Children's Healthcare of Atlanta

EMORY UNIVERSITY

The Emory+Children's Center for Cystic Fibrosis and Airways Disease Research Center (CF-AIR)

CF-AIR

AT EMORY UNIVERSITY AND CHILDREN'S HEALTHCARE OF ATLANTA

Excellence in scientific discovery, education, and community outreach.

A MESSAGE FROM DR. NAEL MCCARTY

Greetings,

Great things are happening in Atlanta, home to several outstanding institutions engaged in high quality research including Emory University, Children's Healthcare of Atlanta, and the Georgia Institute of Technology (Georgia Tech). Research that ties together these institutions. Research that impacts our great city. Research that improves the lives of our patients.

One of the most exciting programs, growing and developing over the past 11 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.

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 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 focus on research, clinical care, and advocacy coupled with education and training, we work toward a world with a cure for severe food allergies and peace of mind for families everywhere.

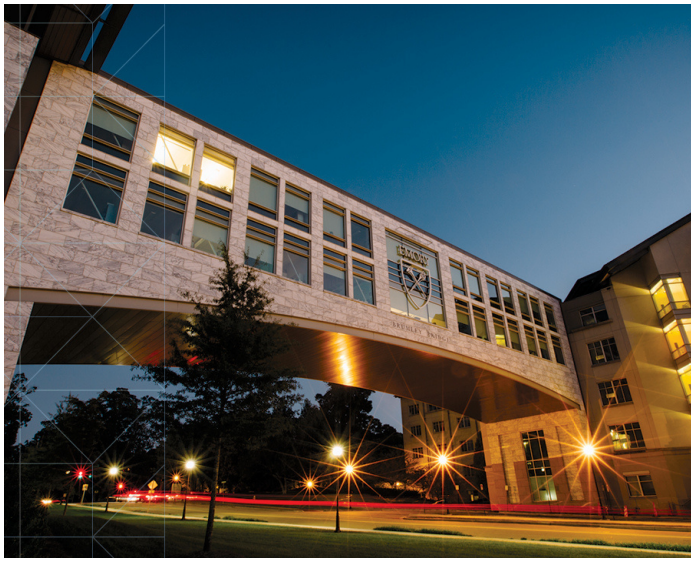
Nael A. McCarty, Ph.D.

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.

Cystic fibrosis is a genetic disease, which impacts many organ systems. Dr. Arlene Stecenko and I 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, bioinformatics, and drug discovery, who work together to develop new therapies. At the center of our work are the ~700 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 11 years, CF-AIR has benefitted from very strong support from our three primary institutions, totaling almost $34 million. 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: peds.research@emory.edu. If you know of a stellar candidate who may be interested, please share this Flipbook with him/her, with our gratitude.



Sincerely,

Nael A. McCarty, Ph.D.

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A BRIEF HISTORY OF CF-AIR

In 2008, Children's Healthcare of Atlanta announced their plans to stimulate pediatric research in the Atlanta area by establishing a number of pediatric research centers. In aggregate these centers would form a city-wide **Pediatric Research Alliance**, encompassing faculty at the major research institutions in Atlanta. Based on this plan, a new **Emory and Children's Center for CF Research** was established in 2010 led by Drs. Nael McCarty and Arlene Stecenko. A substantial amount of support was provided for developing research infrastructure and recruiting nationally recognized CF scientists.

Immediately upon its launch in January 2010, McCarty and Stecenko began developing new collaborative ties to biologists, chemists, translational researchers, and engineers at Emory and Georgia Tech and worked with leaders there to recruit new CF research faculty to these institutions. At the same time, they reached out to the CF clinical care team to become active partners in this CF research enterprise.

In 2013, the Center for CF Research was renamed the Center for CF and Airways Disease Research (CF-AIR) reflecting an expanded research focus. CF-AIR grew to include scientific discovery in asthma, food allergy, and other airway diseases, such as COPD and non-CF bronchiectasis.

