

Tanicia Daley Jean Pierre, MD
EU- Pediatrics

Steve Diggle, PhD
GT - Biology

Eric Sorscher, MD
EU - Pediatrics

Tom Ziegler, MD
EU - Medicine

Lokesh Guglani, MD
EU - Pediatrics

Joseph Kindler, PhD
UGA – Nutr. Sci.

Joanna Goldberg, PhD
EU - Pediatrics

Marvin Whiteley, PhD
GT - Biology

W. Randy Hunt, MD
EU - Medicine

Ben Kopp, MD
EU - Pediatrics

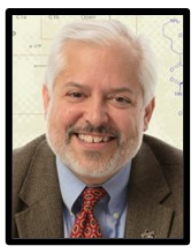
Ryan Harris, PhD
Augusta Univ. – Medicine

Andrés García, PhD
GT – Mech. Eng.

Neha Garg, PhD
GT - Chemistry

Mike Koval, PhD
EU - Medicine

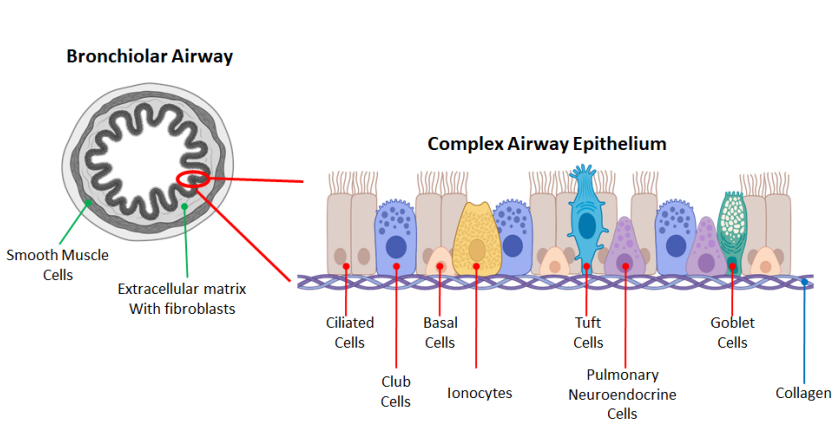
Balázs Rada, PhD
UGA - Inf. Dis.

