Cystic Fibrosis Center of Excellence

Emory University - Children's Healthcare of Atlanta - Georgia Tech

Volume 10, Issue 1 **September 2020**

Inside this issue:

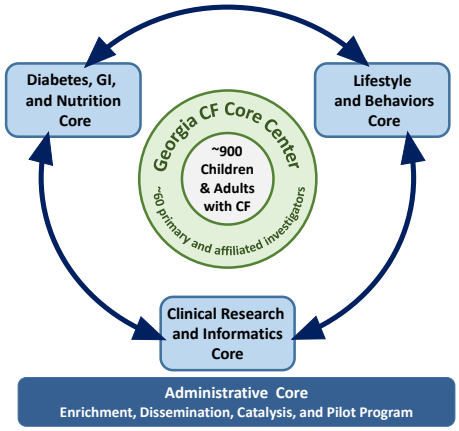
Dear friends, patients, families, and colleagues,

We hope that this message finds you safe and well, in spite of the unsettling times surrounding us these days of pandemic.

While the world is topsy-turvy now, we write to tell you that our important work continues on behalf of our patients and families. Our researchers continue to ask and answer important questions related to the pathogenesis of Cystic Fibrosis (CF), in all of its forms. We continue to study both the pulmonary complications of CF, and the non-pulmonary complications, such as those that attack the endocrine and gastrointestinal systems. We continue to train the next cadre of CF researchers and clinician-scientists, including by way of the innovative CF Scholars Program noted on page 2 of this newsletter. We continue to provide outstanding care for our patients, even while having to adapt to the new realities imposed upon us by COVID-19. This includes the establishment of enhanced programs in Quality Improvement, as described on page 2.

We all look toward the day when our conversations are not driven by the impact of the current pandemic, but it is important to note that several of our CF scientists have been able to pivot a portion of their research efforts toward solving the problems presented by this health crisis. Because the virus is tropic for the lung, the expertise of several CF investigators is immediately relevant and applicable to COVID-19 research. We present on page 4 stories from the lab of Dr. Eric Sorscher and from the lab of Dr. Rabindra Tirouvanziam, who are making important contributions to addressing this urgent research need.

We are happy to report that the NIH has informed us of their plans to fund the P30 grant to establish the "Georgia CF Core Center," as noted in the most recent newsletter. This program will focus on non-pulmonary consequences of CF.



Finally, we include here an invitation to join a virtual presentation on October 14, for a "CF@LANTA Ten-Year Update". The goal of this hour-long presentation is to update you on both the pediatric and adult clinical care programs, and learn about our education and outreach activities. We will update you on our research activities over the past decade since the Center for CF and Airways Disease (CF-AIR) and CF@LANTA were launched, as well as some new directions on the horizon. You will have the opportunity to meet the leaders of our care programs, and some of our key researchers at Emory and Georgia Tech, and hear about our plans. You may register for this event at: https://cfatl.org/events . We hope you can join us.

We send you the very best wishes, and gratitude for your continued interest and support. Please stay safe and well.

~Nael A. McCarty, PhD,
Director, ***CF@LANTA***

Quality Improvement

The Children's+Emory CF Care Center has hired a Process Improvement Specialist, Sydney Schiff, that is dedicated to helping improve quality and efficiency for both our pediatric program at Children's and adult program at Emory. As an industrial engineer with a six-sigma green belt, Sydney is leading quality improvement (QI) initiatives with the help of both care teams in hopes of streamlining care across the entire center. She is working on discipline-specific projects by partnering with our dietitians, genetic counselor, social workers, respiratory therapists, *etc*, as well as leading center-wide initiatives. Some of these initiatives include helping to create an improved scheduling process for labs and oral glucose tolerance tests, mapping out a treatment protocol for non-tuberculous mycobacterium, developing a lung health treatment guideline, creating a G-tube algorithm, and improving overall clinic efficiency. She is also managing our Patient and Family Experience of Care surveys to track trends and patient-reported feedback to assist in improvement efforts.

Both the pediatric program and adult program have been accepted into the CF Learning Network. We are joining this network of top CF centers across the nation to help test and implement best practices to improve clinical outcomes and experience of care for all people with CF. This network is driven by quality improvement and partnering with the CF community to improve care and patient experience. To better partner with our CF community, we now have several Patient and Family Partners joining our QI team for both the pediatric and adult teams. We are quickly realizing how invaluable it is to have their input and participation in this network. Sydney is also serving as the Quality Improvement Leader for both programs and acts as a liaison between the network and center. As a part of this network, both programs are working on a specific CFLN quality improvement project. Both programs have chosen to focus on increasing the number of clinic visits that are collaboratively planned with patients and families. The goal of this project is to empower our patients and families to help drive the agenda during visits to ensure what is important to them is discussed during clinic. This network also gives us access to many clinical outcome metrics and reports while exploring two new measures – FEV_1 Indicated Exacerbation Signal and Health Related Quality of Life.

