Dear Friends of the Emory+Children’s Center for Cystic Fibrosis Research-

We hope this finds you well. It has been about a year since our last newsletter. And what a year it’s been! We have been very active in growing our CF Research program, building upon the strong momentum of our work since the Center began in 2010. We also have made progress in growing the proposed Emory+Children’s Cystic Fibrosis Center of Excellence.

As described in further detail in a subsequent section, we were successful in recruiting to our Center two outstanding new faculty—Dr. Rabin Tirouvanziam (from Stanford University) and Dr. Assem Ziady (from Case Western Reserve University). We greatly appreciate the support from Children’s, who provided the funds to recruit both of these investigators. Drs. Ziady and Tirouvanziam already have had impressive impact on our CF Basic and Translational Research team. They set up their labs in the fall of last year, recruited staff, and immediately added strength to our team’s work.

With additional funds recently provided by Children’s, we are now in the process of recruiting two more faculty to our teams. We hope to be able to repeat in the next newsletter the good news that these investigators also have joined us.

Another major activity over the past year has involved taking the next steps in the development of our research infrastructure. Two major facets are noted here. First the “CF Mouse Models Core” was established to facilitate the provision of murine models of CF for use by investigators trained in the study of disease in vivo in research animals. The core maintains breeding pairs for currently three different genotypes that are most useful in CF research, and also provides those animals to researchers (with approval from their institutional animal care and use committee) at a nominal cost. This core is directed by Dr. Jason Hansen, who may be reached at CFMouseCore@gmail.com.

The Discovery Core serves as the primary piece of infrastructure supporting our translational research. By giving researchers access to samples (biofluids, cells, etc.) donated by our patients, this core helps to ensure that our work is patient-focused—keeping our attention as close to the patient as possible, rather than simply trying to replicate CF disease in a Petri dish (which, by the way, can’t be done!). A prominent component of the Discovery Core is the CF Biospecimen Registry (the CF-BR). Rolled out in the Emory Adult CF Clinic beginning in August 2010, the CF-BR collects from our consenting patients three different samples (blood, sputum and exhaled breath condensate (EBC)) and these samples are processed for analysis using a variety of state-of-the-art methods.

Patients interested in participating in this study can provide samples as frequently or as infrequently as they wish: at each outpatient clinic visit, at only their annual visit (which typically runs long and includes more lab tests), when hospitalized, or any combination of the above. Patients may also agree to let us collect the bacterial and fungal isolates that are grown from their sputum, when they are discarded from the Pathology lab at Emory University Hospital. We also recently began collecting airway fluid during bronchoscopy- this is called bronchoalveolar lavage fluid (BAL).
Update from the Director, Cont’d

We believe that these treasured samples may be the keys that will allow our researchers to unlock the mysteries underlying the changes that occur in the lungs of CF patients as the disease progresses. This information will be critical in our efforts to devise new approaches to keep our patients healthy.

The CF-BR is now being rolled out to the Emory Pediatric CF Clinic and Egleston Hospital, and we hope to establish a satellite at the CF Clinic at Scottish Rite Hospital. The CF-BR is managed by Drs. Nael McCarty and Susu Zughai, with expert assistance of Ms. Beth Helfman as the chief coordinator. Patients interested in the study, and researchers interested in obtaining samples, may contact Ms. Helfman at CFBioregistry@gmail.com.

We continue to build our research infrastructure, in order to facilitate the important work being undertaken by our team. A robust infrastructure for CF-related research, including the availability of mouse models and patient-derived samples, also helps draw into the CF field researchers that have expertise that may help us learn to control this complex disease. Hence, as we are able to obtain further funds, we plan to establish more Cores, including a Systems Biology and Biostatistics Core, a Physiology Core, and an Engineering Core. In order to help us accomplish this development, we have named one of our two new recruits, Dr. Assem Ziady, as Associate Director of Basic and Translational Research within the growing CF Center of Excellence.

Our team also has been busy submitting grant proposals to the NIH and elsewhere, and we have hopeful (but not yet final) news on their funding. Included in this is the submission of ten letters-of-intent for the CF Foundation basic and clinical science grant competitions—this sets a new record for our team.

As you can see, we remain very busy and focused on controlling CF. We look forward to more growth over the coming months, and thank you for your continued interest.

Regards,
Nael A. McCarty, PhD

Faculty Recruitment

The Center for CF Research would like to welcome our newest faculty members, Rabin Tirouvaziam, PhD from Stanford University and Assem Ziady, PhD from Case Western Reserve University. They each bring new perspectives to the team and we are glad to have them here!