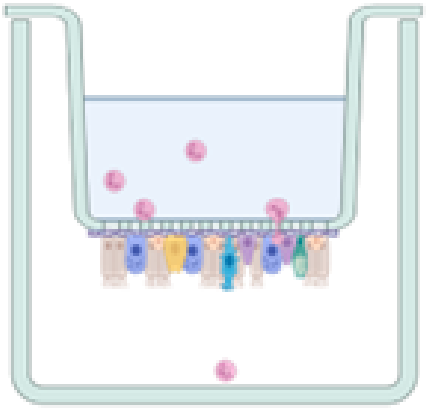


Nael McCarty, PhD
EU - Pediatrics

Contributions to CF Research

Immunologic dysregulation in early CF lung disease: CF@LANTA members have defined integral pathways and markers of early CF immunologic dysregulation. **Chandler**, **Guglani**, and **Tirouvanziam** showed that lung damage identified by chest computed tomography (CT) in 1-to-3-year-olds with CF was associated with myeloperoxidase (MPO) activity in bronchoalveolar lavage fluid (BALF) collected at the same clinic visit, as well as methionine sulfoxide. MPO and methionine sulfoxide were detected in every sample from these CF toddlers and levels were significantly associated with the degree of structural lung damage. **Chandler** developed a new GC-MS detection method for quantification of SCN^- levels in exhaled breath condensate (EBC) and this is important as SCN^- can protect lung cells from lethal damage by methionine sulfoxide. **Tirouvanziam** defined the GRIM (for granule releasing, immunomodulatory, and metabolically active) pathogenic fate of CF airway neutrophils and has developed an airway transmigration model that is now widely used by CF investigators to study recruited immune cell biology in the lung, including monocytes. GRIM fates occur in infants, suggesting that active NE release by live neutrophils is also a critical event in early CF lung disease. Despite the highly inflammatory state of the airways, people with CF are unable to clear routine infections, due in large part to reduced bacterial killing capability of these GRIM neutrophils. **Tirouvanziam** and **Chandler** showed that appearance of GRIM neutrophils in early CF is a harbinger of elevated MPO and hypochlorous acid in the airway lumen, contributing to the earliest stages of lung function decline. Interestingly, **Tirouvanziam and Guglani** showed that airway T cells are engaged during early-life pulmonary exacerbations, prior to the onset of chronic neutrophilic inflammation in CF. **Tirouvanziam and Guglani** also found that early macrophage exhaustion is present in CF, as marked by PD-1 upregulation in BALF. **Rada**, **Linnemann**, and **Stecenko** recently defined auto-antibodies to extracellular components of neutrophils in CF that begin in early childhood and correlate with lung disease severity. In addition to critical studies on defective NOX enzymes and autophagy activation in CF macrophages in response to initial infection, **Kopp** has defined the critical role for CFTR in direct modulation of innate immune function in human macrophages, independent of an altered airway millieu. Importantly, in people with CF (pwCF) on the highly effective modulator therapy Trikafta, restoration of CFTR function in macrophages was more closely linked to clinical outcomes compared to changes in overall sweat chloride. Together, these combined works define a clear role for early innate immune dysfunction in CF. This work is published in top journals (*Eur Res J, Thorax*, *AJRCCM*, *J Immunology, JCF, Cell Rep Med, Autoimmunity*).





Contributions to CF Research

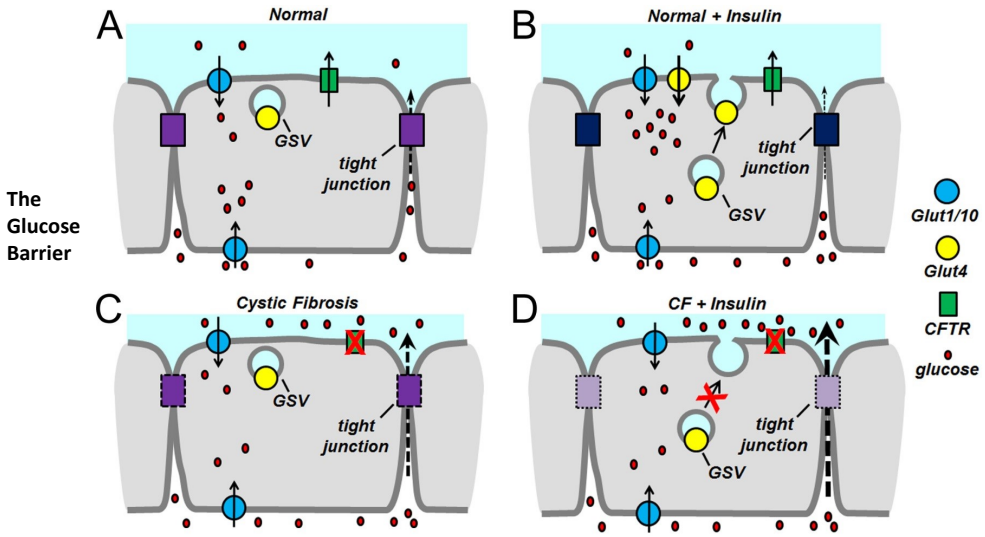
Therapeutic development for rare CFTR variants: **McCarty** and **Cui** made important contributions to understanding CFTR, most recently the conformational changes that occur during channel gating. In addition, they recently identified ortholog-specific responses to novel and known potentiators, and regulation of CFTR activity and pharmacology by lipids. **Cui** and **McCarty** showed that the phosphorylation state of CFTR regulates response to potentiators in many disease-associated mutants. **McCarty**, **Cui**, and **Sorscher** have made multiple important contributions to understanding the evolution of CFTR, including the recent identification of the oldest known CFTR ortholog, from the sea lamprey. **Sorscher** has characterized the structure and biophysical properties of large CFTR domains and provided key information regarding the function of CFTR in epithelia. He has made many important contributions in CFTR folding, molecular mechanisms underlying CFTR mutations, and identification and development of experimental therapeutics. He pioneered efforts to suppress premature termination codons in the CFTR gene and has led efforts to identify CFTR-targeted therapeutics emphasizing the 10% of CFTR variants lacking effective modulators. **Sorscher** has contributed reagents and cell lines (including the largest collection of FRT cell lines bearing CFTR variants) that are used by many CF investigators around the world. This work now ties to inflammation and infection, with new collaborators **Mandal** and **Mocarski** studying the role of CFTR in cell death pathways in both the CF gut and airway. A $1.5M grant to **Sorscher** from a local family foundation identified anti-inflammatory drugs out of a CFTR screen in combination with **Rab**. **Sorscher**, **Stecenko**, and **Linnemann** have developed an approach to personalized medicine that may enable extension of highly effective modulator therapies to pwCF bearing rare mutations. **Oliver** has determined critical factors that regulate translational speed, ribosome fidelity, and mRNA surveillance for CFTR synthesis. This work is published in top journals (*Science, PNAS*, *Dev Cell, Mol Biol Cell, JCI Insight, JCI, AJRCCM, J Biol Chem, J Gen Physiol*, etc.).

