Cure Cystic Fibrosis Columbus (C3) Research Trainee Award Program
Phase 3 Request for Applications

REVISED FOR CHANGE OF DATES

Purpose of this Request for Applications (RFA): The Cure CF Columbus (C3) program was recently awarded Research Development Program (RDP) status. The grant includes **two trainee fellowships**. The purpose of this RFA is to support highly meritorious **trainee projects (due January 8, 2020)**.

Background: C3 Research is a multidisciplinary project that is focused on curing cystic fibrosis (CF). The C3 Research Community includes physicians and scientists who are located at two sites in Columbus, Ohio: Nationwide Children's Hospital (NCH) and The Ohio State University (OSU). Karen McCoy, MD and Daniel Wozniak, Ph.D lead C3 RDP.

C3 Research Mission Statement: Excessive inflammation and recurrent infections are a hallmark of CF pathophysiology. The C3 RDP mission is to develop treatments that prevent this pathophysiology. The C3 RDP will pursue its mission through investigation of the cellular and molecular mechanisms that underlie inflammation and infection in patients with CF.

The broad objectives of C3 Research are to:
- Conduct research in the area of microbial biology, immune dysfunction, and innate immunity in CF.
- Facilitate collaborations among CF researchers and clinicians at OSU and NCH.
- Provide mentoring and training opportunities to CF investigators.
- Recruit new investigators to C3 research who will enhance our focus and emerging interests.

Established focus areas of C3 research are:
- Microbial pathogenesis of CF pathogens (*Pseudomonas*, *Burkholderia*, *Staphylococcus*, *Haemophilus*, respiratory syncytial virus, non-tuberculous mycobacteria).
- Innate immune cell dysfunction in CF.
- Interactions between and among immune cells, the airway epithelium, and CF pathogens.

The C3 Research Community expects to expand its research portfolio to include:
- Adaptive immune cell dysfunction in CF.
- Cellular therapy for CF.
- Effects of CFTR modifiers on immune cell functions.
- CF related diabetes and digestive system disease.
- Polymicrobial therapeutics.

Definition of trainee grants: Trainee grant applications should focus on basic or translational research. Studies that incorporate use of clinical specimens that are recovered from human subjects (e.g. airway cells, immune cells, BAL, serum, etc.) are highly encouraged. Special consideration will be given to projects that: (1) propose innovative and creative approaches to the problems of CF disease; (2) focus on areas of special and emerging interest to the C3 research (above); and (3) utilize the C3 research cores (attachment).

Overview of the C3 research-*training* ***program***

1. The immediate goals are to support trainees who will:
    a. Develop and test new hypotheses
    b. Develop and test new methods
    c. Apply existing methods to CF for the first time
2. The intermediate goal is to continue to develop a competitive **trainee grant program**.
3. The long-term goal is to enable **trainees** to collect data that are relevant to CF and to **recruit and train our next generation of CF researchers and physicians**.

General Guidelines

1. Trainee eligibility:
    a. Applicants should be currently enrolled in an OSU or NCH training program. These typically include individuals who are at the predoctoral, postdoctoral, or fellow phase of their education.
    b. Applicants cannot hold an existing fellowship award (e.g. T32, CFF postdoctoral, F31/F32 or equivalent) that supports their stipend.
    c. Current C3 trainees supported by C3 funds may apply for a 2nd year of support.
    d. There are no restrictions on US Citizenship or Visa Status.
2. Relevant approvals from the Institutional Animal Care and Use Committee, Institutional Biosafety Committee, and Institutional Review Board must be in place at the time that the trainee grant is awarded.

The **two trainee projects** can be either basic or translational. These projects will be selected during the application process. These applications can be an extension of prior funded C3 Research projects or new proposals from any eligible OSU or NCH trainee.

1. Budget
    a. Up to $25,000 (can be used for partial stipend support, supplies, core services, animal costs, travel, etc.).
    b. For trainees with prior C3 support, a second year of funding is contingent on demonstration of satisfactory progress and approval by the C3 Research Internal and External Advisory Boards. A separate budget and justification will be required at this stage.
    c. No indirect costs will be provided.
2. Applications
    a. Scope of the work should encompass a one year project period
    b. NIH formatting must be followed (use template)
    c. Appendices will not be allowed.
    d. Complete Face Page (template attached).
    e. Research Plan maximum length: 6 pages
        i. Research Strategy (6 page limit), include the broad aims of the project and the hypothesis to be tested, relevance of the project to the CFF and research missions, an indication of how C3 core resources will be utilized, a description of supporting preliminary data, approach (research design), anticipated results, and alternatives.
        ii. References (not included in above 6 page limit)
        iii. Trainees with prior support from C3 (second year) must only include a 2-page summary of progress towards the aims of their prior proposal including presentations, manuscripts, or other public communications of progress. These individuals do not need to complete above sections i-ii.
    f. An NIH style biosketch from the trainee and the primary mentor must be included (template attached).
    g. Mentor letter of support and training plan (2 page limit). This should include (i) the merits of the trainee, (ii) a discussion of how the mentor will develop the trainee's capabilities for CF- and C3-related research or clinical activity, (iii) the training environment, and (iv) the relationship of the current application to the trainee's long-term career goals.
    h. C3 strongly encourages that trainees enlist a CF clinical mentor. This would likely be a physician who is involved in CF clinical activities and is knowledgeable about research related to CF.
3. Materials needed for applications (assemble in order below in single PDF)
    a. Face page/signature page as described above (template attached)
    b. Research Plan (new applicant)
    c. Two page progress report (prior funded applicants)
    d. Budget and budget justification (templates attached)
    e. NIH style biographical sketch from trainee and mentor(s). (5 page maximum; template attached)
    f. Mentor training plan
    g. Facilities available (template attached)

