Overcoming Obstacles for Nucleic Acid Delivery for Cystic Fibrosis: Collaborative Research Grant

POLICIES AND GUIDELINES

Published: May 23, 2019
Application Deadline: August 21, 2019
I. ABOUT THE CYSTIC FIBROSIS FOUNDATION
The mission of the Cystic Fibrosis Foundation (CFF) is to cure cystic fibrosis (CF) 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 achieve this mission, various types of awards are offered to support meritorious research in CF.

II. BACKGROUND
Cystic Fibrosis is a 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), a member of the ABC transporter gene family and which encodes a protein that functions as a plasma membrane anion channel in epithelial and other cells. Close to 2,000 variants of CFTR have been identified, many of which result in misfolding of the protein or disrupt chloride channel function.

Clinical development of small molecule CFTR modulators that reverse the folding defect and potentiate channel opening are promising therapies that will likely impact a majority of CF patients. However, there is still an unmet need for patients with CFTR mutations that either do not respond to modulators, do not generate sufficient quantities of protein for correction, or block protein synthesis (i.e. premature stop codon mutations, splice mutations, insertion/deletion mutations etc.). To treat all patients with CF, it will be necessary to develop nucleic acid or genetic-based approaches that can restore CFTR expression and function. In order for these therapeutic strategies to be successful it will be necessary to overcome the challenge of delivering to the appropriate cells and tissues.

To better understand obstacles, limitations, and challenges for developing a permanent cure for CF, the Cystic Fibrosis Foundation held a workshop focused on delivery of nucleic acid-based therapies. As an outcome of the workshop, the Cystic Fibrosis Foundation announces a Request for Applications (RFA) to identify and support highly meritorious proposals that significantly advance the capacity to accurately and selectively deliver nucleic acid therapies to the lungs and/or disease relevant cells. For the purpose of this RFA, nucleic acid delivery is defined broadly, extending beyond delivery of gene editing technologies to manipulate DNA and thus may include technologies and methods to deliver ribonucleoprotein, mRNA, super-exons, antisense oligonucleotides, or any other method that has the potential to restore normal CFTR function.

III. COLLABORATIVE RESEARCH GRANT PROGRAM AWARD OVERVIEW
The objective of the Collaborative Program is to support an integrated, multi-investigator collaborative research program with a well-defined, central focus related to developing strategies to deliver nucleic acid technologies. A single Collaborative Program can include up to four related research projects (each led by a separate PI) that share a well-defined collaborative theme, focus, and/or overall objective.

Each project supported through this mechanism must contribute to a common unifying theme or focus for the overall Collaborative Program. Each individual project should reflect an individual
scientically meritorious research effort. However, the individual research projects should be clearly interrelated and synergistic so that the outcomes of the Collaborative Program will offer a distinct advantage over pursuing individual research projects separately. Multi-institution collaborations are encouraged where synergy is clearly described. However, Collaborative Programs may include multiple investigators at the same institution. Applicants are also encouraged to include investigators who are new to the CF field, but have expertise in topics specifically relevant to this RFA.

One grant application is required for all Collaborative Programs. One PI must submit the application on behalf of all participating collaborators. Each project that is part of the Collaborative Program must provide an independent Research Plan, Budget Detail and Budget Justification which will be incorporated into the single application’s overall Budget Summary (see proposalCENTRAL for instructions).

The lead site for the Collaborative Program grant is eligible for administrative support, up to **US$25,000** direct costs per year. The administrative budget is designed to help support the day-to-day activities across the program, communications among projects, contractual activities (if any), and other overall program activities, such as leadership meetings. The administrative funds should be included in the Budget Detail and Budget Justification for the applying PI/lead project. Indirect costs are not allowable on administrative support costs.

For consultant arrangements with investigators outside the applicant’s or Collaborative Programs’ groups, letter(s) of support should be included with a description of the working relationship and communication/data sharing plan.

Collaborative, synergistic projects are considered particularly valuable when bringing together investigators with complementary expertise to advance the development and application of nucleic acid delivery strategies.

