Advancing Research for Improving Outcomes of Cystic Fibrosis Lung Transplantation

Request for Research Grant and Pilot & Feasibility Applications

POLICIES AND GUIDELINES

June 14, 2016
I. MISSION
The mission of the Cystic Fibrosis Foundation (CFF) is to cure cystic fibrosis and to provide all people with the disease the opportunity to lead full, productive lives by funding research and drug development, promoting individualized treatment, and ensuring access to high-quality, specialized care. To meet this mission, various types of grants are offered to support meritorious research ranging from basic laboratory investigation to clinical management of CF.

II. BACKGROUND
Cystic fibrosis is a common, lethal autosomal recessive disorder that affects 70,000 individuals worldwide. Abnormal mucus production in the respiratory tract is the primary cause of morbidity and mortality in CF, but other organs are also affected including the pancreas, sweat gland, intestine, bile duct of the liver, and male reproductive system. CF is caused by dysfunction of a single gene, Cystic Fibrosis transmembrane Conductance Regulator (CFTR), which codes for an ABC transporter protein that functions as a chloride (Cl-) channel at the apical membrane of epithelial cells.

Close to 2,000 variants of CFTR have been identified, however a single mutation, F508del (a 3bp deletion causing absence of phenylalanine 508) is present in ~90% of patients worldwide. Clinical development of small molecule CFTR modulators that reverse the folding defect holds promise for new therapies for the majority of CF patients. However, there is still an unmet need for improve the quality of life and life expectancy of patients with end-stage CF lung disease.

Lung transplantation is a treatment option for CF patient with advanced obstructive lung disease resulting from decades of lung infection, inflammation, and progressive bronchiectasis. While the transplant surgery replaces the damaged lung, CF patients are susceptible to post-transplant lung infections due to complications of immune suppression, graft rejection, and bronchiolitis which impact long-term survival. Approximately 200 CF patients receive lung transplants each year, however, only around 50% of these patients will survive after 5 years. To address these issues, it will be necessary to better understand transplant biology and the mechanisms of actions for lung rejection.

III. CFFT REQUEST FOR APPLICATIONS
Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), the non-profit drug discovery and development affiliate of the Cystic Fibrosis Foundation, announces a Request for Applications (RFA) to identify and support highly meritorious research proposals in the area of lung transplantation that will improve the understanding of transplant biology and outcomes of lung transplant for cystic fibrosis patients. Currently, treatment options for patients with end-stage CF lung disease are suboptimal and constitute an area of unmet need. Emphasis will be given to studies that focus on topics of transplant immunology, biological mechanisms involved in lung allograft dysfunction, identifying biomarkers of rejection and tolerance, and developing new model systems.

IV. RESEARCH OBJECTIVES AND AWARD OVERVIEW
The objective of this RFA is to fund highly meritorious research projects that will aid in understanding the mechanism(s) of lung transplant rejection and identifying approaches to improve survival in cystic fibrosis patients post lung transplantation. Projects of interest include areas addressing: (1) transplant immunology and, (2) advancing technology platforms and animal models to support studies of lung infections and acute and chronic allograft dysfunction, particularly bronchiolitis obliterans syndrome.
Areas of interest include, but are not limited to:

- Understanding the biological pathways and mechanisms of action of immune modulation involved in ischemia-reperfusion injury and primary graft dysfunction
- Understanding cellular and humoral immune changes corresponding to lung infections after lung transplantation in CF and non-CF patients
- Identifying the risk factors and pathogenesis of chronic lung allograft dysfunction/bronchiolitis obliterans syndrome (BOS)
- Advancing the technology platforms (e.g. RNA Seq, proteomics, microbiome) to understand the clinical phenotypes and to identify new targets to prevent and treat chronic lung allograft dysfunction
- Developing novel animal models of chronic airway rejection
- Discovering novel biomarkers to identify CF patients at high risk for chronic lung allograft dysfunction and to guide studies of prevention and early treatment of chronic lung allograft dysfunction

A goal of this RFA is to promote collaboration between investigators with complementary expertise. Collaborations between academics and industry are also encouraged.

