Biology of Fibrosis in Inflammatory Bowel Diseases

Request for Proposals (RFP)

Program Guidelines & Policies

Effective June 11, 2018

Crohn's & Colitis Foundation
National Office
Research Department
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MISSION:
To cure Crohn's disease and ulcerative colitis, and to improve the quality of life of children and adults affected by these diseases.

Key Dates

RFP Announcement	**June 11, 2018**
Application deadline	**September 7, 2018**
Anticipated funding notification	**December 20, 2018**
Anticipated start date	**January, 2019**

1. Overview

Half of all Crohn's Disease (CD) patients will develop disease complications, one of which is development of fibrotic strictures (fibrostenosis), leading to GI tract obstruction and severe clinical consequences. Fibrostenosis is also a serious problem for ulcerative colitis (UC) with approximately 8% incidence over the lifetime. Currently there is no clinical solution for preventing or treating fibrostenosis in patients with inflammatory bowel disease (IBD), except for surgical intervention. Therefore, there is a great unmet need to understand fibrotic complications in IBD and how to prevent and treat them.

Contributing factors: Fibrosis is a complex process, involving multiple types of cells, cytokines and proteins. Based on the current knowledge, chronic inflammation and excessive mucosal and submucosal deposition of extracellular matrix proteins (ECM) contribute to the development of fibrostenosis.

To explore the question of who is at risk to develop IBD complications requiring surgical intervention, the Crohn's & Colitis Foundation (Foundation) funded a risk stratification study in pediatric Crohn's disease (the RISK study). The objective of the RISK study was to identify at diagnosis, risk factors of developing stricturing or penetrating (fistulizing) disease within three to five years. This study found that, in addition to a number of clinical and serological risk factors, unregulated expression of ECM genes at diagnosis correlated with development of stricturing complications within three to five years (Kugathasan, *et al*. 2017). These findings suggested that these ECM gene expression signatures might be explored as a prognosis biomarker of stricturing disease, and that they might also play a role in the development of fibrosis by mechanisms yet to be elucidated. The RISK study also found that, unlike penetrating disease, fibrotic or stricturing disease did not appear to respond to anti-TNF biologics given early in the course of the disease (Kugathasan, *et al*. 2017).

Surgical treatment: It has been observed that strictureplasty, a surgical procedure for alleviation of fibrostenosis, which does not involve removal of the diseased intestinal tissue, may be associated with fibrosis resolution and may be protective against disease recurrence at the stricture location (Fazio *et al*, 1989). Understanding the biological mechanisms of how strictureplasty affects the local conditions of active Crohn's disease to resolve fibrosis and prevent disease recurrence at the site of surgery may lead to development of novel pharmacological-based therapies that could treat stricturing by mimicking the strictureplasty anti-fibrotic effects.

Together these observations and discoveries suggest that studying the mechanisms of IBD-related fibrosis may be a fruitful area in the search for potential therapeutic advances for IBD. The Foundation seeks to accelerate research focused on elucidating the biological mechanisms underlying fibrosis in IBD, which can lead the way to future development of diagnostics and therapeutics for this important unmet clinical need.

2. Scope

The Foundation seeks to fund studies focused on investigating the biological mechanisms leading to, and protecting from, fibrosis in IBD. Particular interest will be on proposals that address one or more of the following areas:

- **Pathophysiology of fibrosis based on documented patterns of gene expression:** To identify mechanisms and potential causal role of gene expression patterns associated with increased risk and/or with protection from fibrostenosis, for example as described by the RISK investigators (Kugathasan, *et al*. 2017).
- **Cell biological mechanisms of fibrosis:** Areas of interest could include investigation of the cell and molecular mechanisms of the interplay between the gut microbiota, human intestinal cells (epithelial cells), myofibroblasts, mesenteric fat, creeping fat, stem cells and inflammatory cells, leading to, and/or protecting from fibrosis.
- **Biology of strictureplasty**: To understand the biology underlying the still unknown mechanism(s) for how strictureplasty resolves fibrosis at the site of intervention, which in turn could lead to the identification of potentially druggable targets for future discovery of pharmacological agents that could mimic the beneficial effects of strictureplasty.

To ensure that the research stays focused on preclinical experiments that are related to IBD fibrosis experienced by patients, the research approach must demonstrate this relationship through a connection with clinical observations and/or published evidence in human fibrosis in general, and IBD fibrosis in particular. Studies including analysis of samples collected from IBD patients to validate clinical and/or *in vitro* and *in vivo* findings will be preferred.