To bring new technologies and expertise to the CF field, investigators without experience in CF are encouraged to apply. Information about CF resources may be found at [http://www.cff.org/Research/Research-Resources/Tools-and-Resources/](http://www.cff.org/Research/Research-Resources/Tools-and-Resources/). Additional questions may be directed to [grants@cff.org](mailto:grants@cff.org).

Applicants are strongly encouraged to contact John Sheridan at [jsheridan@cff.org](mailto:jsheridan@cff.org) prior to submission to ensure alignment with the goals and objectives of this RFA.

**Research Areas of Interest:**

Many basic pathophysiological questions remain that need to be addressed in order to effectively deliver nucleic acid therapies. Specifically, it is unknown which region of the lung (upper or lower airways) primarily contributes to CF pathogenesis and whether restoring CFTR function in the submucosal glands is necessary. Additionally, the airway epithelium is a heterogenous mix of various cell types that may have differing roles in the pathogenesis of CF. Identifying the relevant cellular targets in the lung for CFTR correction is needed.

The CF lung in particular presents unique challenges for delivering an inhaled or aerosolized therapy. A delivery vehicle must be able to efficiently navigate through the airways, deposit in the correct
anatomical location, penetrate a concentrated and dehydrated mucus layer while simultaneously avoiding the immune cells that infiltrate the lung. Once the vehicle reaches the lung epithelium, it then must have the appropriate biochemical properties for cellular uptake, escape the endosome, and efficiently deliver the cargo to the appropriate cellular location in order to restore normal CFTR function. Designing a vehicle or delivery method that has all of these properties is a significant challenge.

An alternative strategy would be to deliver the therapy systemically, which would mitigate the necessity to navigate through the airways and mucus and could potentially be used to target other tissues affected by CF, such as the biliary tree, pancreas, GI epithelium, and endocrine tissues. However, a systemic delivery approach has its own challenges that need to be addressed, such as migrating from the vasculature to reach the target tissues and cells.

Successful proposals will focus on technologies, strategies, tools, and model systems that will advance the efficacy, selectivity, and accuracy of delivering nucleic acid therapies for CF. These include, but are not limited to, studies aimed at:

- Developing and optimizing the chemistry and formulation of delivery vehicles, both viral and non-viral, that can target disease relevant cells and/or lung progenitor cells
- Understanding the role of various pulmonary cell types in CF disease pathogenesis (i.e. ciliated cells, club cells, ionocytes, etc.) and the region of the lung that is necessary to target to prevent, halt, or reverse disease
- Developing and optimizing delivery strategies to evaluate how the route of administration impacts efficacy, safety and off-target effects of nucleic acid therapies
- Creating tools, including animal models and in vitro cell models, that will facilitate and accelerate the assessment of nucleic acid delivery methods and vehicles
- Developing biomarkers, assays, and biological endpoints to functionally characterize the impact of nucleic acid delivery in a CF animal model
- Developing and optimizing methods to overcome barriers that limit delivery to the airway epithelium, such as navigating CF mucus, avoiding respiratory immune cells, enhancing endosomal escape, etc.
- Understanding and developing assays to monitor potential immune responses as they may impact repetitive dosing of the delivery vehicle, cargo, or CFTR protein
- Developing and conducting studies in model systems to evaluate impact of genetic manipulation, duration of efficacy, and to better understand the rate of cellular turnover in the lung

General Guidelines and Eligibility:

- Funding limits are up to US$775,000 per year plus up to twelve percent (12%) of indirect costs may be requested for the Collaborative Program for up to three (3) years. Each Collaborative Program may consist of up to four projects (maximum US$250,000 per project per year plus up to twelve percent (12%) indirects). An additional US$25,000 per year may be requested by the Collaborative Program Lead PI for administrative support of the individual projects.
- To qualify as a Collaborative Program, a minimum of two (2) projects are required. The applicant/lead PI will submit each of the outlined components for the Collaborative Program.
- To foster the next generation of CF researchers, applicants are encouraged to include a project led by a Junior Investigator. A Junior Investigator is defined as an individual who has not received
a CFF/CFFT Research Grant or NIH equivalent (e.g. R01, R21) as a Principle Investigator OR is within their first five years of their academic appoint at the level of Assistant Professor or equivalent.