CF@LANTA is proud to report that Sydney Schiff, our Children's and Emory CF process improvement specialist, was selected for a leadership role in the national CF Foundation-sponsored CF Learning Network (CFLN)! Sydney will serve as Co-Chair of the CFLN Quality Improvement Lead Workgroup.

In 2020, the CFLN selected both our pediatric and adult CF clinical programs to join its national collaborative quality improvement network, which aims to improve health outcomes for individuals with CF. Sydney quickly proved herself to be a star in the network, and this is a very exciting opportunity for Sydney to help lead cutting-edge CF quality improvement work across the country, as well as bring national recognition to our Children's and Emory CF Center.

Congratulations, Sydney, and thanks for your dedication!

CF Scholars Program — New Cohort

The CF Scholars Program relaunched in 2019, and this week has welcomed in an excellent group of Scholars for the 2020 cohort. The following new Scholars joined the eight from the 2019 cohort, in this two-year program:

Heather Brandt, MD - Emory
Alexandre Cammarata, PhD - Emory
Andrew McAvoy , BS - Georgia Tech
Morgan Schafer, BS - Emory
Brittany Ross, PhD - Georgia Tech
Erin Kallam, MD - Emory

Dr. Marvin Whiteley

Dr. Marvin Whiteley joined the Georgia Tech faculty in 2017 as Professor of Biological Sciences, Bennie H. & Nelson D. Abell Chair in Molecular and Cellular Biology, and Georgia Research Alliance Eminent Scholar. He is an adjunct professor in the Department of Pediatrics at Emory University School of Medicine and Co-Director of CF@LANTA. Dr. Whiteley's research focuses on bacterial infections including *Pseudomonas aeruginosa* and *Staphylococcus aureus* infection of the CF lung. His work has defined how microbes within the CF lung communicate with one another and how this communication enhances the ability of bacteria to persist and tolerate therapies including antibiotic treatment. Since arriving in Atlanta, Dr. Whiteley's lab has worked extensively with CF@LANTA clinicians and patient-derived sputum samples to utilize machine learning to improve the models that are used to study CF infection and identify new therapies.

Before arriving in Atlanta, Dr. Whiteley was Professor of Molecular Biosciences and Director of the John R. LaMontagne Center for Infectious Disease at the University of Texas at Austin. He has received numerous awards for his work including the Merck Irving S. Sigal Memorial Award for national research excellence, the Burroughs Wellcome Investigators in Pathogenesis of Infectious Disease award, and recognition as a Kavli fellow of the National Academy of Sciences. He has served as Chair of Division D of the American Society for Microbiology, on numerous editorial and scientific boards, and was elected to the American Academy of Microbiology in 2014.

In the Atlanta area, Dr. Whiteley works with the Center for Microbial Dynamics and Infection at Georgia Tech to promote microbiological and CF research. He also serves as the anchor faculty member of CF@LANTA's branch at Georgia Tech, and continues to bring new GT faculty into our research team.

Major New CF Research Grant

Dr. Whiteley and his colleagues have recently received a major grant from the Cystic Fibrosis Foundation, to understand the impact of choice of experimental infection models on the ensuing results, At $2.6M total costs over three years, this represents one of the largest grants the CF@LANTA team has received thus far.

PROJECT TITLE: Quantitative evaluation and improvement of CF infection models

ABSTRACT: Whether screening for new antimicrobials or studying basic aspects of bacterial physiology and social behavior in CF, the infection model used can have a profound effect on the experimental outcomes. However, the degree to which common CF infection model systems capture bacterial traits during CF lung infection is virtually unexplored. While no laboratory model can encapsulate all of the complexities of a human infection, the specific strengths and limitations of each model system are not always clear, leaving researchers to rely on limited data, or intuition, to rationalize their model choice. The goal of this application is to develop a model evaluation and improvement framework that provides guidance to CF researchers and companies on model selection for studying *P. aeruginosa* CF lung infection and antimicrobial tolerance.

Collaborators on this project include Dr. Joanna Goldberg, Professor of Pediatrics at Emory, and Dr. Jen Bomberger, Associate Professor of Microbiology & Molecular Genetics at the University of Pittsburgh.

Congratulations to Dr. Whiteley and his colleagues!