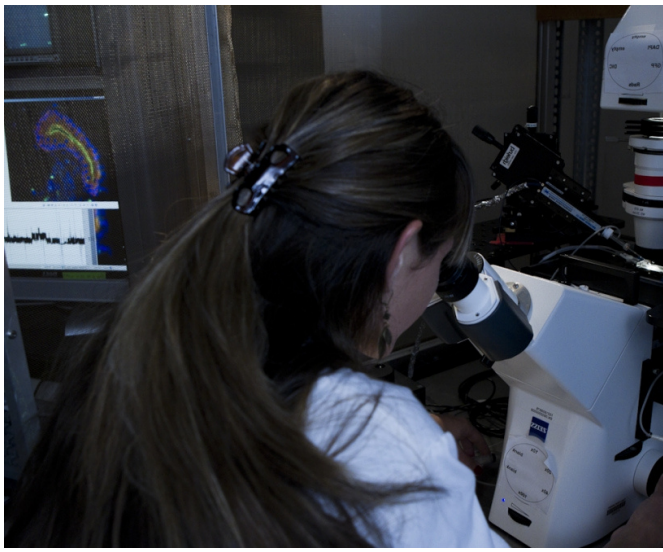
Following his recruitment in 2017, Dr. Marvin Whiteley has taken the lead as Georgia Tech's anchor CF faculty and also serves as Co-Director of CF-AIR.

Drs. Brian P Vickery and Anne Fitzpatrick lead our food allergy and asthma research programs respectively.

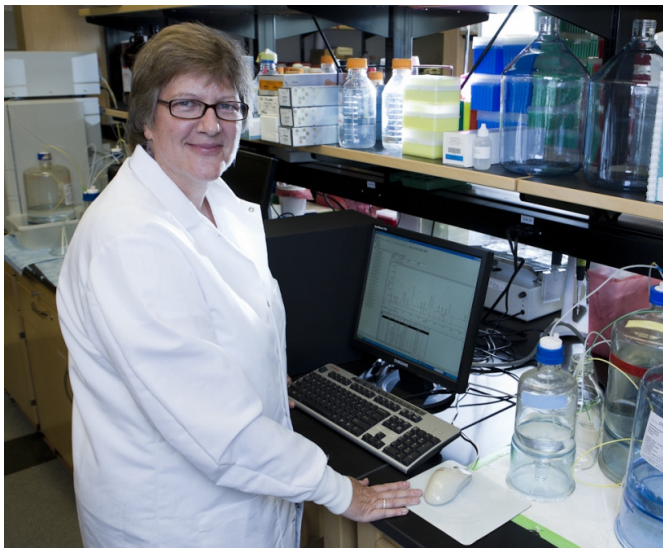
CF-AIR has attracted to Atlanta many outstanding CF investigators, including Whiteley, S. Brown, Diggle, and Garg at Georgia Tech, and Tirouvanziam, Goldberg, Wuest, Chandler, Noto, and Sorscher at Emory.

ENVIRONMENT

The Robert W. Woodruff Health Science Center of Emory University (Emory), Children's Healthcare of Atlanta (Children's), as well as The Georgia Institute of Technology (Georgia Tech), have **tremendous resources and a rich infrastructure** that support operations for CF-AIR scientific discovery. Specifically, Emory and Children's have a strong history in basic and translational biomedical research, including longitudinal follow-up of large patient cohorts and clinical trials, while Georgia Tech has a strong history in engineering approaches and quantitative measurements to translate research findings into models, devices, and platforms that impact patients.



Both Emory and Georgia Tech have **excellent records in the establishment of multidisciplinary centers.** Administrative structures for accountability are in place to ensure compliance with all federal regulations.



Emory and Children's operate in the same location (often in the same buildings), while Georgia Tech is 25 minutes away by free hourly inter-institutional shuttle service, or other motorized vehicle, with joint physical facilities in the HSRB building at Emory (Biomedical Engineering Department) and EBB building at Georgia Tech (Pediatric Research Alliance). Therefore, **collaborative research, work meetings, and resources and data sharing** between our institutions are extremely easy streamlined.

CF-AIR currently operates or support the following research cores:

1. Biomarkers Core
2. Biostatistics Core (via Pediatric Research Alliance)
3. CF Discovery Core, including the CF Biospecimen Repository
4. CF Animal Models Core
5. P30 Diabetes, GI, and Nutrition Core
6. P30 Lifestyle and Behavior Core
7. P30 Clinical Research and Informatics Core

LEADERSHIP

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Download PDF to follow links to faculty descriptions.