Rabindra Tirouvanziam, Ph.D. earned his PhD at the Embryology Institute of CNRS and College de France near Paris, France, and also holds an Engineering Degree from France's leading biotechnology school, Agro Paris-Tech. Before joining Emory University, he worked as Research Scientist and later as Instructor at Stanford University School of Medicine with affiliations in the Departments of Pediatrics, Genetics, and Psychiatry and Behavioral Sciences. Dr. Tirouvanziam’s laboratory focuses on mechanisms of innate immunity in humans and their relations to chronic human disease, with emphasis on target identification for the development of novel therapies. Dr. Tirouvanziam has led efforts to redefine the fate of neutrophils in the fatal cystic fibrosis disease and served as principal scientist on phase 1 and 2 clinical trials in CF and autism. Dr. Tirouvanziam's research has been published in the Proceedings of the National Academy of Sciences, Blood, and the Journal of Allergy and Clinical Immunology. Dr. Tirouvanziam joined the Center and the Department of Pediatrics in September 2011, as Assistant Professor.

Assem Ziady, Ph.D. Dr. Ziady received his undergraduate education at Boston College in biochemistry. He completed his graduate studies in cell physiology and received his Ph.D. degree in 1999 from Case Western Reserve University. Following his postdoctoral training at the Department of Pediatrics at Case Western Reserve University, he began a year long externship at the Cleveland Clinic Proteomic facility in early 2002. In 2003, Dr. Ziady joined the faculty at the Case Western Reserve University Department of Pediatrics as an Assistant Professor. His laboratory focuses on the use of proteomic-based Systems Biology to understand differential regulation of signaling pathways in cystic fibrosis. In addition, Dr. Ziady's lab develops and characterizes DNA nanoparticles for gene delivery. In October 2011, Dr. Ziady joined the faculty at the Emory University Department of Pediatrics as an Associate Professor. His research is supported by the CF Foundation and the NIH.
To the left is our 2011 CF@TLANTA Great Strides team. We had a great year, and contributed to the record-breaking success of GS 2011, which was the first walk in the history of the CFF to net over $1,000,000. Great support from a great city!

To the right is our 2012 CF@TLANTA Great Strides team. Word from the CF Foundation, so far, is that the 2012 walk has raised even more money than in 2011. We are excited by this outpouring of support for CF in Atlanta.
Meet one of the CF Center Co-Directors

Arlene Stecenko, MD, Marcus Professor of Pediatrics and Medicine

The Children’s Center for CF Research is led by Dr. Nael Mccarty as its Director, along with Drs. Arlene Stecenko and Michael Schechter as Co-Directors. In each of the first editions of this newsletter, we will highlight one of these leaders. Next newsletter: Dr. Michael Schechter to be highlighted.

Some diseases are inherent in children. Cystic fibrosis (CF) is one of those. As more children and young patients live longer with CF, their future treatment options become limited. This is what Arlene Stecenko, M.D., is trying to change. Her research primarily focuses on CF diabetes. “Since 42 percent of adults with CF develop diabetes, we have to look at the big picture of how to treat them long-term,” says Stecenko.

Dr. Stecenko is trying to understand the molecular pathways in the lungs that turn on the response to injury and repair and why they go wrong in certain lung diseases. By gaining insight into the origins of the disrepair response in lung diseases, she hopes to find a way to restore the normal pulmonary repair response. “Every time you breathe in, there’s always a little damage to the lungs,” she says. “The body naturally repairs it, but people with CF have a delayed or damaged repair response.”

By studying the pre-diabetic phase in CF, when the lungs are already beginning to decline, Dr. Stecenko hopes to find the molecular pathways that can cause the spiraling, downhill, and eventual development of CF diabetes. “Ultimately, this could lead to treatment that would prevent the development of diabetes in these patients,” she adds. “This will be a life-changing breakthrough for CF patients because their lung disease becomes even more virulent because of diabetes.”

The key to much of her research is the link between pediatric and adult pulmonology patients. By studying trends in adult patients, she hopes to learn more about the root causes of complications in pediatric patients. “Pediatric pulmonology is a relatively young field in the U.S. compared to adult pulmonology”, says Dr. Stecenko. “There is not as much research done in pediatrics so I hope to take the information gathered from adults and collaborate with my colleagues to further pediatric research.” Combining her team-science approach and working across disciplines, such as with endocrinology, Dr. Stecenko is examining a standard treatment option for CF in kids and questioning its consequences. Her goal is to prevent diabetes deaths in adults. “If we take adult research and work backwards, we may be able to discover the causes of some of the complications that plague CF patients,” she says. “For the last twenty years, physicians have prescribed high calorie diets in CF kids in order to promote weight-gain,” she says. “For many, the way to achieve such a high calorie diet is to have a high intake of fat calories. In fact, we tell the parents of these kids not to eat what the CF kids are eating, as it is too high in calories, particularly fat calories. Experience tells us weight gain can be normal with this diet.” Stecenko adds that she worries it may be at too high a price. “Patients had to eat more calories and fat, but now there is an epidemic of diabetes among adults with CF. It’s comparable to the way we’re having a national epidemic of type II diabetes.”