A multidisciplinary approach is preferred, for example including *in vitro* models (*e.g.* human intestinal organoids), analysis of human biopsies, animal models of fibrosis, biophysical studies, and imaging approaches.

3. Eligibility

Applications from a team with the relevant expertise is required, with one lead Principal Investigator (PI) and at least one Co-PI. The lead PI must be a senior faculty member (Professor, Head of Research, Associate Professor, etc) expert in fibrosis research preferably in IBD but experts in fibrosis in other therapeutic areas are encouraged to apply in collaboration with a Co-PI with expertise in IBD research (basic or clinical). Lastly, at least one Co-PI must be a junior Co-PI (Instructor or Assistant Professor) with experience in IBD (basic research or clinical), who is committed to IBD research as a part of his or her career development (generally, junior Co-PI candidates should not be more than ten years beyond the attainment of their doctoral degree). At the time of application, PI and Co-PIs must be employed by an institution (public non-profit, private non-profit, or government) engaged in health care and/or health related research. There are no geographical restrictions regarding research site location(s). Proposals involving multiple institutions are welcome.

4. Grant Funding Terms

One award will be granted for 3 years with a maximum amount of $300,000 per year, inclusive of all indirect expenses. Specific milestones will be agreed upon project onset, and continued funding in years 2 and 3 is dependent on acceptable reasonable progress towards specified milestones. Indirect expenses must not exceed 10%.

5. Submission Guidelines

A. The application should include the following (**Appendix A for details**):

- **i.** Summaries (abstracts) of the proposed project (lay and scientific)
- **ii.** Brief description of how this project is explicitly related to IBD and how it aligns with the research priorities of the Foundation
- **iii.** Cover page describing background and expertise of the PI, Co-PI and relevant investigators, and the role/ tasks to be performed by each investigator
- **iv.** Research proposal: specific aims, background, including rationale and preliminary data, experimental plan, and expected outcomes. These sections should not exceed 10 pages total
- **v.** Budget pages specifying the total funds requested, budget justification, and a list of the current support for PI and Co-PI
- **vi.** A short biosketch (4 - 5 pages maximum, NIH format) of the PI and Co-PI
- **vii.** Professional development plan for Co-PI (junior faculty)
- **viii.** Mentorship plan
- **ix.** Timeline for completion of project (Gantt chart or similar format), including milestones by aim projected for every six months of the project period
- **x.** Letters of support from collaborators and junior Co-PI chairman

Additional notes: The proposed research plan and budget should include the list of milestones, specified in 6 months' time intervals. Justification of the budget must be described. Alternative approaches and risk mitigation strategies should be included. Proposals should include preliminary evidence to support the hypothesis of the proposed study and describe accessible resources needed for achievement of the proposed aims.

6. Application Review

The investigators will provide a full research proposal and the accompanying document by the application deadline (see *Key Dates*, above) and according to the guidelines for proposal preparation and electronic submission (Appendix 1, below). The proposals will undergo peer review by a multidisciplinary review committee and evaluated based on the following criteria:

- Alignment with the scope for this RFP (see section 2 above).

- Clinical relevance: The proposed project should investigate pathophysiological mechanisms of fibrosis in human IBD, with the potential to inform eventual therapeutic strategies and/or identification of novel therapeutic targets. The hypothesis should be based on observations made in patients and/or address aspects of human pathophysiology.
- Research strategy: The proposal should have a translational approach, which is relevant for clinical application, sufficient preliminary data, well defined goals, clear experimental design and alternative strategies.
- The proposal must be well written and understandable by the scientific audience. The lay summary must clearly summarize the proposal and be understandable for non-scientific reviewer.
- Feasibility of success: Demonstration of capabilities, personnel and infrastructure to conduct the proposed study, organizational resources, collaborators.
- Investigators' professional accomplishments: The senior investigator must show a successful track record in acquiring funding and published research in the field of fibrosis. At least one investigator must be a proven expert in IBD research. The junior investigator should be on the clear trajectory for, and have prior accomplishments required to becoming an independent investigator in the field of IBD.