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Eric Sorscher, MD

Arlene Stecenko, MD

Vin Tangpricha, MD, PhD

Rabin Tirouvanziam, PhD

Brian Vickery, MD

David Weiss, PhD

Marvin Whiteley, PhD

Bill Wuest, PhD

Tom Ziegler, MD

CONTRIBUTIONS TO CF RESEARCH

CF@LANTA has existed for only ~11 years, but many of our faculty have been active in CF research for decades. We report here some recent accomplishments by our faculty. References are for a subset of the most recent publications from our faculty shown in the display on page 14.

A. Growing a CF research team.

One overarching major accomplishment of CF@LANTA is that we **enabled CF translational research in Georgia.** CF-AIR launched in 2010 with a goal of enabling Atlanta-area investigators to engage in translational CF research. The CF Biospecimen Repository (CF-BR) was a key component of our research plan and provides access to: (1) patient-derived samples including blood, sputum, bacterial isolates, exhaled breath condensate (EBC), nasal epithelial cells, BAL Fluid; (2) clinical metadata associated with those samples and collected longitudinally as the patient develops complications, their disease progresses, and/or new therapies are started; and (3) clinical expertise in the form of our physician-scientists to consult on experimental design and interpretation of results. **This has led dozens of local investigators to engage in CF research for the first time.** More importantly, the CF-BR and CF-AIR attracted to Atlanta many outstanding CF investigators, including **Whiteley**, **S. Brown**, **Diggle**, and **Garg** at Georgia Tech, and **Tirouvanziam**, **Goldberg**, **Wuest**, **Chandler**, **Noto**, and **Sorscher** at Emory. Over 90% of PwCF in our large patient cohort are participating in the CF-BR, which enables us to do innovative studies to add to those occurring on the national scale.

This outstanding resource has been leveraged for acquisition of many NIH grants. Foremost among them is our NIH P30 grant that focuses on non-pulmonary aspects of CF. We also have been funded by the Cystic Fibrosis Foundation's RDP Center mechanism. Indeed, the Emory School of Medicine in recent years has received more funding from the CF Foundation than any other non-governmental foundation. Additionally, our Center is a very active site in the CF Foundation's Therapeutic Disease Network, and through the P30 grant is now collaborating with Augusta University in order to be able to provide access to CF clinical trials throughout Georgia.

B. Microbial community dynamics of the lung ecosystem.

Members of CF@LANTA have contributed extensively to evolutionary biology, ecological modeling, genomics, bioinformatics, and model development for CF microbiological research, asking how microbial communities are structured and how they interact with other components of the lung ecosystem in the context of antibiotics and CFTR modulators.

- Key to this work is the **Whiteley** lab which has developed new approaches to understanding the role of the environment in determining microbial gene expression (1-3.)
- **Whiteley** developed synthetic CF mucus (SCFM2) that replicates the CF lung environment, and is now used by labs across the world (4-5.)
- The team at Georgia Tech's Center for Microbial Dynamics and Infection (CMDI) (e.g., S. **Brown**, **Diggle**, and **Whiteley**) specialize in studying the community dynamics of CF microbiota and discovery of the molecular mechanisms controlling bacterial interactions, using both experiment and computational modeling (6-11.)
- **Whiteley** has used machine learning to enable gene expression profiling of *S. aureus* and *P. aeruginosa* to identify differences in expression that occur in the lungs of people with CF (PwCF) (1,2.) Many of these differentially expressed genes are related to metabolism (1, 2.)

CONTRIBUTIONS TO CF RESEARCH

- **Goldberg** has explored the role of emergent genotypes and phenotypes of bacterial infections in CF (12-15).