Another part of her research focuses on another chronic lung disease called idiopathic pulmonary fibrosis (IPF). IPF is typically fatal, usually within about five years of diagnosis. No treatment is effective, other than lung transplant. Dr. Stecenko and her colleague, Dr. Ana Mora, are interested in the link between IPF and Epstein-Barr virus (EBV). Their research in mice shows that infection with the mouse equivalent of EBV causes progressive pulmonary fibrosis with most of the features of human IPF. Anti-viral therapy in these mice well after the infection has established that the lungs block the development of fibrosis. Dr. Stecenko and her team are now initiating studies that question whether antiviral therapy in people with IPF will slow down the progression of IPF and decrease lung fibrosis. Stecenko is also interested in evaluating whether EBV can be implicated in some children with IPF.

In the last two years, Dr. Stecenko has developed collaborations with Children’s Healthcare of Atlanta, The Centers for Disease Control, Georgia Tech, and Georgia Pediatric Pulmonary Associates. “I am very proud of the strong collaborations at work in our research efforts,” she says. “I look forward to what we can accomplish moving forward to bridge academic medicine and practical clinical care.”

Funding for her research continues to be supported by grants from the National Institutes of Health and also the Cystic Fibrosis Foundation. She has published widely in peer-reviewed journals, including the Am. Journal of Respiratory and Critical Care Medicine, the Am. Journal of Respiratory Cell and Molecular Biology and the American Journal of Physiology.

Under her leadership and that of colleagues at Georgia Pediatric Pulmonary Associates, Children’s was named as one of the top five Pediatric Pulmonary programs in the country by Child Life magazine in 2007.
Visitors

Mehmet Kesimer, Ph.D., University of North Carolina-Chapel Hill, traveled to Atlanta to give a seminar on “The Macromolecular Basis of Airway Mucosal Protection: From Mucins to Mucus” on April 12, 2012.

Amit Gaggar, M.D., Ph.D., University of Alabama at Birmingham, joined the team to discuss how to strengthen the connection between our Center and the CF Center at UAB on February 23, 2012.

Michael Kinter, Ph.D., University of Oklahoma Health Sciences Center joined us in Atlanta to discuss “Using targeted quantitative proteomics to study the effects of lipids on the heart” on January 25, 2011.

Mitchell Drumm, Ph.D., Case Western Reserve University traveled to Atlanta to give a seminar on “Understanding cystic fibrosis-modifying genes through mouse models” on January 18, 2011.

William E. Balch, Ph.D., The Scripps Research Institute, attended the EAB meeting and gave a seminar on “Re-balancing the System in Cystic Fibrosis” on December 19, 2011.

Joanna Goldberg, Ph.D., University of Virginia, traveled to Atlanta to discuss “Surface structures of CF pathogens: virulence studies and vaccine development” on March 24, 2011.

External Advisory Board Meeting

In December of 2011 the CF Center of Excellence held the first annual External Advisory Board (EAB) Meeting in Atlanta, Georgia. The board came from around the U.S. and Canada to spend time with faculty and staff and provide recommendations. According to the EAB: "We were particularly impressed by the leadership team, most notably Drs. Nael McCarty, Arlene Stecenko, and Michael Schechter. They are enthusiastic leaders who have a good grip on the multiple entities that will need to be brought together to achieve success.” In addition, the EAB was impressed with the other clinical and research faculty, the integration of the clinical and research enterprises in the Program, the interaction among the faculty at Emory, Children’s Healthcare of Atlanta (Children’s), and Georgia Tech, “the moral support by the senior leadership at Emory and Children’s, and the financial support by Emory and Children’s”.

Additionally, the EAB mentioned that “CF@TLANTA” is a highly worthwhile effort and provided 4 major useful recommendations:

1. The Program is encouraged to focus on areas where they can truly be distinctive as a CF Research/Clinical Care Center, such as CF Related Diabetes (CFRD) and exacerbations/inflammation and related biomarkers, areas where CF@TLANTA has considerable strengths;
2. The Strategic Plan also should focus on areas where they can truly be distinctive as a CF Research/Clinical Care Center;
3. Accelerate faculty recruitment, notably funded investigators into the areas where CF@TLANTA will be distinctive; and
4. Develop a concise business plan.