Emerging role for dysregulated immunometabolism in CF pathogenesis: The CF@LANTA team has made critical contributions to understanding altered immunometabolism as a new therapeutic target in CF. By high-content flow cytometry, **Tirouvanziam** showed that airway neutrophils in CF adults adopt an unusual fate, featuring hyperexocytosis of primary granules rich in neutrophil elastase (NE), loss of phagocytic receptors, anabolic signaling, metabolic hyperactivity, and immunomodulation including T-cell inhibition. These results are recapitulated by the *in vitro* system that **Tirouvanziam** developed for studying neutrophil reprogramming upon transmigration through airway cells in response to CF airway fluid; this unique model is now being extended to high-throughput design with **Takayama**. Among other consequences, **Chandler** showed that reprogramming increases airway MPO, which generates the profoundly toxic hypochlorous acid which is believed to underlie a major cause of lung damage. **Tirouvanziam** also showed that the GRIM neutrophils suppress other immune cell populations in CF airways, including T cells via secretion of arginase 1 (Arg1) from the primary granules which cleaves the essential amino acid arginine required by T cells for T-cell receptor signaling. Additionally, **Kopp** has shown how environmental exposures lead to altered macrophage metabolic derangements in arachidonic acid signaling leading to heightened inflammation and fatty acid derangements, suggesting a role for prostaglandin modulation in

Contributions to CF Research

CF. **Kopp** also has demonstrated multiple altered inflammatory metabolite networks associated with clinical severity using a variety of biofluids. **Rada** and **Goldberg** recently demonstrated that short chain fatty acids from anaerobic bacteria metabolically suppress CF neutrophil function. **Alvarez and Tangpricha** led a clinical trial to study dietary metabolites and immune recovery during exacerbations. Immunometabolic signaling is an ongoing target for pre-clinical and clinical studies by CF@LANTA team members. This work has been published in several top journals (*Cell, J. Immunol., AJRCCM, Autoimmunity, J Innate Immun, PNAS, Eur Respir J, JCF,* etc.).