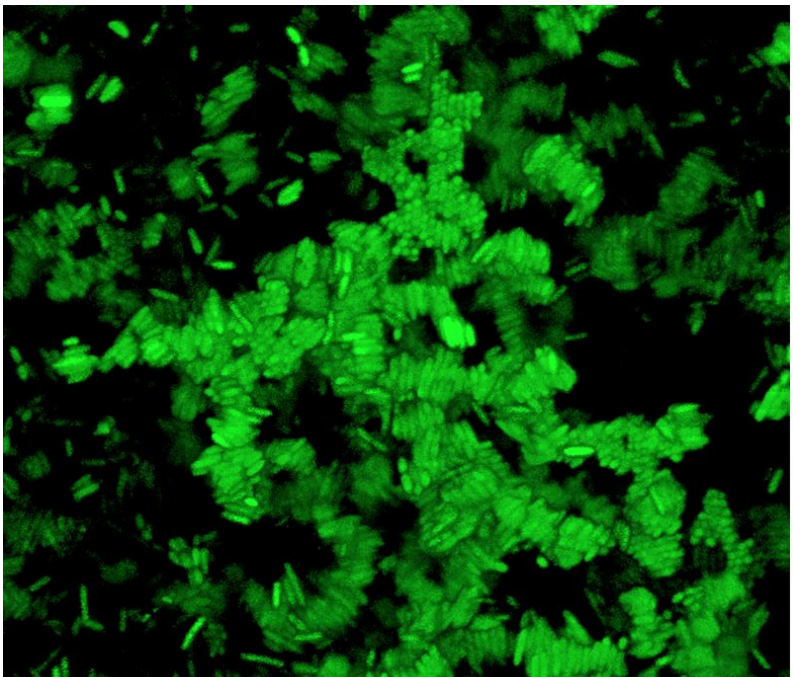
- **Garg** studied microbe-microbe interactions in CF relevant media and response to antibiotics by mass spectrometry (16, 17.)
- **Fernández**, **Stecenko**, and **McCarty** used novel MS-based identification of biomarkers of disease progression during acute pulmonary exacerbations (APEs), finding that many are bacterial metabolites (18, 19.)
- **Read** and **Goldberg** are comparing the genomes of *S. aureus* strains that were isolated from PwCF with vs. without *P. aeruginosa*, to identify factors responsible for the survival and persistence of *S. aureus* in the CF lung (12, 13.)
- **Garg**, **Whiteley**, and **Goldberg** have described the geographical heterogeneity in microbiome and metabolome within explanted lungs, and demonstrated non-uniform antibiotic penetration and metabolism and consequential change in the microbial community (20, 21.) This cutting-edge research, often in the hands of senior investigators doing work not being pursued elsewhere, has led to new insights into the CF lung ecosystem.

This work has led to 85 publications in these top journals in the past six years (e.g., *mBio, PNAS, J. Bacteriol., PLoS One, J Biol. Chem., J Infect Dis., Infect Immun.*)

C. Antibiotic resistance in CF lung infections.

Work is being done on bacteriophage and antibiotic resistance by many CF@LANTA investigators, including full professors.

- **Whiteley**, **S. Brown**, **Diggle**, and **Weiss** (Director of the Emory Antibiotic Resistance Center) have studied the dynamics of development of antibiotic resistance in CF microbiota, including new observations of heteroresistance (22-38.)
- **Diggle** showed that phenotypic diversity in *P. aeruginosa* populations in CF lungs impacts antimicrobial resistance and that bacteriocins shape competition between *P. aeruginosa* isolates (39, 40.)
- **Stecenko** and **McCarty** showed that chronic MRSA and *P. aeruginosa* co-infection may be associated with increased rate of lung function decline and prevalence of APEs compared to patients with either pathogen alone (41.)
- **S. Brown** has identified novel 'evolution-proof' therapeutics (23, 29, 30.)
- **García**, **McCarty**, and **Goldberg** have engineered biomaterials for delivery of bacteriophage to eradicate bacterial infections in the CF lung, to circumvent issues of antibiotic resistance (42.)