**Research Grants:** Funding up to $150,000 per year (for 2 years), plus eight percent (8%) indirect costs. A limited number of larger awards will be considered for funding up to $250,000 per year (for 2 years), plus eight percent (8%) indirect costs, with strong justification (e.g., animal models).

**Pilot and Feasibility Studies:** Funding of up to $75,000 for one year, plus eight percent (8%) indirect costs.

Applications must be submitted online at Proposal Central: [https://proposalcentral.altum.com/](https://proposalcentral.altum.com/)

V. **ELIGIBILITY**
United States residents and applicants from outside the United States are welcome to apply for Research Grants and Pilot and Feasibility Studies.

VI. **SUBMISSION INFORMATION & GENERAL TIMELINE**

**Application Deadline:** Friday, September 2, 2016, 5:00 PM (Eastern)

Applications must be submitted through Proposal Central, [https://proposalcentral.altum.com/](https://proposalcentral.altum.com/) by 5:00 pm (Eastern). Email a pdf copy of the signed Face Page to awards@cfft.org by the same date. Late applications will not be accepted and the deadline will not be waived. The Foundation reviews applications electronically, and only the documents submitted online will be reviewed.

**General Timeline**

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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<tbody>
<tr>
<td>Application Deadline</td>
<td>September 2, 2016</td>
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<tr>
<td>Review Committee Meeting</td>
<td>early November 2016</td>
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<tr>
<td>Applicant Notified/Award Letter Issued</td>
<td>mid November 2016</td>
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<tr>
<td>Earliest Start Date</td>
<td>December 1, 2016</td>
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VII. REVIEW AND AWARD

Applications will be reviewed by a CFIT ad hoc review committee. Formal award of programs is based upon the availability of funds, the merit of the application, and the recommendations of the reviewers. All awards will be made in compliance with the regulations and CFIT policies.

Proposals should clearly demonstrate how the research will advance our understanding of transplant biology and outcomes of lung transplant for cystic fibrosis patients.

Applications will be evaluated on the following:

- Relevance to the priority areas stated above
- Scientific merit of the project as described in the applicant’s Research Plan
- PI’s background and experience
- Adequate facilities for the project
- Collaborative projects
  - How the individual applicant fits within the larger collaboration?
  - Synergy among the groups
  - Value added from the collaboration with other applicants to this program
  - How individual applicants will communicate and collaborate (e.g., sharing reagents and data)
  - Consultant arrangements and/or collaborations (if any) with other investigators outside the applicant’s group

Low priority scores in the reviews commonly result from the following shortcomings of the application:

- Failure to address the evaluation criteria described above
- Insufficient information or documentation
- Inadequate statement of hypotheses, experimental design or methods
- Failure to demonstrate awareness of and plans for coping with key problems and pitfalls associated with the proposed research
- Insufficient or improper controls
- Failure to describe potential relevance of the proposed study to issues in CF
- Failure to document the necessary skills or training to accomplish the goals of the proposal
- Failure to identify access to resources outlined in the application (e.g., airway epithelial cells)
- For collaborative projects, insufficient justification for collaboration or inadequate description of how the collaboration will be carried out.

VIII. APPLICATION INSTRUCTIONS

- Font: Times New Roman 12 or Arial 11 font
- Margins: Standard ½”
- When all the documents have been uploaded to Proposal Central, the system will compile them into a single PDF file in the correct sequence

1. FACE PAGE (System Generated)

The Face Page is populated automatically with data entered in the online application (applicant’s name, institution, title of application, etc.). The Face Page can be downloaded after completing the application and clicking on the “Validate” button (Proposal Section 11). The Face Page must be signed by the Principal Investigator and Authorized Institutional Official. Co-Principal Investigators, if any, are not expected to sign the Face Page. However, signed letters of collaboration from Co-
Principal Investigators should be provided in the Appendix. Scan and email the signed Face Page to awards@cfft.org by the deadline. No hardcopy is required.

2. ABSTRACTS - SUMMARY OF RELEVANCE – KEYWORDS
Enter the abstracts and relevance information online (Proposal Section 6). A system-generated page will get attached to the application. There is no need to upload the same information in a separate document.

