

The Center for Cystic Fibrosis Research Children's Healthcare of Atlanta



Request for Applications and Announcement of Availability of Resources

1. Announcement and Overview

Children's Healthcare of Atlanta (Children's), in collaboration with the Department of Pediatrics at Emory University, recently announced the establishment of the new Center for Cystic Fibrosis Research, a component of the Emory-Children's Cystic Fibrosis Center of Excellence.

Cystic Fibrosis (CF) is the most common life-shortening, autosomal recessive disease among Caucasians in the United States. Although substantial improvements in quality and longevity of life for CF patients have been achieved over the seven decades since the disease was first described, the median predicted age at death remains less than half of that for the non-CF population; children and young adults are still dying from this disease (Appendix A). What will it take to solve this problem? **We need to find new ways to think about CF, new ways to focus on wellness, to turn this "disease" into a "condition".**

Emory University, Children's, and the CF Foundation have made large investments in CF care and research at the Emory-Children's CF care center over the past two decades, including support for the clinical operations, the hiring of new clinician-scientists and basic scientists dedicated to CF research, and the recent establishment of an independent adult CF program. The Emory-Children's program serves more pediatric and adult CF patients than almost any other CF care center in the country. With support from Children's, we are now establishing the Center for CF Research: a collaborative research team centered around translational and basic research in CF that takes advantage of the availability of CF patients at our CF care center and other assets at Children's, Emory, Georgia Tech, and elsewhere in Atlanta. This will be achieved by supporting research projects and research cores that will draw together investigators with various expertise to solve critical problems associated with CF disease.

The goal of the Center for Cystic Fibrosis Research is to engage Atlanta researchers in basic and translational research that will lead to a better understanding of the pathophysiology of this disease and/or generate new devices and treatments to increase the length and quality of life for CF patients. To achieve this goal, the Center for CF Research will make available to Atlanta area investigators a set of resources to enable research that directly impacts CF, including:

- A. **Pilot Project Grants**
- B. **Specialized Research Cores**
- and C. **Clinical samples:** tissues, cells, and body fluids of CF patients.

2. Research Objectives

CF is a multi-organ disease, with a plethora of functional defects. Gastrointestinal complications of CF are usually the first to appear, but are well-managed with nutritional support and enzyme replacement therapies. Most of the morbidity and mortality results from the progressive loss of lung function. As CF patients age, other organ systems also become impacted. For example, nearly half of the CF patients over age 18 years exhibit CF-related diabetes, which further exacerbates the rate of decline of lung function.

CF lung disease is due to chronic inflammation, persistent infection, impaired mucociliary clearance, and susceptibility to damage from oxidative stress. The airway is a complex environment, with multiple lung cell types working to generate and regulate the composition of the airway surface fluid, in concert with components of the innate immune system that are responsible for clearing pathogens. In the CF airway, the delicate balance between these cell types, and the signals that are passed between them, are disrupted. Hence, the CF lung can be considered an ecosystem and studied using the combined approaches of community ecology and systems biology. We will only achieve a complete understanding of the pathogenesis of progressive lung disease in CF by studying this complex environment *in situ*, with all of the relevant components in place.

The leadership team of the Center for CF Research hypothesizes that it is by taking such a systems view of CF disease that the research community will be able to achieve the next major improvements in life-expectancy for CF patients. With this sort of thinking in mind, the novel scientific theme for the Center for CF Research is “**The Systems Ecology of the CF Lung**”.

Researchers supported by the Center will use a variety of approaches to characterize the changes in activities of each of the cell types that make up the community – the epithelial cells, the macrophages, the neutrophils, *etc.* – and in the signals by which they communicate within the community, to identify those changes (including biomarkers of a variety of molecular categories) that are associated with progressive lung disease. A goal of the Center is to apply systems biology approaches and computational modeling to understand how these components of the community interact. These approaches will identify new therapeutic routes. Center researchers will also collaborate with engineers to design a device that monitors the airway of CF patients for those changes, which will allow CF clinicians to recognize the warning signs of impending pulmonary decline in order to initiate aggressive treatment.