Systemic complications of aberrant glucose control in CF: The CF@LANTA team has national leaders in CF endocrinology (**Tangpricha, Daley**) and nutrition (**Alvarez**) who serve on CF Foundation advisory committees. Given the extremely high prevalence of CF-related diabetes (CFRD) and severe pathological consequences, future CF research must make steps to accelerate our understanding of systemic consequences of CFRD. For example, despite the significant impact of CFRD on lung disease, the mechanisms by which hyperglycemia accelerates pulmonary dysfunction in response to infection are unknown. **McCarty, Koval, and Hunt** developed the concept of the "glucose barrier" in the airway, comprised of control of paracellular flux of glucose from the blood/interstitial fluid into the airway by tight junctions and removal of glucose from the airway by insulin-sensitive transport in airway epithelial cells. They showed that both components of the glucose barrier are defective in CF airway cells. They also developed a novel murine CFRD model and showed that CFTR knockout mice made diabetic exhibited enhanced neutrophilic infiltration but reduced ability to clear *Pseudomonas* airway infection. **Hunt** and **McCarty** showed that advanced glycation end products (AGEs) are elevated in CFRD and correlate with worse lung function. **Koval** and **McCarty** also optimized primary nasal and lung airway epithelial cell models for CFRD research and showed that CF cells have differential expression of genes encoding key components of the glucose barrier. They are now collaborating with **Goldberg**, **Whiteley**, **Chandler**, and **Daley** to explore the mechanisms by which airway epithelial cells, airway immune cells, and airway bacteria adapt to hyperglycemia. In a study of 234 pwCF with or without CFRD, **Stecenko** and **Goldberg** found that those with CFRD were more likely to be co-infected with both *S. aureus* and *P. aeruginosa* than with only one pathogen and co-infection was associated with worse lung function and more frequent exacerbations. **Stecenko and Hunt** found that glucose ingestion induces severe redox imbalance in CF, which may play a role in CFRD development.



Contributions to CF Research

Stecenko was one of the first to show the utility of the Disposition Index as a sensitive tool to assess islet cell health. The **Stecenko** team showed that glucose control worsens during acute pulmonary exacerbations. **Fernández** leads a team with **Stecenko** and **McCarty** to develop metabolomic assays of airway glucose from EBC in order to better understand changes in the airway metabolome as hyperglycemia develops. Most recently **Fernández** has developed a novel method that requires only submicroliter volumes of sample. Using this method and in collaboration with **Stecenko**, they discovered that in pwCF with prediabetes, glucose ingestion causes an acute change in EBC metabolomic profile including increases in early markers of programmed cell death and *Pseudomonas* virulence factors. This work is published in top journals (*JCF, JAMA, AJRCCM, AJPLung*, *Nat Comm, etc.*).

Microbiology of severe CF lung infections: CF@LANTA team members (**Whiteley, Goldberg, Diggle, Brown, Garg, Azimi, Gurney, Fernández,** etc.) have made seminal discoveries on the microbial community dynamics of the lung ecosystem. The team at the Center for Microbial Dynamics and Infection (e.g., **Diggle, Brown, Garg,** and **Whiteley**) specialize in studying the community dynamics of CF microbiota and discovery of the molecular mechanisms controlling bacterial interactions, using both experimental approaches and computational modeling. In addition to numerous bacterial pathogenesis studies, recently, **Whiteley** discovered *sicX*, a *Pseudomonas aeruginosa* small RNA that regulates chronic and acute lifestyle switching during infection. **Whiteley** also developed a transcriptomics quantitative framework to improve the accuracy of CF bacterial infection models. **Whiteley** developed synthetic CF mucus (SCFM2) that replicates the CF lung environment and is now used by labs across the world including in ours**. Goldberg** has defined the role of emergent genotypes and phenotypes of bacterial infections in CF. **Diggle** showed that phenotypic diversity in *P. aeruginosa* lung populations impacts antimicrobial resistance and that bacteriocins shape competition between *P. aeruginosa* CF isolates and are potential therapeutic targets. **Garg** demonstrated the unique 3D microbiome-metabolite map of the CF lung to assess mechanistic responses to drugs. **Fernández, Stecenko,** and **McCarty** used novel MS-based identification of biomarkers of disease progression during acute pulmonary exacerbations (APEs), finding that many are bacterial metabolites. **García, McCarty, and Goldberg** have engineered biomaterials for delivery of bacteriophages to eradicate bacterial infections in the CF lung and circumvent antibiotic resistance issues. **Brown** has identified novel ‘evolution-proof’ therapeutics. **Gurney** has utilized phage steering to combat antibiotic resistance. This work is published in top journals (*Nature, PNAS, mBio, Cell Host Microbe, Nat Microbiol, Nat Biomed Eng*, etc.).