- U.S. citizens, permanent residents, individuals with appropriate U.S. work visas, and applicants from outside the U.S. are welcome to apply.
- International applicants and institutions are required to submit additional information in accordance with the U.S. anti-terrorism restrictions.
- Applicants must be independent investigators, which is defined as an individual who is out of fellowship training and whose institution allows them to submit applications for research funding as a Principle Investigator.
  - Must be a M.D., Ph.D., or dual M.D., Ph.D., or equivalent
  - Must demonstrate a track record of discovery, investigation, and external funding resulting in long-term commitment of salary, personnel and research resources.
  - Candidates who are still in training positions (i.e. postdoctoral fellows) should apply to the Overcoming Obstacles for Nucleic Acid Delivery for Cystic Fibrosis Postdoctoral Fellowship program.
- Clinical studies are not permitted under this RFA.

IV. REVIEW AND AWARD

Upon receipt, applications will be reviewed for completion and responsiveness to the application guidelines. Applications that are not complete, do not meet the outlined requirements, or are deemed non-responsive by CFF staff will not be reviewed and will be withdrawn from consideration.

All eligible applications will be evaluated by a CFF established external ad-hoc review committee. Funding of awards is based on the priority score given to each application, recommendations of the review committee, and mission of the CF Foundation. The priority score assigned to the proposal will be generated by three criteria: scientific merit, relevance to the RFA objectives, and synergy of the individual projects. All awards are subject to compliance with applicable regulations and CFF policies and are contingent upon the availability of CFF funds.

Collaborative Research Grant applications will be evaluated on the following:
- Relevance to one or more of the priority areas described in the RFA
- Overall merit of the program in moving the field forward
- Scientific merit of individual projects as described in the individual Research Plans
- Preliminary data for the approaches/methodologies should be included. CF-specific preliminary data is not required but encouraged for key components of the study
- Project integration and synergy as it relates to the overall program
- Value added (synergy) from the collaboration
- PI’s/PIs’ background and experience
- Adequate site facilities and resources for the project
- How the individual applicants will communicate and collaborate (e.g. sharing reagents and data)
Chief causes for assigning low priority scores to applications during review include the following:

- Failure to meet the directives of the RFA
- Lack of synergy demonstrated among collaborative investigators
- Insufficient information or documentation
- Inadequate statement of hypothesis (if applicable), experimental design or methods
- Failure of the applicant to demonstrate awareness of and plans for coping with key problems and pitfalls associated with the proposed research
- Insufficient or improper controls
- Failure of the applicant to document the necessary skills or training to accomplish the goals of the proposal
- Failure of the applicant to meet all the criteria described in the policy statement for a given award program

V. SUBMISSION INFORMATION & GENERAL TIMELINE

Application Deadline: Wednesday, August 21, 2019 at 5:00 PM (ET)

Submit online through proposalCENTRAL: https://proposalcentral.com/
(Refer to Section VI of these guidelines for specific submission instructions.)

An application will be considered incomplete if it fails to comply with the instructions, or if the submitted material is insufficient to permit adequate review. CFF reviews applications electronically, and only documents submitted online at proposalCENTRAL will be reviewed. Late applications will not be accepted, and the deadline will not be waived.

General Timeline:

Application Deadline ________________________________ August 21, 2019
Review by Research and Research Training Committee __________________ mid-November 2019
Notification to Applicants _____________________________ early-December 2019
Start Date for Awarded Projects ________________________ February 1, 2020

VI. FULL APPLICATION GUIDELINES

Applications must be submitted online at proposalCENTRAL: https://proposalcentral.com/

Documents should be typed using:

- Font: Times New Roman 12 or Arial 11
- Margins: No less than a half inch on each side

Note: When all the documents have been uploaded to proposalCENTRAL, the system will compile them into a single PDF file in the correct sequence.

Log-in at proposalCENTRAL: https://proposalcentral.com/
First-time applicants must register to create a user name and password for proposalCENTRAL and will need to complete a profile online before applying. If you are registered and cannot remember your password, click on the “Forgot Your Username/Password?” link below the “Application Login” fields.