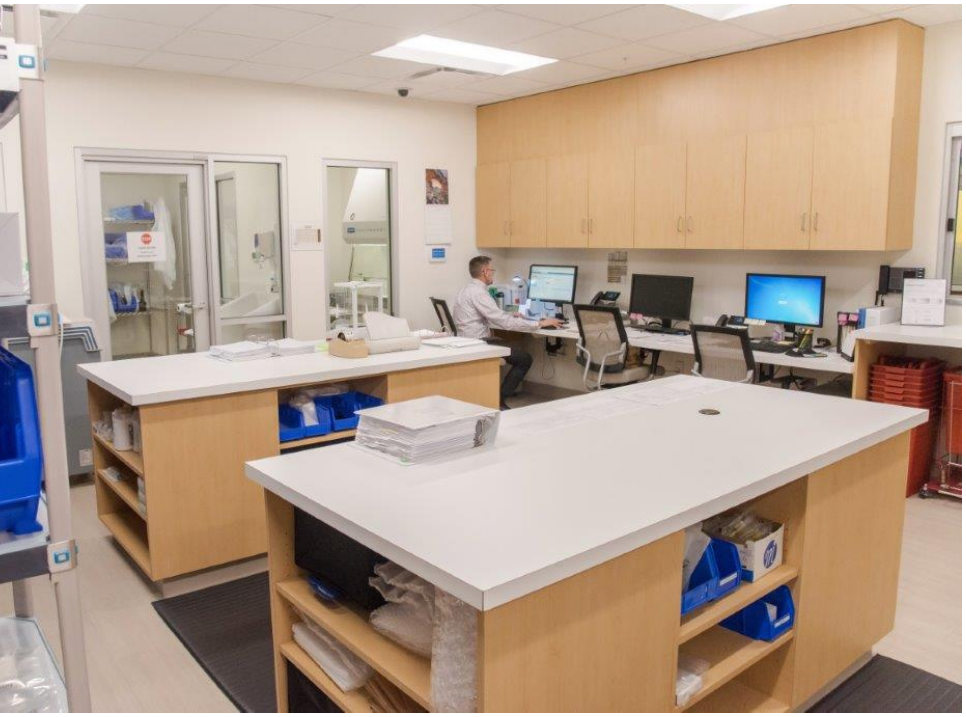


This work has led to 36 publications in top journals (e.g., *mBio, PNAS, J. Bacteriol., PLoS One, Nat. Biomed. Eng., J Infect Dis., Nat. Microbiol., Nat. Rev. Microbiol.*) over the past six years.

CONTRIBUTIONS TO CF RESEARCH

D. CFTR: function, regulation, pharmacology, mechanisms of mutations.

- **McCarty** and **Cui** have made many important contributions to understanding CFTR, most recently the conformational changes that occur during gating (43-45.) They recently identified ortholog-specific responses to novel and known potentiators (46, 47,) and regulation of CFTR activity and pharmacology by lipids (48-51.)
- **Cui** and **McCarty** showed that the phosphorylation state of CFTR regulates response to potentiators in many disease-associated mutants (52.)
- **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 (lamprey) (53.)



- **Sorscher** has characterized the structure and biophysical properties of large CFTR domains and provided key information regarding the function of CFTR in epithelia (54, 55.) He has made many important contributions in CFTR folding, molecular mechanisms underlying CFTR mutations, and identification and development of experimental therapeutics (56, 57.) 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 (53, 56, 58.)

- **Sorscher** has contributed reagents and cell lines that have been used by many CF investigators around the world (59.) 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 family foundation identified anti-inflammatory drugs out of a CFTR screen.
- **Sorscher**, **Stecenko**, and **Linnemann** have developed an approach to personalized medicine that may enable extension of highly effective CFTR modulator therapies to PwCF bearing rare mutations.

This work has led to 31 publications in these top journals (*Science, Dev. Cell, Mol. Biol. Cell, JCI Insight, J. Clin. Invest., Am J Respir Crit Care Med., PLoS One, J. Biol. Chem., J. Gen. Physiol., Sci. Rep.*, etc.) over the past six years.

CONTRIBUTIONS TO CF RESEARCH

E. Role of immunity and inflammation in pathogenesis of CF lung disease.

CF lung disease is characterized by the triad of chronic inflammation, defective mucociliary clearance, and persistent polymicrobial infection (60-62.) PwCF exhibit airway inflammation soon after birth, characterized by intense neutrophilia that lasts the lifetime of the patient (63, 64.) The CF@LANTA team has made seminal contributions to understanding the fate of neutrophils in the CF lung.