4. **Due January 8, 2020, midnight EST**
5. Submit a single PDF of the application to: PulmonaryGrants@nationwidechildrens.org
6. Review
    i. Members of the C3 Research Internal Advisory Board will conduct the initial review.
    ii. Each reviewer will submit a written review using the CFF review template (see attached).
    iii. Each grant reviewer will provide 4 scores (see reviewer template):
        a. Applicant (30%)
        b. Training plan, mentor, and environment (30%)
        c. Scientific Merit (30%)
        d. Relevance to CFF and the C3 research mission (10%)
    iv. The C3 Research Internal Advisory Board will review the applications and decide on potential funding

Key Dates:

RFA released:	November 8, 2019
Full Grants Due:	**January 8, 2020 (midnight EDT)**
Award Notifications:	Late February, 2020
Earliest Start Date:	**March 1, 2020**

Attachments

a. C3 Research Core Descriptions
b. Review template

Required Form Templates (Separate files)

a. Face page template
b. Research plan template
c. Detailed budget template
d. Budget justification
e. Research plan template
f. NIH Biosketch template

Epithelial Cell Core (ECC) (Directors: Mark Peeples, Estelle Cormet-Boyaka, and Susan Reynolds)

Our ECC evolved from our CFF-funded "Lung Cell Facility" which has procured and supplied CF lung explants to UNC, Chapel Hill, for the past 10 years. The UNC CF Center isolates airway epithelial progenitor cells and differentiates them into primary human bronchial epithelial (HBE) cultures. HBE cultures closely model the *in vivo* airway epithelium and are a critical tool for CF research. The UNC staff trained our staff to produce HBE cultures and we used the CFF funds to isolate airway progenitor cells from non-CF donor lungs, differentiate them, and supply HBE cultures to a number of NCH or OSU scientists. Recent advances in the efficiency of progenitor cell expansion, speed of maturation, and level of ciliation (up to 90%) in HBE cultures have greatly enhanced the quality of these cultures. With additional funding from CFF, our ECC has been able to provide more HBE cultures to more investigators and to use a small portion of the airways from explanted CF lungs to also produce CF-HBE cultures. More recently, we have begun to provide differentiated nasal epithelial (HNE) cultures from both CF and non-CF patients. We also have the ability to measure multiple chemokines and cytokines in the apical and basolateral secretions. In addition, we provide services and expertise related to ion channel expression and function as well as the assessment of mucociliary function. These measurements include: 1) CFTR and ENaC ion channel function using Ussing chambers; 2) CFTR channel expression using immunoblotting and immunofluorescence; 3) Mucociliary clearance function including airway surface liquid (ASL) height and composition and ciliary beat frequency (CBF); and 4) mucociliary transport (particle tracking). HBE cultures are provided to investigators with a product sheet describing the sex, age, CFTR genotype and smoking history of the donor, and the CFTR and ENaC ion channel functions of cultures from that donor. We are developing methods to quantify cell types in HBE cultures and will also include that information with the cultures. We have also developed methods to initiate and sustain bacterial colonization of HBE cultures.

Immune Core (IC) (Directors: Benjamin Kopp and Amal Amer)

CF patients are prone to infections by several pathogens including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Burkholderia cenocepacia*, and non-tuberculosis *Mycobacteria*. CF patients also tend to exert hyper-inflammatory responses, which are associated with tissue damage. Therefore, it is now recognized that CF immune cells such as macrophages, neutrophils, and T cells are intrinsically dysfunctional. Our services will support projects and C3 RDP members who seek to understand complex CF host-pathogen interactions and inflammation and thereby develop novel therapeutic strategies that prevent the establishment of chronic infections and tissue destruction. The immune core will facilitate this research through 1) the isolation and analysis of live immune cells, including live neutrophils, lymphocytes, monocytes, and monocyte-derived macrophages from the blood of patients with and without CF. Isolation of alveolar macrophages and neutrophils from bronchoalveolar lavage (BAL) and tissue-resident macrophages from parenchymal explanted lung tissue will be also provided to laboratories. 2) 'Omics study design and analysis which will be performed in conjunction with the NCH Flow Cytometry Core and the Institute for Genomic Medicine's Genomic Services Core including single-cell transcriptomics, whole blood or BAL transcriptomics, and metabolomics. Chemokine and cytokine measurements of BAL samples or whole blood will also be performed. Finally, 3) functional analysis including halide efflux and patch-clamp electrophysiology for CFTR and other ion channels within immune cells.

CF Translational Core (CFTC) (Directors: Karen McCoy and Nilsa Ramirez)

Research is integral to understanding disease and developing potential treatments. The C3 Translational Core seeks to aid researchers by establishing a conduit for translational research study design and simultaneous access to patient-derived materials that will be obtained, linked with patient data, and de-identified for distribution to the cores outlined above and to individual CF researchers upon request. We also maintain a bank of targeted biospecimens (BAL, sputum, bacterial strains) to which our researchers have easy access. Some of the biospecimens will be received as residual specimens from Projects, and others will be processed directly from CF patients as part of normal clinical care and from normal healthy controls. While a small number of specimens will be processed for long-term storage until distribution for research, the majority of specimens will be in response to requests from investigators.