We were thrilled to have them here in Atlanta and look forward to their next visit.

CF EAB Members:

Bruce Stanton, PhD
Dartmouth University

John LiPuma, MD
University of Michigan

John Repine, MD
University of Colorado

William Balch, PhD
The Scripps Research Institute

Felix Ratjen, MD/PhD
University of Toronto
On June 6, 2010, our own Dr. Daniel Caplan was presented a Lifetime Achievement Award by the Department of Pediatrics and Children’s Healthcare of Atlanta. The following is taken from the introduction of Dr. Caplan given by Dr. Arlene Stecenko.

“Dr. Daniel Caplan is truly deserving of this lifetime achievement award as he has been, for his entire career, a compassionate advocate for children and adults with cystic fibrosis.

Dr. Caplan’s greatest gift to the children of Georgia was to start the CF Center. He began it at Grady and in 1985, the clinic moved to Egleston. The center grew under Dr. Caplan’s leadership to become one of the largest in the country. He and the interdisciplinary team that he built took care of over 450 patients with CF. The CF Center has grown to become a premier center for CF clinical care, research, and education. Dr. Caplan has remained the heart and soul of our center as we have grown.

I have had the privilege of being Dan’s colleague for 10 years and am still amazed at what a kind soul he has. He is a gentleman, a caring physician, and an advocate for our CF patients.”
New Health Sciences Building Update

This past year construction began on a $90 million Health Sciences Research Building on the Emory University campus, which is scheduled for completion in April 2013. More than half of the new building on Haygood Drive will focus on pediatric research through the Emory-Children's Pediatric Research Center, a partnership between Emory and Children's Healthcare of Atlanta. The Pediatric Research Center will also work with Georgia Tech and Morehouse School of Medicine, according to Emory officials.

Thank You to our friends at Bank of America

Dear Friends,

On behalf of the Emory+Children’s CF Center of Excellence, it is an honor to write to thank you for your commitment to our efforts.

You all have been our foundational community partners. Personally, I can’t overemphasize how important you are to our hopes and dreams. I remain ever grateful for our partnership and friendship, and for the opportunity you give us to get our story out into the Atlanta community. Each time that you lead your “Pathway to Retirement” course that you have been presenting across Atlanta, you spread the word about what we are trying to do to put an end to the life-threatening lung damage that CF patients now experience.

With help from our community partners as a body, and the support of individuals like you, we will transform the approach to this deadly disease and save the lives of CF patients for generations to come. But as a partnership, this should benefit both sides of the table. Therefore, please do let me know how I can help you to benefit as much from this partnership as we do.

We cannot thank you enough for your partnership in our mission and getting us one step closer to making our hopes for every child and adult fighting this disease become a reality.

Sincerely,

Nael A. McCarty, PhD
2011-2012 Pilot Awardees

Congratulations to our Center for CF Research Pilot awardees for 2011 and 2012!

2011

Colonic Bicarbonate Transport in Cystic Fibrosis
Criss Hartzell, Emory University, and Nael McCarty, Emory University

Mechanisms of Dysregulated Leukocyte Adhesion and Phagocytosis in CF Patients
Cheng Zhu, Georgia Institute of Technology, and Nael McCarty, Emory University

Metabolomic Investigation of Molecular and Physiologic Mechanisms of Accelerated Lung Decline in CFRD
Arlene Stecenko, Emory University, Prabha Dwivedi, Georgia Institute of Technology, and Facundo Fernandez, Georgia Institute of Technology

2012

Alveolar Macrophage Functioning in the Neonatal CF lung
Theresa Gauthier, Emory University

Development of a CFRD Mouse Model
Jason Hansen, Emory University

Phage-Nanoparticles to Reduce Cystic Fibrosis-Associated Infections
Andres Garcia, Georgia Institute of Technology, Nael McCarty, Emory University, and Susu Zughaier, Emory University

NACFC 2012 Abstracts

Compilation of abstracts submitted from the Atlanta team for the 2012 NACFC Conference

1. PURE, FACS-SORTED, LIVE NEUTROPHILS FROM CF AIRWAYS DISPLAY MARKED CHANGES IN THEIR TRANSCRIPTIONAL PROFILE, CONSISTENT WITH REPROGRAMMING
Preinninger, M.; Diaz, D.; Tirouvanziam, R.