- 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 (65, 66.) These results are recapitulated by the in vitro system that Tirouvanziam developed for studying the reprogramming of neutrophils upon transmigration through airway cells in response to CF airway fluid supernatant (67.)
- Among other consequences, **Chandler** showed that this reprogramming increases airway myeloperoxidase (MPO), which generates the profoundly toxic hypochlorous acid which we believe underlies a fundamental cause of lung damage (65.)
- **Tirouvanziam** has shown that these **g**ranule-**r**eleasing, **i**mmuno**m**odulatory (GRIM) neutrophils are observed in airways of PwCF as young as three months old and are associated with progressive lung disease (64.)
- **Chandler**, **Guglani**, and **Tirouvanziam** recently showed that lung damage identified by chest computed tomography (CT) in 1-to-3-year-old CF patients was associated with MPO activity in BALF collected at the same clinic visit, as well as methionine sulfoxide (68.) 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 68.
- **Tirouvanziam's** new data show that the GRIM pathogenic fate of airway neutrophils occurs in infants, suggesting that active NE release by live neutrophils is a critical event in early CF lung disease (67, 69.)
- **Chandler**, **Guglani**, and **Tirouvanziam** 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 (70.)
- **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 (71.)
- **Rada** has identified the mechanisms of neutrophil extracellular trap (NET) release induced by CF respiratory pathogens (72-75.)
- In collaboration with **Stecenko** and **Linnemann**, **Rada** has pioneered work on exploring a potential autoimmune component of CF that may contribute to lung disease progression. This group has identified systemic autoantibodies to NET components that appear as early as two years of life, can be as high as other autoimmune diseases like systemic lupus and rheumatoid arthritis, and whose blood levels correlate with worsening CF lung disease (76, 77.)
- **Tirouvanziam**, **Peng**, and **Tangpricha** showed that resistin (a granule protein associated with induction of insulin resistance) is elevated in CF sputum and correlates negatively with lung function (78.)

This work has led to 42 publications in these top journals (*Cell, J. Immunol., Am J Respir Crit Care Med., J Allergy Clin Immunol., J Innate Immun., PNAS, Eur Respir J., J Cyst Fibros.*) in the past 6 years.

CONTRIBUTIONS TO CF RESEARCH

F. CF outside of the lung, and mechanisms underlying CF-Related Diabetes (CFRD).

The CF@LANTA team recently has added national leaders in CF endocrinology (**Tangpricha**) (79-87,) GI/hepatology (**Freeman**) (88-91,) and nutrition (**Alvarez**) (92-96,) investigators of national stature who are serving on important advisory committees for the CFF, and now key leaders in our NIH P30 grant project. Their addition brings new expertise to our research program on CFRD which already has made significant contributions.

- Given the extremely high prevalence of CFRD and the resultant severe pathological consequences (97-99,) the next five years of CF research must make steps to accelerate our understanding of the causes of CFRD and the mechanisms by which systemic hyperglycemia accelerates pulmonary dysfunction in response to infection.
- **McCarty**, **Koval**, and **Hunt** developed the concept of the "glucose barrier" in the airway, comprised of control of paracellular flux of glucose into the airway by tight junctions and removal of glucose from the airway by insulin-sensitive transport in epithelial cells; both components are defective in CF airway cells (100, 101.) They also developed a novel murine model of CFRD exhibiting reduced ability to clear an acute Pseudomonas airway infection (102.)
- **Hunt** and **McCarty** showed that advanced glycation end products are elevated in CFRD and correlate with worse lung function (103.)
- **Koval** and **McCarty** also optimized primary nasal and lung airway epithelial cell models for CFRD research and showed that CF and non-CF cells have different patterns of expression of genes encoding some components of the glucose barrier (101.)
- **McCarty** and **Koval** are now collaborating with **Goldberg**, **Whiteley**, **Chandler**, **Tirouvanziam**, 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 diagnosis of normal glucose tolerance vs. CFRD, **Stecenko** and **Goldberg** showed that the latter were more likely to be co-infected with both *S. aureus* and *P. aeruginosa* than with only one pathogen (104.)
- **Stecenko**, **Hunt**, and **Daley** recently examined the relationship between glycemic status and systemic redox balance and found that glucose ingestion induces redox imbalance in CF, which may play a key role in CFRD development (105.) They have contributed studies on preventing the onset of CFRD and designing better treatments and have developed sensitive tools to assess islet cell health such as disposition index and measures of beta cell apoptosis (106.)
- **Stecenko**, **Hunt**, and **Alvarez** showed that visceral adipose tissue is linked to elevated fasting blood glucose (92.)
- The **Stecenko** team showed that glucose control worsens during APEs (104.)
- **Fernández** leads a team with **Stecenko** and **McCarty** to develop metabolomic assays of airway glucose from EBC (18, 107) in order to better understand changes in the airway metabolome as hyperglycemia develops (108.)
- **Fernández** has developed a novel mass spectrometry method that requires only submicroliter volumes of sample. Using this method and in collaboration with **Stecenko**, they have shown that in CF patients with prediabetes, glucose ingestion causes an acute change in EBC metabolomic profile including increase in early markers of programmed cell death and *Pseudomonas* virulence factors.