CF@LANTA Striking at COVID-19

COVID-19 studies in the Tirouvanziam Laboratory, March-August 2020

SARS-CoV-2, a new lung-tropic coronavirus and causative agent of COVID-19, has taken the world by storm. In the Tirouvanziam laboratory, we were fortunate to have at our disposal experimental tools and know-how that could be immediately applied to the study of COVID-19. In particular, we leveraged a novel *in vitro* model of human lung infection and inflammation that we previously validated for studies of CF and acute respiratory distress syndrome (ARDS) to study how human lung cells interact with this new virus.

SARS-CoV-2 is a highly transmissible virus requiring work to be performed in biosafety level 3 (BSL3) conditions. To conduct our studies, we teamed up with the laboratory of Prof. Raymond Schinazi, a pioneer of antiviral research (Dept. of Pediatrics at Emory), who generously provided access to a BSL-3 suite and a SARS-CoV-2 isolate. Brian Dobosh, a graduate student in the Tirouvanziam laboratory, worked in close collaboration with Dr. Kevan Zandi in the Schinazi laboratory to study infection of human lung epithelial cells differentiated at air-liquid interface, and of human monocytes and neutrophils migrated through the infected epithelium to mimic human lung inflammation in COVID-19.

Supported by an early award from the National Science Foundation (EAGER 2032273), we were able to propagate SARS-CoV-2 in our epithelial model and identify a population of human monocytes recruited to the lung that directly interacts with the virus and mounts an inflammatory response devoid of interferon but associated with high IL-1β and CXCL8, consistent with the pattern observed in patients. We demonstrated that this model is amenable to screening of antiviral and immunomodulatory drugs targeted at host epithelial cells and immune cells. This work conducted from March to August 2020 has led to a research manuscript and a patent application (pending). Expansion of this pilot effort includes the systematic testing of drug combinations to promote repurposing of existing agents to curb down COVID-19 pathophysiology. In addition, advanced bioinformatic analyses are conducted in the laboratory by Dr. Diego Moncada, to unravel signaling pathways and targets for intervention in human epithelial cells and immune cells that are in the front line of SARS-CoV-2 infection.
New proposals based on this approach are in review intramurally by the Woodruff Health Science Center CURE Program [drug repurposing], and extramurally by the CF Foundation [interaction of CF and COVID-19], Department of Defense [role and therapeutic modulation of neutrophils in COVID-19], and NIH [role and therapeutic modulation of monocytes in COVID-19].

COVID-19 studies in the Sorscher Laboratory, March-August 2020

The Sorscher laboratory has experience pursuing studies of lung epithelial biology, CFTR-dependent generation of airway surface liquid, endocytosis of clathrin-coated vesicles, and machinery of the endoplasmic reticulum and trans Golgi network. Because many of these same cellular mechanisms impact SARS-CoV-2 propagation, we have provided resources and expertise to numerous groups on campus for their protocols regarding COVID-19. Through commitment of Dr. Candela Manfredi, during the recent period of laboratory closures our team was able to furnish essential primary airway cell technology for five grant submissions and a paper in *Journal of Virology*, as well as a number of other ongoing projects. We also have a growing interest in genes that regulate epithelial responsiveness to SARS-CoV-2, including a possible role for several candidate human loci during viral propagation. In these studies, we have been collaborating with the International Host Genetics Initiative (organized by the Broad Institute at MIT). Our laboratory also collaborates with the intramural NIH-NIAID Rocky Mountain Laboratory investigating SARS-CoV-2. Small molecules developed for CF therapy (such as those that blunt pulmonary inflammation) are being tested for their potential palliative effect on COVID -19.

Research Highlight—Dr. Kathryn Oliver

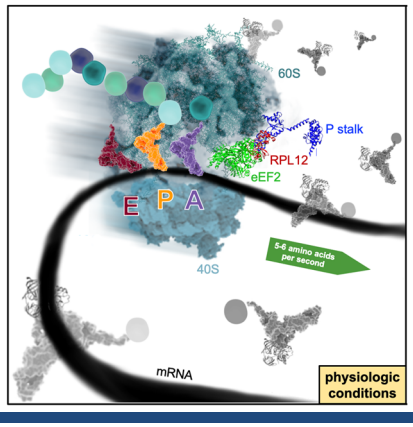
Dr. Kathryn Oliver joined Emory in 2017 as a postdoctoral fellow in the laboratory of Dr. Eric Sorscher. She completed a B.S. and M.S. at Auburn University, followed by Ph.D. (2016) from the University of Alabama at Birmingham (UAB). At Auburn, Dr. Oliver investigated chronic persistence strategies employed by *Pseudomonas aeruginosa*, a leading source of morbidity and mortality among individuals with CF. After graduating, she worked one year as a Lecturer at the University of Alabama in Huntsville. It was during that time that Dr. Oliver gave birth to her daughter and learned that she has a rare and mild form of CF. Based on her growing interest in CF for both personal and professional reasons, Dr. Oliver enrolled in the Genetics, Genomics, and Bioinformatics graduate program at UAB to study CF disease mechanisms. She was supported by an NIH F31 Individual Predoctoral Fellowship, and her dissertation project utilized genome-wide yeast phenomics coupled to studies of membrane protein biochemistry/function to characterize novel genetic modifiers of the most common CF-causing variant, F508del-CFTR.