The four integrative focus areas for the Center for CF Research are:

Airway Ecology – provides the early-warning system for pulmonary exacerbation

Oxidative Stress – the ultimate driver of lung destruction in CF

Innate Immunity – imperfect defenders against infection in CF

CF Diabetes – markedly accelerates the progression of lung disease

As a consequence of this research program, we hope to be able to intervene early, as a CF patient with established disease transitions from preclinical to clinical status with each acute pulmonary exacerbation, as the newborn begins to show signs of airway colonization by the *Pseudomonas* bacteria, and as the adolescent starts to show signs of CF-related diabetes, thus improving pulmonary outcomes. This will enable **Prospective Healthcare for CF patients: an approach to healthcare that is proactive, predictive, preventative, participatory, and personalized** to the relevant stage of life with the disease.

3. Resources Available – Research Cores

The Center for CF Research will make available to area researchers the following specialized research cores.

- A. CF Clinical Research Lab: providing access to CF patients for the collection of clinical specimens, including tissues, blood, and other bodily fluids, and initial processing of those specimens.
- B. CF Discovery Center and Biospecimen Resource: providing access to stored clinical specimens that are associated with known disease status, for biomarker discovery.
- C. Statistical Modeling and Computation Core: providing access to expertise in statistical modeling and computational biology for application to CF-related studies.

- D. CF Mouse Models Core: providing access to the following mouse models of CF:
1. The C57Bl6 CFTR knockout mouse.
 2. The C57Bl6 CFTR knockout (S489X) gut-corrected mouse.
 3. The Δ F508 CFTR mouse.
 4. The conditional CFTR null allele mouse.

For more information regarding the CF Mouse Models Core, see Appendix B or contact Dr. Jason Hansen, Director of this Core, at jhansen@emory.edu. For more information regarding the other cores, contact Dr. Nael McCarty, Director of the Center for CF Research, at namccar@emory.edu.

4. Resources Available – Pilot Projects

The Center for CF Research invites applications for pilot projects to enable research related to the Center's objectives, as described above.

- A. The goals of the pilot project program include:
1. to produce innovative advances in child health research
 2. to develop new science which will further the Center
 3. to increase collaborative and interdisciplinary CF-related science between Children's, the Emory Department of Pediatrics, and partners at Emory, Georgia Tech, and Morehouse School of Medicine
 4. to achieve a level of preliminary data and project development that will result in successful NIH R series grants and other extramural awards
 5. to synergize the efforts of investigators to reach the critical mass needed for multi-investigator extramural awards, such as NIH Program Project grants

The pilot project program will not be used to support ongoing research of established investigators.

- B. To achieve these goals, proposals for pilot projects must meet the following criteria:
1. All proposals need to include at least one investigator who is a Children's professional staff member, or a faculty member in the Department of Pediatrics at Emory.
 2. Collaborative submissions that include other departments, institutions, centers, etc. are encouraged.
 3. Applications should propose research that targets one or more of the four focus areas listed above.
 4. Budgets should be for \$50,000 to \$100,000 per year for one or two years.
 5. Funding for the second year will be contingent upon satisfactory progress, as determined by the Center for CF Research Steering Committee, and dependent upon the availability of funds.
 6. For the first year, pilot project funding will run from March 1 through December 31, 2010.
 7. First-year awards will be expected to be spent in full by December 31, 2010.
 8. The PI on a pilot project must devote at least 5% of his/her effort to the project for every \$50,000 of annual funding (e.g., for a \$100,000 annual pilot project budget, the PI must devote 10% effort).
 9. The maximum amount that can be applied toward the PI's salary is 25% of the overall annual total.
 10. Equipment (i.e., items over \$5,000) cannot be purchased with pilot project funds.
 11. Indirect costs are not allowed.
 12. Any required institutional compliance protocols (IRB, IACUC, etc.) must be at least submitted by the pilot project application due date.