This includes 45 publications in top journals (J Cyst Fibros., JAMA, Am J Respir Crit Care Med., Am J Physiol Lung., Nat. Comm.) over six years.

FUTURE PLANS

Our plans for the next two years will include application of quantitative approaches to understanding the lung ecosystem from the perspective of microbes, epithelial cells, and immune cells that interact to wreak havoc on the CF lung: a systems approach. One important area of focus is ***immunoinflammation***, reflecting the strong involvement of the immunoinflammatory system in CF disease and its likely strong involvement in the response to highly effective modulator therapies (HEMTs). Few institutions have the potential to address the consequences of this dysfunctional pulmonary immunoinflammatory system that Emory has. Our team is prepared to answer key questions, including: (i) how airway inflammation is affected by HEMT as it is introduced in young children, (ii) how gene therapy impacts and is impacted by immunoinflammatory responses, and (iii) whether new adjunctive strategies are needed to maximize immunoinflammation's benefits (bacterial killing, epithelial repair, inhibition of autoimmunity) and minimize its drawbacks (proteolysis, oxidation, fibrosis).

With regard to ***CF microbiology***, we need to understand the dynamics of individual species during infections, and the dynamics of multiple species interacting together in the polymicrobial environment of the lung. Hence, our team builds upon the availability of excellent microbiology researchers at both Emory and Georgia Tech but adds to them other investigators with expertise in quantitative modeling. Faculty at Georgia Tech have provided new expertise in evolutionary biology, ecological modeling, genomics, bioinformatics, and CF microbiological model development. Recruitment of these individuals has allowed CF@LANTA to expand its focus and develop a critical mass in CF microbiology with unique strengths. CF@LANTA microbiology is now at the forefront of understanding the multi-scale dynamics of microbial infections in people with CF and across communities and is uniquely poised to address key questions including: (i) understanding the evolution and function of the CF microbiome, to facilitate improved treatment regimens and patient outcomes and the impact of new and upcoming therapies on the airway microbiome; (ii) evaluating the impact of antimicrobial use on the evolution of the CF microbiome; (iii) development of CF-relevant models to facilitate studies into microbial physiology and function and testing safe and effective treatments; and (iv) optimizing treatment strategies in the context of patient health metrics (CFRD, lung function, BMI).

Finally, CF@LANTA is building a unique architecture to support data science initiatives centered upon the ~700 patients in our clinical program (the second largest in the U.S.). ***The Georgia CF Data Warehouse*** will link novel omics data, clinical phenotypes, genotypes, behavior, and outcome data, to generate an integrated portrait of CF patients, an essential step towards truly personalized, precision medicine. This data infrastructure will have major consequences for big data analytics that aim to improve outcomes, quality of life, detect disease in earlier stages, and explore personalized interventions. By providing investigators access to data, sharing technical capabilities, and ensuring data quality, the data integration component of this core will facilitate cross-clinic/laboratory collaboration for the current research base, and for future CF researchers as well.

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