Award opportunities, including this Request for Applications (RFA), are listed on the opening screen, but you must be logged in first to see them.

Select the gray tab labeled “Grant Opportunities” found in the upper right-hand side of the page.

Click on the light blue “Filter by Grant Maker” button to the left and scroll down to locate Cystic Fibrosis Foundation in the list.

Locate the listing for the “Overcoming Obstacles for Nucleic Acid Delivery for CF: Collaborative Research Grant” program. Click on the “Apply Now” button in the column on the far right to open the application form.

Applicants may stop at any point but must click the “Save” button before exiting in order to save their work. When logging in to continue, click on the blue tab, “Proposals”, and then the “Edit” button next to the in-progress application.

The following sections are listed in the navigation menu to the left of the application screen. Click on each section and follow the directions:

1. Title Page: Enter the title of your project, indicate whether the Principal Investigator (PI) is an investigator new to CF. In addition, using the drop-down selection, indicate the number of projects encompassed in the Collaborative Program (up to four).

2. Download Templates & Instructions: Download the available templates applicable to the project, fill them out and upload them when completed in Section #9. Templates available include: Biographical Sketches of Key Personnel, Results of Past and Current CFF/CFFT Support, Other Support, Facilities Available, Budget Detail, Budget Justification, Collaborative Program Summary, Communication Plan, Research Plan, and International Institution Form (if applicable).

3. Enable Other User to Access this Proposal: Complete this section online if you wish to designate access to another individual, such as an assistant who has registered on proposalCENTRAL. Enter the email address of the individual and in the “Permissions” column, use the pulldown menu to select the type of access you wish to give. Please note that only delegates who are granted “Administrator” rights can submit applications on behalf of the applicant. Check the “Auto Notify” box and then “Save”.

4. Applicant/PI: If a profile was completed upon registration, the fields in this section will already be populated with the information entered in your Professional Profile. If you need to make any changes, click the “Edit Professional Profile” button and follow the instructions. If a profile was not completed, enter the required information and click “Save”.

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5. **Institution & Contacts:** If a profile was completed upon registration, the Principal Investigator’s (PI) institution will be preloaded as Lead Institution. If a profile was not completed, enter the required information and click “Save”. Be sure to use the full legal name of the institution.

6. **Abstracts/Relevance/Keywords:** In the space provided online for abstracts, provide a statement of no more than 2,000 characters (including spaces) explaining the subject of the research proposal and its relationship to CF. Two different abstracts are required, as follows:
   - **Lay Abstract:** This statement will be used to inform the non-scientific departments of CFF and the general public of the nature of this work. Applicants should not include any confidential or proprietary information, including intellectual property, in the lay abstract.
   - **Scientific Abstract:** This statement will be used to inform the scientific community.
   - **Summary of Relevance to CFF mission and RFA Objectives:**
     All applications are reviewed and scored not only on scientific merit but also on relevance to CFF’s mission and this RFA’s Objectives.
     
     Provide a statement of no more than 2,000 characters (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.

**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.*

**RFA Objectives**

*The objectives of this RFA are to develop technologies, tools, and model systems that will advance the efficacy, selectivity, and accuracy of delivering nucleic acid therapies for Cystic Fibrosis.*

7. **Budget Summary:** Fill in the start and end date and applicable amounts for each year of support requested by completing the online fields (Period 1, 2, 3). All Collaborative Research Grants are for a maximum of three (3) years. The total Collaborative Program budget request may not exceed US$775,000 per year plus twelve percent (12%) indirect costs. The total request of each project (up to four) in the Collaborative Program shall not exceed US$250,000 per year plus twelve percent (12%) indirect costs. The applicant/lead site may request an additional US$25,000 per year for administrative support costs with proper justification, increasing the Project Lead PI’s budget limit to US$275,000 per year plus twelve percent (12%) indirects. Indirect costs are not allowable for administrative support costs.