Pilot project applications will be evaluated by a study section comprised of members of the Emory-Children's CF Center of Excellence Steering Committee listed below and supplemented by other local researchers with appropriate expertise. Pilot project applications will be scored using the new NIH scoring system, with overall scores ranging between 1.0 and 9.0. Investigators that will serve as PI, co-I, or collaborator on a submitted proposal will not be able to serve on the study section. The Center Director will oversee the activity of the

study section, serving in the Program Officer's role. Depending upon the size of requested budgets, two to four pilot projects will be funded in the first year. It is hoped that the number of pilot projects receiving funding will increase in the second year of the program.

5. Key Dates

December 18, 2009	RFA released
February 1, 2010	Deadline for Pilot project application submission
February 15, 2010	Deadline for scores from review panel
March 1, 2010	Pilot project funding to begin with 12 months equivalent of funding
September 1, 2010	Interim progress report due
December 31, 2010	End of project period

6. Application and Submission Information for Pilot Project Proposals

Pilot project proposals will follow the new format for NIH proposals, which can be viewed at: http://grants.nih.gov/grants/funding/424/SF424_RR_Guide_General_Adobe_VerB.pdf, albeit with fewer pages.

In brief, the research component of proposals will be limited to 6 pages, not including references. Use Arial type font, with no less than 11 pitch, with 0.5 inch margins all around.

Proposals must include the following sections:

- A. Face page, using the NIH SF424 form
- B. A scientific abstract, no more than 30 lines in length. The abstract should address the following two additional review criteria:
 - Extramural Funding Plan: Provide specific plans for extramural funding applications related to this project.
 - Leveraging of resources: Explain how the seed grant will stimulate additional opportunities and resources from the parent institutions that will promote sustainable interactions and ongoing collaborations.
- C. Specific Aims page (one page maximum)
- D. Research Strategy, including Significance, Innovation, and Approach (five pages maximum)
- * Note that sections B and C, together, cannot exceed 6 pages.
- E. Literature cited
- F. Vertebrate animals
- G. Human subjects protection plan
- H. Resource sharing plan
- I. Biosketches for all key personnel (using the NIH format, no more than 4 pages each)
- J. Requested budget and budget justification including detailed information for the following categories, separately for each year of requested funding:
 - Personnel
 - Supplies
 - Animal care costs
 - Patient reimbursement costs
 - Other
- * Note that travel costs cannot be reimbursed from pilot project funds unless the travel is required for the accomplishment of the project goals (such as for collection of samples)
- K. NIH format Other Support page for the Principal Investigator
- L. Letter of Support from Department Chairs or Institutional Officials agreeing to the goals of the project and the terms of the award, including absence of institutional overhead costs if award is funded.

* Note that Appendices are not allowed.

Applications should be submitted as a single PDF, containing all sections, to Dr. Nael McCarty at namccar@emory.edu, by 5:00 p.m. on the deadline date listed above.

7. Contact Information

For general information regarding the Center for CF Research, or the Emory-Children's CF Center of Excellence, contact:

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For information regarding the Children's Healthcare of Atlanta Vision Endowment program and the research centers, please see: www.pedsresearch.org.

8. Leadership Team

Center for CF Research
Director, Nael A. McCarty, Ph.D.

Emory-Children's CF Center of Excellence
Director, Nael A. McCarty, Ph.D.
Co-Director, Arlene A. Stecenko, M.D., Dept. of Pediatrics, Emory University
Co-Director, Michael S. Schechter, M.D., M.P.H., Dept. of Pediatrics, Emory University
Other members of the Steering Committee:
David Guidot, M.D., Dept. of Medicine, Emory University
Lindy Wolfenden, M.D., Dept. of Medicine, Emory University
Richard Cummings, Ph.D., Dept. of Biochemistry, Emory University
Peter Scott, M.D., Children's Healthcare of Atlanta at Scottish Rite
Eberhard Voit, Ph.D., Georgia Institute of Technology