Lay Abstract
In the space provided online, provide a statement of no more than 250 words (up to 2,000 characters max, including spaces) explaining the subject of the research proposal and its relationship to CF. This statement will be used to inform the general public of the nature of this work.

Scientific Abstract
In the space provided online, provide a statement of no more than 250 words (up to 2,000 characters max, including spaces) explaining the subject of the research proposal and its relationship to CF. This statement will be used to inform the scientific community.

Summary of Relevance to CFF mission
All applications are reviewed and scored not only on scientific merit but also on relevance to CFF’s mission.

The mission of the Cystic Fibrosis Foundation is to cure cystic fibrosis and to provide all people with the disease the opportunity to lead full, productive lives by funding research and drug development, promoting individualized treatment, and ensuring access to high-quality, specialized care.

Provide a statement of no more than 250 words (up to 2,000 characters max, including spaces) summarizing the relevance of the proposed research to the health and well-being of CF patients, for a scientific audience who may or may not have a background in the subspecialty of the proposed research.

3. RESULTS OF PAST AND CURRENT CFF/CFFT SUPPORT
Use the form provided for download on Proposal Central. Applicants are requested to identify the results of past and current CFF/CFFT support (e.g., subsequent funding from other sources, journal articles, and invited presentations) and the CFF/CFFT grant/award from which they resulted for the past three to five years. The form should be completed by the applicant, and uploaded to the application. Please note that the following information must be included with each research project identified:

- CFF/CFFT Account #
- Principal Investigator (PI)
- CFF/CFFT Project Title
- Applicant’s Title on Project
- Project Start/End Dates
- Total CFF/CFFT Award Amount
- Results of Support
4. **BUDGET AND JUSTIFICATION**

Complete the online budget summary in addition to a detailed budget and budget justification (templates provided online in Proposal Section 9) for each year of the research plan. Be sure the detailed budget matches the online budget summary. Budget restrictions are based on the type of application submitted, and are as follows:

**Research Grants:** Funding up to **$150,000 per year (for 2 years)**, plus eight percent (8%) indirect costs. A limited number of larger awards will be considered for funding up to will be considered for funding up to $250K per year (for 2 years), plus eight percent (8%) indirect costs, with strong justification (i.e. animal models).

**Pilot and Feasibility Studies:** Funding of up to **$75,000 for one year**, plus eight percent (8%) indirect costs.

**Detailed Budget – Direct Costs**

**Personnel** - List the name and title of the applicant. Indicate dollar amounts separately for salary and fringe benefits. Fringe benefits may be requested if they are treated consistently by the applicant institution as a direct cost to all sponsors.

**Consultant Costs** – Give the name and institutional affiliation of any consultant who has agreed to serve in this capacity, including statisticians and physicians in connection with patient care if they are not listed under personnel. In the budget justification, briefly describe services to be performed, the number of days, rate of compensation, per diem and any other associated costs.

**Equipment** - List all items of equipment requested, their cost and a brief justification. If funds are requested to purchase equipment that is equivalent to items listed under Facilities Available, justify the duplication.

**Supplies** - Itemize supplies e.g., glassware, chemicals, animals, in separate categories and give the estimated cost of each category. If animals are involved, state the number, unit purchase cost, and unit care cost.

**Travel** - Describe the purpose of any travel. All travel expenses must comply with the *Cystic Fibrosis Foundation Volunteer/Vendor Expense Reimbursement Policies*. Expenses for travel outside the North American continent are not allowable. Also note that request for travel funds should be limited to **$2,000 per person per year**.

**Other Expenses** - Itemize other expenses by major categories, such as duplication costs, publication costs, etc. Justify all items.

**Subcontracts** – The total cost of each subcontract (directs plus indirects) should be listed under “Other Expenses” and included in the applicant’s direct costs. The applicant institution may request indirects only on the **first $25,000 of each subcontract**. Detailed budgets for each subcontract must be provided for each year of support. Negotiations of subcontracts are between the applicant institution and the subcontractor.