**Note:** The Budget Detail and Budget Justification templates downloaded in Section #2 need to be completed and uploaded in Section #9 for each year and for each project individually. The sum of which will be entered in the Budget Summary in Section 7. The sum of the amounts included in the uploaded Budget Detail must match the amounts entered in the Budget Summary online.
8. **Organization Assurances:** Select the type of assurances that are applicable to the project and provide all required information (i.e. IRB, IACUC, and/or IBC/rDNA approval letter and status at the time of submitting the application). Refer to Section L. ORGANIZATION ASSURANCES & CERTIFICATIONS in these guidelines for details.

9. **Collaborative Program Summary & Supporting Documents:** In this section, upload the completed templates downloaded in Section #2 above in PDF format. Fill out the fields describing the attachment, select the attachment type from the pulldown menu, enter a description for the attachment in the corresponding field, choose the file to be uploaded, and click the “Upload Attachment” button to upload the file. Do this for each attachment.

A. **Biographical Sketches of Key Personnel (template available online)**
   Complete and upload an NIH Biographical Sketch for all key project personnel, beginning with the Applicant/Principal Investigator. International applicants can upload a biosketch that is equivalent in content to the NIH template provided. (CFF defines “key 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.

B. **Results of Past and Current CFF/CFFT Support (template available online)**
The Principal Investigator (PI) and any Co-Principal Investigator(s), if applicable, are requested to identify the results of past and current Cystic Fibrosis Foundation (CFF) or Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT) support (e.g., subsequent funding from other sources, journal articles, and invited presentations) and the CFF/CFFT award from which they resulted for the past five (5) years. Please note that the following information must be included with each research project identified:
   - CFF/CFFT Award #
   - Principal Investigator (PI)
   - CFF/CFFT Project Title
   - Applicant’s Title on Project
   - Project Start/End Dates
   - Total CFF/CFFT Award Amount
   - Results of Support

C. **Other Support (template available online)**
   Complete and upload the Other Support form for all key project personnel, beginning with the Applicant/Principal Investigator. There is no page limitation. Information on other support assists CFF in the identification and resolution of potential sources of overlap. Scientific and budgetary overlap should be minimized. Commitment of an individual’s effort greater than 100 percent, is not permitted.

D. **Facilities Available (template available online)**
   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.

E. Budget Detail and Budget Justification (separate templates available online)

Fill out the Budget Detail and Budget Justification templates for each and all years of support requested. In the space provided on the templates, indicate the year or period as well as start and end dates for the proposed budget period. For each project as part of the Collaborative Program separate Budget Detail and Budget Justification is required. (Be sure the amounts entered in the Collaborative Program Budget Detail(s) match the amounts entered in the online Budget Summary in Section #7).

- **Budget Detail – Direct Costs**
  
  **Salary & Benefits** - List the names and positions of all professional and non-professional personnel involved in the project, whether or not salaries are requested. Indicate the percent effort on the project for all personnel. For each individual, be sure to complete all fields on the Budget Detail in full on the template provided. In accordance with National Institutes of Health (NIH) policy, salary requests may not use an institutional base salary in excess of the current federal salary cap of **US$192,300**. Fringe benefits may be requested if they are treated consistently by the applicant institution as a direct cost to all funding agencies and foundations.

  **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 the project 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.

  **Subcontractors** – Detailed budgets for each subcontract, including indirects, must be provided for each year of support (complete and upload a Budget Detail and Budget Justification template for each subcontract). For applications that include a subcontract with a third party, the applicant may request indirect costs on the first **US$25,000** of each subcontract per project period. Negotiations of subcontracts are between the applicant institution and the subcontractor.

  **Major Equipment** - List all items of equipment greater than **US$5,000** requested and the cost of each item. If funds are requested to purchase equipment that is equivalent to items listed under “Facilities Available”, justify the duplication. Justify any item of equipment for which the need may not be obvious.

  **Travel** - Describe the purpose of any CF-relevant travel. Please note: expenses for travel outside the North American Continent, including travel to Hawaii, Puerto Rico, and other U.S. territories are not allowable expenses without prior written approval from the CFF Grants and Contracts Office. **Travel expenses may not exceed US$1,250 per person per year**. Registration fees associated with conferences are in addition to this allowance should be listed under “Other Expenses”.

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Consumable 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.