Appendix A.: Brief Overview of Cystic Fibrosis

CF is the most common life-shortening recessive genetic disease among Caucasians in the US, affecting approximately 1:2750 live Caucasian births. CF is the second most common inherited disorder occurring in childhood in the United States overall, second only to sickle cell anemia (Am. Lung Assoc.). There are ~30,000 CF patients in this country today, and ~70,000 worldwide. Due to the establishment of CF newborn screening nationwide in January of this year, new patients are being identified at a very young age – young enough to greatly benefit from a new model of prospective healthcare for CF. We need to bring these advances to the forefront soon in order to have the greatest impact on the lives of these new patients.

CF results from mutations in the gene encoding the Cystic Fibrosis Transmembrane Conductance Regulator, CFTR, which forms a chloride ion channel localized to the outer membranes of many types of cells. CFTR plays a variety of physiological roles, most of which are related to the secretion of chloride and water. CFTR function is critical to the physiology of several organ systems: those that are most closely tied to the sequelae of disease are the airways, the intestine, the pancreas, and the sweat duct.

While CF is a multi-organ disease, with a plethora of functional defects, most of the morbidity and mortality associated with CF results from the progressive loss of lung function. CF lung disease is due to chronic inflammation, persistent infection, impaired mucociliary clearance, and susceptibility to damage from oxidative stress. Much of the new knowledge that has been accomplished by the CF research community has arisen from studies of reduced preparations such as, for example, CFTR channel activity in cultured airway epithelial cells. However, the airway is a complex environment, with ~20 different epithelial cell types working together in the context of oxidative burden, many invading pathogens such as bacteria and viruses that all of us are exposed to every day, and multiple immune system cell types charged with preserving sterility, often with added insult from cigarette smoke or other environmental exposures. In the CF airway, the delicate balance between these cell types, and the signals that are passed between them, are disrupted.

Although substantial improvements in quality and longevity of life for CF patients have been achieved over the seven decades since the disease was first described, the median predicted age at death remains less than half of that for the non-CF population (Fig. 1).

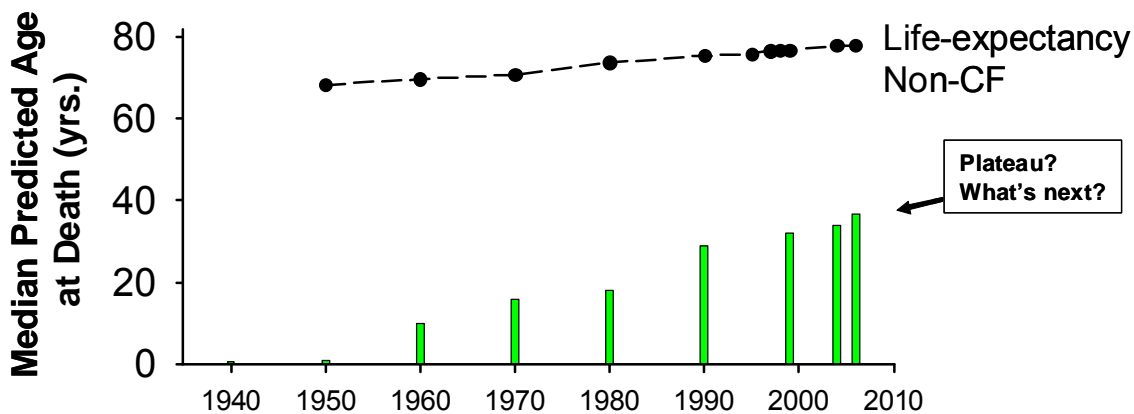


Figure 1. The life-expectancy for CF patients has increased substantially since the disease was first described in 1938. The gene was cloned in 1989. Since then, there have not been increases in life expectancy as rapidly as one might hope. Consequently, CF remains the most common life-shortening disease among U.S. Caucasians, and the quality of life diminishes rapidly as lung function declines toward death. Unfortunately, life expectancy for CF currently is half that of the non-CF population. While we obviously have learned a lot about how to keep CF patients alive longer, CF healthcare at present involves interdisciplinary care of the patient to treat symptoms as they arise. We need new ways to think about CF in order to achieve the next breakthroughs, to close the gap between the CF and non-CF populations.