**Indirect Costs** – Indirect costs up to 8% are allowable on these awards.
Budget Justification
Describe costs listed in the Detailed Budget. Use major categories, such as Personnel, Supplies, and Travel.

5. FACILITIES AVAILABLE
Use the template available for download on Proposal Central. Describe the facilities and equipment available at the applicant’s institution that will be used for this project, such as laboratory, clinical, animal, computer, office, etc. Provide any additional information about the environment, including any support services available that will be utilized. Describe their pertinent capabilities, proximity and anticipated extent of use. If facilities or equipment at a consultant’s or collaborative site will be used, they should be identified and clearly described. There is no page limit. Use continuation pages, if necessary.

6. BIOGRAPHICAL SKETCH
Complete and upload an NIH Biographical Sketch for all key project personnel, beginning with the Applicant/Principal Investigator (fellow). (CFFT defines “key project personnel” as any individual with an advanced degree that will play an instrumental role in the accomplishment of the research project.) Do not exceed five (5) pages per person. A sample NIH Biographical Sketch is available for download on Proposal Central.

7. OTHER SUPPORT
Complete and upload an Other Support form, for all key project personnel, beginning with the Applicant/Principal Investigator (fellow). (CFFT defines “key project personnel” as any individual with an advanced degree that will play an instrumental role in the accomplishment of the research project.) There is no page limitation.

8. RESEARCH PLAN
Key figures and legends must be included in the Research Plan.

Page limit: Ten (10) single-sided pages, not including the Literature Cited. A template is available for download on Proposal Central. At the top of each page, type the PI’s name. Each page must be sequentially numbered at the bottom.

Include sufficient information to permit effective review. Information should be presented in a clear and concise manner, while being specific and informative.

Hypothesis and Specific Aims. State concisely and realistically the intent of the proposed research and the hypothesis to be tested. The specific aims should be relevant to the mission of the Cystic Fibrosis Foundation. Do not exceed one page.

Background and Significance. Briefly describe the background. Critically evaluate existing knowledge and specifically identify the gaps that the project is intended to fill. Concisely state the importance and rationale of this research by relating the specific aims to longer-term objectives. This section should also show the potential importance of the proposed work to CF in particular those listed as areas of special interest to CFFT. In addition, for postdoctoral fellowship applications, describe the relationship of the proposed work to your long-term career goals.

Preliminary Results. If applicable, provide a detailed discussion of any preliminary results.
Experimental Design and Methods. Provide a detailed discussion of the experimental design and methods to be used to accomplish the specific aims. Describe the protocols, including methods for new techniques, and explain potential advantages over existing methodologies. Discuss the data expected to be obtained and the means by which data will be analyzed and interpreted. If clinical studies are involved, provide details of the methods for patient selection and care. Discuss potential difficulties and/or limitations of the proposed procedures and alternative approaches to achieve aims. Point out any procedures, situations or materials that may be hazardous to personnel or patients and the precautions to be exercised.

*For sample size estimates*, please provide all estimates of means, standard deviations, rates or proportions used to calculate each of your sample size or power estimates. Please include in the statistical section whether you will use a one or two-tailed test, the power selected for such a test (if making a sample size calculation), and the reference for your sample size or power calculation. In instances of pilot studies where some of these parameters are unknown, we will accept your best estimates of the unknown parameters if preliminary data are not available, and if your calculation is a preliminary estimate before formal sample size can be calculated for a larger study. Please identify if you are making estimates from data or from personal estimates. This section must document access to adequate numbers of subjects. The number of CF patients in the participating CF Center(s), as well as the number in relevant control groups, must be specified. Discuss the potential difficulties and limitations of the proposed procedures and alternative strategies for achieving the aims. If the Sponsor(s) is not a CF Center Director or Co-Director, a letter of support from the Center Director is required. Please provide a copy of your institution’s IRB approval and/or protocol with proposed patient consent forms.

Literature Cited. References should be numbered in the sequence that they appear in the text and listed at the end of the Research Plan. Each citation must include the names of authors, the name of the journal or book, volume number, page number and year of publication (titles are optional).