Other Expenses - Itemize other expenses by major categories, such as administrative support costs (US$25,000 max), duplication costs, publication costs, minor equipment (under US$5,000), computer charges, conference registration fees, etc. Tuition costs may be requested for personnel supported through this study but may not exceed US$10,000 per person per year.

• Budget Detail – Indirect Costs
  Indirect costs of up to twelve percent (12%) may be requested from CFF. Indirect costs may be requested for all expenses except for the following:
  • Major equipment (items over US$5,000 in value)
  • Computer software
  • Software licenses
  • Tuition
  • Administrative Support costs for Collaborative Programs

• Budget Justification
  Describe costs listed in the Budget Detail. Use major categories, such as Salary & Benefits, Consultant Costs, Major Equipment, etc. Justify all items and make sure amounts and figures listed in the narrative are consistent with those listed in the Budget Detail(s).

F. Collaborative Program Summary (template available online)
  • Page limit: Five (5) single-sided pages. Applications exceeding this page limit will not be reviewed. The summary should clearly identify:
    o The PI who will assume the overall lead of the program and describe how the PI will coordinate with the other PI’s.
    o The overarching aims of the proposal with the PI name for each project under the collaboration.
    o Clearly articulate and outline the goals and importance of each individual project.
    o An explanation of how synergy between projects contributes to the overall aims of the collaboration.
    o A description and justification of any consultants or external collaborations as applicable.

  Note: Consultant agreements or outside collaborations are allowed but should be justified.

G. Communication Plan (template available online)
  • Page limit: Two (2) single-sided pages. Applications exceeding this page limit will not be reviewed. The plan should clearly outline:
    o How research activities will be coordinated among investigators.
    o How the collaborative nature of the program will be maintained.
    o How reagents and data will be shared within the program.
o How conflict and scientific disagreements will be managed and resolved

H. Research Plan (template available online)
   • Page limit: Twelve (12) single-sided pages, not including the Literature Cited for each project included in the Collaborative Program. Research Plans exceeding this page limit may not be reviewed. Collaborative programs must include at least two (2) and no more than four (4) projects (including the lead project).
   o Type the PI's name in the space available in the header of the document. The template available will track page numbers at the bottom.
   o Include sufficient information to permit effective review without reference to any prior applications. Information should be presented in a clear and concise manner, while being specific and informative.
   o Key figures and legends must be included in the Research Plan and should be of sufficient quality and size to be evaluated by the reviewer. If uploaded as Appendices, they will NOT be reviewed.

a. Hypothesis and Specific Aims: State concisely and realistically the intent of the proposed research and the hypothesis to be tested, if applicable. It is understood that proposals submitted to this RFA may focus on developing technologies, tools, or model systems, so a typical hypothesis may not be included. The specific aims should be relevant to the mission of the Cystic Fibrosis Foundation. Do not exceed one page.

b. Background and Science: 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 areas listed as areas of special interest to CFF.

c. Preliminary Results: If applicable, provide a detailed discussion of any preliminary results. These may be provided in a separate section or incorporated into the experimental design and methods. As new investigators to CF are encouraged to apply, CF-specific preliminary data is not necessary.

d. 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. 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.

e. Consultant Arrangements: If the proposed project includes consultant arrangements and/or collaboration with other individuals outside the applicant's group, describe the working relationships and support this description by letter(s) of intent signed by collaborating individual(s). If clinical material required by this award is to be furnished by other individuals, include a statement from these individuals agreeing to their participation and precautions taken to ensure anonymity of patients.

f. 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
I. Letter(s) of Reference for Junior Investigators (upload as PDF documents, if applicable)
CFF defines “junior investigator” as any individual who has not received a CFF Research Grant or NIH equivalent (e.g. R01, R21) as a Principal Investigator OR is within their first five (5) years of their first academic appointment at the level of Assistant Professor or equivalent. Letters of Reference for junior investigators must be submitted by the following individuals:

- The Chair of the Applicant’s Department at the Applicant Institution – The letter of reference from the Department Chair should indicate the release of sufficient space and facilities for the work described, as well as guarantee the time commitment of the investigator to the project. If the applicant is currently a fellow, the letter of reference should include confirmation of the pending faculty-level appointment.
- At least two (2) other individuals familiar with the applicant's scientific interests and abilities.