Appendix B.: The CF Mouse Models Core

The purpose of the CF Mouse Models Core is to provide several useful mouse models of cystic fibrosis to members of the surrounding scientific community, as a mechanism to procure an *in vivo* model of this disease. The advantage of the core is that numerous research projects, all of which converge on CF pathology, would benefit from having these various mouse models readily available to them. While these mice will be available to anyone that requests them and has prior IUCAC approval, there are a number of specific investigators that will benefit scientifically from access to an established CF mouse core, both in the short-term as well as the long-term. The core will maintain at least 4 different CF mouse colonies and 1 related colony (full description below). Many of these colonies are established at other institutions and an aim of the core will be to procure these animals and establish breeding colonies. For CF investigators, having a single local CF mouse core will: (1) decrease the time spent on obtaining animals from other institutions (usually after receiving animals from other institutions there is a lengthy mandatory quarantine period that could be averted), (2) decrease costs to investigators that would normally have to fund the entire colony themselves, (3) give investigators immediate access to animals when they need them, and (4) provide investigator consultation as to which mouse may provide the best model to address their specific project.

The mice that will be included in the CF mouse Models Core are available for purchase or through agreement with other investigators. The four CF mouse models that we will obtain include:

1. The C57Bl6 CFTR knockout mouse ⁽¹⁾.
2. The C57Bl6 CFTR knockout (S489X) gut corrected mouse ⁽²⁾.
3. The ΔF_{508} CFTR mouse ⁽³⁾.
4. The conditional CFTR null allele mouse ⁽⁴⁾.

The CF Mouse Models Core will also have access to the CCL-Cre-recombinase mouse. This is not a CF mouse model but crossing this mouse with the conditional CFTR null allele mouse will allow us to target CFTR knockout in the lung, which is of primary interest to many CF researchers. It is also important to note that we can also obtain other Cre-recombinase mice to facilitate the targeted CFTR knockout in other tissues as well, but this will be based on need by investigators.

On a daily basis, mice will be cared for (providing food and water and changing bedding) by veterinary staff of the Emory Department of Animal Resources (DAR). A technician (50% effort) under the employ of the CF Mouse Models Core will also be hired. His/her responsibilities will include setting up breeding pairs to address the animal needs of investigators, maintaining colonies to a reasonable size (to keep costs down), obtain tail snips for genetic processing, and genotype the different colonies via polymerase chain reactions (PCR) to verify their genetic background. He/She also will work with Dr. Jason Hansen (the core director) to arrange for mice to be shipped and transferred to investigators that request them.

Mice will be made available to area CF researchers at minimal cost.

References:

1. Snouwaert JN, Brigman KK, Latour AM, Malouf NN, Boucher RC, Smithies O, *et al.* An animal model for cystic fibrosis made by gene targeting. *Science* 1992; **257**: 1083-1088.
2. Zhou L, Dey CR, Wert SE, DuVall MD, Frizzell RA, Whitsett JA. Correction of lethal intestinal defect in a mouse model of cystic fibrosis by human CFTR. *Science* 1994; **266**: 1705-1708.
3. Zeiher BG, Eichwald E, Zabner J, Smith JJ, Puga AP, McCray PB, Jr., *et al.* A mouse model for the delta F508 allele of cystic fibrosis. *J Clin Invest* 1995; **96**: 2051-2064.
4. Hodges CA, Cotton CU, Palmert MR, Drumm ML. Generation of a conditional null allele for *Cftr* in mice. *Genesis* 2008; **46**: 546-552.