9. **COLLABORATIVE PROJECT DESCRIPTION (if applicable)**

Maximum two (2) pages. Include a list of collaborators and institutions, and describe the following:

- How the individual applicant fits within the larger collaboration
- The synergy among the groups
- Value added from the collaboration with other applicants to this program
- How the individual applicants will communicate and collaborate (e.g. sharing reagents and data)
- Consultant arrangements and/or collaborations (if any) with other investigators outside the designated collaboration.

10. **LETTERS OF SUPPORT FROM COLLABORATORS/CONSULTANTS**

Co-Principal Investigator(s). A signed letter from Co-PIs (if any) must be uploaded with the letters of support.

Collaborative Projects. Signed letters of support must be provided from all collaborators and should include a brief description of the collaboration, and the value added from the collaboration.

Consultants/Collaborators. For consultant arrangements with investigators outside the applicant’s or Collaborative Project’s group, the letter should describe the working relationship.
**Collaborators who are furnishing required clinical materials.** The letter should include a statement agreeing to their participation and precautions taken to ensure anonymity of patients.

11. **VERIFICATION OF APPLICANT INSTITUTION’S TAX STATUS**
Per Internal Revenue Service (IRS) stipulations for grant-making organizations, CFFT’s Grants and Contracts Office must have a copy of the applicant institution’s current W9 and 501(c)3 letter, or other documentation verifying its Federal tax status, on file. CFFT’s Grants and Contracts Office will not issue Award Letters to Grantees if these documents are not on file.

Applicants from for-profit organizations must submit a copy of the applicant institution’s W9 and IRS Form 147C, or other documentation verifying the organization’s Federal tax status. Awards are not issued prior to having these documents on file with the CFFT Grants and Contracts Office.

Non-U.S. applicants must provide a copy of the W-8BEN-E form (required). In addition, a tax equivalency letter should be uploaded, if available. If a tax equivalency letter is not available, applicants must upload a letter stating this documentation is not available.

12. **INTERNATIONAL INSTITUTION FORM** (Upload as an attachment, if applicable)
Applicants whose sponsoring institution is not based in the United States must complete the International Institution Form. The template is provided for download on Proposal Central. **Upload a PDF version of the completed and signed form, together with the following documents:**

a. A copy of your organization’s most recent Mission Statement.

b. A copy of your organization’s Tax Exemption Letter, if organization is not-for-profit.

c. A description of other sources of support, such as official grants, private endowments, and commercial activities, received by your organization.

d. A copy of your organization’s Standard Operating Procedure(s) or relevant policy to ensure that funds provided are neither distributed to terrorists or their support networks nor used for activities that support terrorism or terrorist organizations.

e. For-profit organizations must submit a complete list of key employees, members of the governing board, and/or other senior management.

English translations must be provided for any documents that are written in the applicant’s or sponsoring institution’s native language, including material provided in support of the Research Plan.

IX. **ORGANIZATION ASSURANCES & CERTIFICATIONS**

**Research Involving Human Subjects**
The IRB application must be submitted to your institution **prior to** the CFFT application deadline. CFFT policy pertaining to the protection of individuals as research subjects requires that for each proposal submitted, the applicant institution certify in writing that an Institutional Review Board (IRB) has reviewed and approved the procedures for the use of human subjects, or human organs, tissues and body fluids, in the proposed research, in accordance with Department of Health and Human Services regulations. This certification should accompany the application and **must be** received prior to activation of any grant. If the approval is pending, give the date when it is expected. The approved certification should be submitted as soon as it is available.
If clinical material required by this grant is to be furnished by other investigators, indicate how the clinical material will supplement the project and what precautions will be taken to ensure anonymity of patients.

**Research Involving Recombinant DNA**
All research involving recombinant deoxyribonucleic acid (DNA) techniques and human gene transfer supported by CFFT must meet the requirements contained in the document *NIH Guidelines for Research Involving Recombinant DNA Molecules*. The purpose of these guidelines is to specify practices for the construction and handling of: (i) recombinant deoxyribonucleic acid (DNA) molecules, and (ii) organisms and viruses containing recombinant DNA molecules. As defined by those guidelines, recombinant DNA molecules are either: (i) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell; or (ii) molecules that result from the replication of those described in (i) above.