J. Letter(s) of Support for Investigators new to CF Research (upload as PDF documents, if applicable)

*Note: *Not required for experienced CF investigators, e.g. recipients of CFF/past CFFT funding, investigators with recent publications in the field.*

Investigators new to CF research are strongly encouraged to consult or collaborate with an established CF investigator/clinician either at their own institution or another. An investigator is considered new to CF if they have not previously (1) published in CF or (2) received extramural funding for a CF-focused research project. A letter of support from the collaborator/consultant should be included with the application, explicitly describing how the proposed work is relevant to CF and how the collaborator/consultant will assist the investigator (such as providing scientific expertise or CF-relevant samples and reagents).

K. Verification of Applicant Institution’s Tax Status (upload as PDF documents)
The CFF Grants and Contracts Office must have a copy of the applicant institution’s current W-9 and 501(c)3 letter, or other documentation verifying its Federal tax status and will not issue Award Letters to Awardees if these documents are not received and on file.

- Applicants from for-profit organizations must submit a copy of the applicant institution’s W-9 and IRS documentation verifying the organization’s Federal tax status. Awards are not issued prior to having these documents on file with the CFF 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.

L. Organization Assurances & Certifications
CFF requires, as applicable, that all U.S.-based awardees obtain Institutional Review Board (IRB) approvals for human subject research, Institutional Biosafety Committee (IBC) approval for recombinant or synthetic nucleic acid research, and Institutional Animal Care and Use Committee (IACUC) approval for animal research, (see additional information regarding these approvals below). Copies of these approvals, if available at the time the application is
submitted, must be uploaded with the application as appendices. CFF will not release payments to awardee institutions until these documents are received and on file with the CFF Grants and Contracts Office.

Awardees based outside of the U.S. must comply with the applicable equivalent regulations in their respective countries and provide copies of approvals as soon as they are available. CFF will not release payments until these documents are received and on file with the CFF Grants and Contracts Office.

**Research Involving Human Subjects:** CFF policy pertaining to the protection of individuals as research subjects requires that for each proposal awarded, the awardee 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 the Department of Health and Human Services policies found at [https://www.hhs.gov/ohrp/regulations-and-policy/index.html](https://www.hhs.gov/ohrp/regulations-and-policy/index.html). In the event the IRB has determined a study is exempt, documentation demonstrating the exempt status must also be submitted to the CFF Grants and Contracts Office.

**Research Involving Recombinant or Synthetic Nucleic Acid Molecules:** All research involving recombinant or synthetic nucleic acid and human gene transfer studies supported by CFF must meet the requirements contained in the document *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (updated April 2019).* This publication and announcements of modifications and changes to the *NIH Guidelines* are available from the Office of Science and Policy, National Institutes of Health, 6705 Rockledge Drive, Ste 750, MSC 7985, Bethesda, MD, 20892-7985 or online at [https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf](https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf).

**Research Involving Animals:** Applications submitted to CFF involving the use of animals must meet the guidelines of the National Institutes of Health found at [https://grants.nih.gov/grants/olaw/olaw.htm](https://grants.nih.gov/grants/olaw/olaw.htm), which require that all proposed studies be reviewed and approved by an Institutional Animal Care and Use Committee (IACUC). In addition, CFF awardee 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.

**M. International Institution Form (template available online, if applicable)**

Applicants whose institution is not a United States based-entity must complete the International Institution Form. **Upload a PDF version of the completed and signed form, together with the following documents***:

- A copy of the institution’s most recent Mission Statement.
- A copy of the institution’s tax status documentation or equivalent, or a letter stating it is not available.
- A brief description of other sources of support, such as official awards, private endowments, and commercial activities, received by the institution.
• A copy of the institution’s Standard Operating Procedure(s) or relevant policy to ensure that funds provided are neither distributed to terrorists or their support networks, nor are funds used for activities that support terrorism or terrorist organizations.

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

Applicants who have provided these documents within the past three (3) years are not required to resubmit them. However, if any of the above documents have been updated since they were previously submitted, please upload any updated documents. The CFF Grants and Contracts Office will contact applicants if documents are outdated or missing.