As a postdoctoral fellow, Dr. Oliver has continued to work toward an academic career in basic and translational science. She is currently a member of the Emory CF Scholars Program, and her research focuses on addressing feasibility of ribosomal protein suppression as a means to overcome refractory CFTR defects – with particular emphasis on premature stop codons. This includes mechanistic evaluation of global and transcript-specific effects on translational velocity/fidelity, in addition to biochemical assessments of protein biogenesis and activity. Dr. Oliver's recent findings suggest that inhibiting a specific ribosomal protein, RPL12, slows translation kinetics (see illustration below; *J of Clinical Investigatin* 129(12): 5236-5253, 2019) and rescues functional expression of F508del and other rare CFTR variants to a degree predicted to offer clinical benefit. She previously received a CF Foundation (CFF) Postdoctoral Research Fellowship (2017-2020) and Burroughs Wellcome Fund Collaborative Research Grant (2018-2019) to support her work, and is presently funded by a prestigious NIH K99/R00 Pathway to Independence Award. In 2021, Dr. Oliver plans to establish an independent research program that pursues relationships between ribosomal function and impact on protein synthesis for CF and other inherited conditions.

Dr. Oliver has been well-recognized for her research, including awards at local, regional, and international scientific meetings. She received the 'Junior Investigator Best Abstract in Basic Science' distinction (among ~150 international competitors) at the 2017 North American CF Conference (NACFC), as well as first place honors for oral presentations at the 2019 Gordon Research Conference entitled 'Translation Machinery in Health and Disease' and the 2020 Emory Pediatrics Research Symposium. She has made fourteen invited presentations over the past few years, including four talks at NACFC and five posters at invitation-only CFF-sponsored summer research meetings. In addition, Dr. Oliver co-chaired NACFC workshops in 2017 and 2019, including "CFTR 2017" and "Addressing unmet needs for nonsense and rare CFTR variants".

Outside of the laboratory, Dr. Oliver enjoys spending time with her family and participating in civic outreach initiatives. Her favorite activities include beach vacations, road trips, horseback riding, swimming, and playing softball with her husband and daughter. Dr. Oliver also volunteers at the 'Miles For Cystic Fibrosis' foundation and fundraises for the annual 'Wish for Wendy' softball tournament by playing on Andy Lipman's team. Due to her strong passion for educating, equipping, and empowering the next generation of women in STEM, Dr. Oliver additionally serves as Founder and President of the Georgia Chapter of the Association for Women in Science (AWIS; https://www.awisga.org).

~ submitted by Kathryn Oliver, Ph.D



Events for Researchers

Each month there are several opportunities for CF@LANTA researchers to get together to discuss their work.

Full CF@LANTA Calendar of Events

- CF@LANTA Faculty and Trainees Research Joint Lab Meeting:
  Meets on the 1st and 3rd Wednesday at 3:00 pm, virtual only for now Chalk talk style talks for faculty and trainees.
- CF@LANTA Workshop:
  Meets on the 1st and 3rd Wednesday at 4:00 pm, virtual only for now. Research-in-progress and journal club presentations.
- CF Scholars Meetings:
  A monthly program for CF Scholars, Friday afternoons; see website schedule.

Interested in more information?
Send an email to Dr. McCarty (namccar@emory.edu) or to our new Program Coordinator, Mrs. Lilly Meier (lilly.chriszt@emory.edu)

Clinics:

Pediatric Clinics at the CAP
1400 Tullie Road NE
Atlanta, GA 30329
404-785-KIDS

Emory Adult CF Clinic
1605 Chantilly Dr. NE
Atlanta, GA 30324
404-778-7929

New Website:

https://.cfatl.org

If you are interested in supporting our research and outreach programs please visit: https://cfatl.org/donate

Contact:
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Program Director
namccar@emory.edu

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