Many types of studies involving recombinant DNA are exempt from the *NIH Guidelines* while others are prohibited. The applicant organization is required to establish and implement policies that provide for the safe conduct of the research in full conformity with the *NIH Guidelines*. This responsibility includes establishing an Institutional Biosafety Committee to review all recombinant DNA research to be conducted at or sponsored by the applicant organization, and to approve those projects it finds are in conformity with the Guidelines.

CFFT policy pertaining to recombinant DNA research requires that the applicant institution certify in writing that an institutional committee has reviewed and approved the procedures involving recombinant DNA in accordance with the *NIH Guidelines*. Applicants that do not have institutional committee approval must submit a recombinant DNA application to the applicant institution BEFORE the CFFT application deadline. Certifications need not accompany the application, but all required certifications should be available upon request by CFFT.

**Research Involving Animals**
Grant applications submitted to CFFT involving the use of animals must meet the guidelines of the National Institutes of Health, U.S. Public Health Service, which require that all proposed studies be reviewed and approved by an Institutional Animal Care and Use Committee (IACUC). In addition, CFFT grantee institutions and laboratories must be accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC) and/or have other verifiable assurances that the institution and laboratory meet appropriate standards. **Applicants that do not have institutional committee approval must submit an IACUC application to the applicant institution BEFORE the CFFT application deadline.** Certifications need not accompany the application. Applicants must be able to provide copies of all required certifications upon request by CFFT.
X. ONLINE SUBMISSION

DEADLINE: September 2, 2016 by 5:00 pm (Eastern)

a. Registration and Log In: If you are a first time user, register at Proposal Central https://proposalcentral.altum.com. If you have registered before, and cannot remember your password, click on the “Forgot Password” button.

- Select the gray tab labeled **GRANT OPPORTUNITIES**.
- Locate Cystic Fibrosis Foundation Therapeutics in the list.
- The APPLY NOW button will be visible next to the program name: “Advancing Research for Improving Outcomes of Cystic Fibrosis Lung Transplantation.” Click on the APPLY NOW button to begin.

Start and Continuation: Application Sections are listed in the gray menu box to the left of the screen. The sections need not be complete sequentially. Click the red SAVE button after completing each section.

Enter your project title as **“Improving Outcomes of CF Lung Transplantation.”**

You may stop at any point in the application, each time remembering to SAVE your entries, and return to continue, revise, and upload until you have actually hit the SUBMIT button.

When you log in to continue, click on the blue tab, MANAGE PROPOSALS, and then the Edit button next to your application’s title. Do not start a new application.

b. Designating Access to Another: Complete Section 3 online if you wish to designate access to another individual, such as an assistant who has registered on proposalCENTRAL. Enter the full name and email address and in the Permissions column, then use the pulldown menu to select the type of access you wish to give.

c. Final Steps

1. **Validate**: Upon completing your application, click on the blue VALIDATE button on the main screen. Attend to any omissions/errors as prompted onscreen, if prompted, and validate again.

2. **Print face page**: After validation, follow the prompts to print the system-generated face page.

3. **Submit**: Click on the gray button with blue lettering. **Submit** CFFT will not receive your application until and unless you have submitted it. You will receive an email confirmation from proposalCENTRAL (not from CFFT) that your application has been successfully uploaded. This email will be your only acknowledgment. If you do not receive it, please contact proposalCENTRAL immediately to ensure that the application is properly submitted.

4. **Sign, scan and email the face page** to awards@cfft.org by the deadline date, November 9, 2016. The Program Director, as well as the authorized institutional official must sign it. No hard copy is necessary.
For technical support with the online application:
Proposal CENTRAL at pcsupport@altum.com or
800-875-2562 on weekdays, 8:00 a.m. to 5:00 p.m. (Eastern)

For program/content information:
CFFT Grants & Contracts at awards@cfft.org or 301-841-2614