*Applicants must provide English translations for all non-English documents, including material provided in support of the Research Plan.

N. Appendices (upload materials as PDF documents, if applicable)
Appendices are restricted to the following two (2) categories:
• Certification of organization assurances (i.e. IRB, IACUC and IBC approvals), if applicable.
• Up to three (3) reprints of the applicant’s work relating to the general area of research in the proposal may be uploaded in PDF format.

10. PI Data Sheet: Fill in the required fields, save and exit.

11. Print Face Pages: Follow the prompts on the screen to generate and print a Face Page. The Face Page will be populated automatically with data entered in the online application (applicant’s name, institution, title of application, etc.). The Face Page must be signed by the Principal Investigator and Authorized Institutional Official and uploaded in Section #9. Co-Principal Investigators, if any, are not expected to sign the Face Page.

12. Validate: Upon completing the application, click on the “Validate” button on the main screen. Attend to any omissions/errors as prompted onscreen, and then click “Validate” again.

13. Submit: Click on the blue button with white lettering. CFF will not receive your application unless the “Submit” button is clicked.
**Confirmation:** Applicants will receive an e-mail confirmation from proposalCENTRAL (not from CFF) that the Application was successfully submitted. This e-mail will be your only acknowledgement. If you do not receive this confirmation, please contact proposalCENTRAL immediately to ensure that your submission was submitted and processed.

<table>
<thead>
<tr>
<th>For technical support with the online application:</th>
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<tbody>
<tr>
<td>proposalCENTRAL at <a href="mailto:pcsupport@altum.com">pcsupport@altum.com</a> or</td>
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<tr>
<td>800-875-2562 on weekdays, 8:00 a.m. to 5:00 p.m. (Eastern)</td>
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<tr>
<th>For program/content information:</th>
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<tbody>
<tr>
<td>CFF Grants and Contracts at <a href="mailto:grants@cff.org">grants@cff.org</a> or 301-841-2614</td>
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VII. ELECTRONIC APPLICATION CHECKLIST

Application Deadline: Wednesday, August 21, 2019 at 5:00 PM (ET)

Applications must be submitted at proposalCENTRAL: https://proposalcentral.com/

Face Page which includes:
- Signatures
- Principal Investigator (Co-PI’s are not required to sign)
- The Official authorized to sign on behalf of the Awardee Institution
- Applicant/PI information (online)
- Complete Institution and PI Contact Information, including correct mailing address (online)
- Organization Assurances (check those that apply online/completed the required information)
  - Human Subjects Certification
  - Recombinant or Synthetic Nucleic Acid Molecules/Biosafety Information
  - Research Involving Animals Approvals

Research Plan, Supporting Documents and Appendices:
- Abstracts ~ Summary of Relevance ~ Keywords - (complete online)
- Biographical Sketches for Key Personnel - (upload)
- Results of Past and Current CFF/CFFT Support - (upload)
- Other Support (NIH Format) - (upload)
- Facilities Available - (upload)
- Budget Detail for each year - (upload)
- Budget Justification for each year - (upload)
- Collaborative Program Summary – (upload)
- Communication Plan – (upload)
- Research Plan for each project - (upload)
  - Hypothesis and Specific Aims
  - Background and Significance
  - Preliminary Results
  - Experimental Design and Methods
  - Consultants/Collaborative Arrangements
  - Literature Cited (not included in Research Plan page limitation)
- Letter(s) of Support for Junior Investigators – (upload, if applicable)
- Letter(s) of Support for Investigators New to CF Research (upload, if applicable)
- Verification of Applicant Institution’s Tax Status - (upload)
  - W-9 (U.S. applicants) or W-8BEN-E (non-U.S. applicants)
  - Federal (IRS) tax status letter (U.S.-based applicants) or equivalent tax status letter, or letter indicating it is not available (non-U.S.-based applicants)
- International Institution Form (non-U.S.-based entities only - upload, if applicable)
  - Institution’s most recent Mission Statement
  - Applicant institution’s tax status documentation or equivalent, or a letter stating it is not available
  - Description of other sources of support, such as official awards, private endowments, and commercial activities, received by institution
o Institution’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
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