2. DIFFERENTIAL EXPRESSION OF THE IMMUNOMODULATORY CLEC12A AND MELANOCORTIN1 RECEPTORS IN NEUTROPHILS HOMING TO CF AIRWAYS
Laval, J.; Sitbon, M.; Tirouvanziam, R.

3. ELEVATED AIRWAY AND SYSTEMIC GLUCOSE IMPEDES LUNG BACTERIAL CLEARANCE IN A MURINE MODEL OF CYSTIC FIBROSIS RELATED DIABETES
Hunt, W.R.; Zughaier, S.M.; Shenep, M.A.; McCarty, N.A.; Hansen, J.M.

4. COMBINATORIAL TRANSCRIPTOMIC, PROTEOMIC, AND METABOLOMIC ANALYSES REVEAL DYSREGULATION OF GLYCOLYSIS IN PRIMARY CF AIRWAY EPITHELIA AND NEUTROPHILS.
Ziady, A.G.; Luo, Y; Pazharskaya, V.; Gibson, G.; Stecenko, A.A.

5. EXTRACELLULAR LOOP 1 IS INVOLVED IN MAINTAINING THE OUTER VESTIBULE PORE ARCHITECTURE OF CFTR
Cui, G.; Kuang, C; Prince, C.Z.; McCarty, N.A.

6. TARGETED MOLECULAR DYNAMICS SIMULATIONS OF THE CFTR GATING CYCLE
Rahman, K.S.; Cui, G.; McCarty, N.A.; Harvey, S.C.
7 Modeling the Translocation Mechanism of the ABC Transporter P-Glycoprotein Using Targeted Molecular Dynamics
Speir, E.; Rahman, K.S.; McCarty, N.A.; Harvey, S.C.

8 Trends in Fat-Soluble Vitamin Intakes and Blood Concentrations in Adult Subjects with Cystic Fibrosis
Siwamogsatham, O.; Alvarez, J.; Enders, J.; Tangpricha, V.

9 Neonatal Alveolar Macrophages Are Impaired in the CFTR Mutated Mouse Pup
Gauthier, T.W.; Ping, X.; Brown, L.A. S.

10 Expression of ΔF508-CFTR Leads to Disruption of the Airway Glucose Barrier in CF-Related Diabetes
McCarty, N.A.; Hansen, J.M.; Koval, M.H.

11 Pyocyanin Modulates Iron-Limiting Innate Immune Defenses in Macrophages
Zughaier, S.M.; Leavey, J.; McCarty, N.A.

12 Origin and Evolution of the CFTR Regulatory R-Domain
Sebastian, A.; Rishishwar, L.; Bernard, K.; McCarty, N.A.; Jordan I. K.

13 Redox Imbalance in the Development of CFRD
Stecenko, A.A., Dasari, G., Pazharskaya, V., Hansen, J.M.

14 High Dose Vitamin D for Prevention and Repletion of Vitamin D Deficiency in a Pediatric CF Population: Results of a Quality Improvement Project
Revilla, E.B.; Das, M.D.; Pendley, S.L.; Caplan, D.B.; Freedman, J.N.; Schechter, M.S.

15 Relationship of Socioeconomic Status and Environmental Tobacco Smoke Exposure with Disease Outcomes in the EPIC Observational Cohort
Schechter, M.S.; Emerson, J.; Rosenfeld, M.; The EPIC Study Group

16 Pancreatic Enzyme Replacement Therapy in Children With Cystic Fibrosis: A Tale of Two Models
Haupt, M.E.; Kwasny, M.J.; Kim, S.; Schechter, M.S.; McColley, S.A.

17 A Pilot Study Evaluating the Effect of Sulforaphane in Broccoli Sprouts on NRF2 Activation, Measures of Oxidative Stress, and Neutrophil Migration to Mucosal Surfaces in Healthy Volunteers and Subjects with Cystic Fibrosis

18 Activation of NRF2 by Triterpenoids in CF Epithelia Results in Increased Levels of GSH and the Decreased Oxidation of Protective Proteins
We are thrilled to announce that we had 10 members of the CF Center submit Letters of Intent this Spring to the CF Foundation for their basic science or clinical science research grant competitions:

Nael McCarty, PhD
Assem Ziady, PhD
Arlene Stecenko, MD
Michael Schechter, MD
Michael Koval, PhD
Jacob Kohlmeier, PhD
Jason Hansen, PhD
Rabin Tirouvanziam, PhD
Theresa Gauthier, MD
Balazs Rada, PhD