7. Progress Oversight

The investigators will be required to convene with the members of the review committee and Foundation staff once a year. During the annual face-to-face meetings, the investigators will present and discuss their findings and the strategy of the ongoing study with the committee members. These meetings will be scheduled before the end of each budget year and the annual budget renewal will be contingent upon approval of progress by the review committee. Expenses related to these meetings will be funded by the Foundation and they do not need to be included in the project's budget. In addition, written reports must be submitted once per year according the Foundation's standard progress report template. In addition to the in person meetings and written annual reports, teleconferences at months 6, 18 and 30 will be scheduled to evaluate 6 months intervals interim progress. These teleconferences will include the review committee and Foundation staff in addition to the PI and Co-PI of the project.

8. Submission Instructions for Proposal Central

A. All applications should be submitted through the proposalCENTRAL portal at the following URL: https://proposalcentral.altum.com/
B. Please complete all indicated sections.
C. Review **Appendix A** for complete instructions of the electronic application process

9. Contact Information

For additional information please submit your queries to Dr. Nataly Shtraizent, Research Manager : NShtraizent@crohnscolitisfoundation.org

10. Cited Literature

Kugathasan S, *et al*. (2017). "Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study." *Lancet* 389: 1710-1718.

Fazio VW, *et al*. (1989). *"*Strictureplasty in Crohn's Disease.*" Ann. Surg.* 210: 621–625.

APPENDIX A: Instructions for Electronic Application

General information

The full application is due on **September 7, 2018.**

The application should be submitted to proposal central at: https://proposalcentral.altum.com

Paper copies of the application are not accepted.

To start the application process, follow the steps below:

xi. If you are a first-time user, register by clicking on “First time user.” This will generate a confirmation number which will be emailed to the email connected to this account. Confirm your registration by submitting this number when prompted.

xii. Once you are a registered user, please click on “Grant opportunities” on the far right of the page and select Crohn’s and Colitis Foundation under “Filter by Grant Maker” drop down menu on the upper left of the page.

xiii. Locate the “**Fibrosis in IBD**” announcement and click “Apply now”.

xiv. To activate the navigation bar on the left, enter the title of your proposal on the title page and “save” the application. The navigation bar on the left will now become interactive for you to continue your application.

xv. Once completed, please validate and submit the application.

Detailed Instructions for Electronic Submission

Title page

Enter your title and “save” the application

Templates and Instructions

PI Biosketch and a New Vendor Form are available for download.

New Vendor Form *Required (part of Attachments section)

Complete this form to authorize your institution to receive payment from the Foundation. This document contains the instruction on how payment will be transferred to your institution and should not include information on the Investigator. This is required even if institution has received Foundation funding in the past.

Enable other Users to Access the Proposal

Add personnel that can have access to review and edit the proposal.

Applicant /PI

Principal Investigator (PI) is defined as the one person responsible to report to the Foundation for scientific and technical direction of the project. Although Co-PI is required, only one person can be indicated as the main point of contact. Note: If the research (entirely or partially) is to be conducted in the Co-PI's laboratory, a subcontract budget needs to be proposed.

Institution and Contacts

Provide contact information of the signing staff officials at the institution where the lead PI is located and where the study will take place.

Co-PI(s), Collaborator and Key Personnel

Add the roles and the contact information for Co-Principal Investigator (Co-PI) and key personnel that you would like to include on this application.

Effort

Percentage estimation of amount of time allocated to this project: describe how the time (in percentages of full time effort) is allocated in your current position at this institution.

Summary

Lay Summary

The Foundation has instituted a Patient/Caregiver Reviewer Program, in which selected lay patients participate as voting members of the various review committees. Your lay summary should be a clear, concise overview in simplified language, appropriate for non-scientific reviewers. You need to provide enough essential information that the Patient/Caregiver Reviewers will be able to evaluate your application. The lay summary should include the following information:

1. What question will this project attempt to answer?
2. Why is this question important to IBD?
3. What is the study design?
4. How do the hypothesis and specific aims fit with Foundation's scientific priorities?
5. Will this research, if successful, further the Foundation's mission to find the causes and cures of IBD and/or to improve quality of life for IBD patients? If so, how will this project do so?

Please note that a lay summary that does not fully addresses these questions and which is not clearly written using lay language could affect the score provided by the Patient/Caregiver Reviewer.

Template for Writing the Lay Summary

Investigator: Burrill Bernard Crohn, MD; Mount Sinai Hospital

Project: Gender differences in growth in pediatric patients with Crohn's disease

Description: Growth failure is a unique and important problem for children with IBD. The exact causes of growth failure, and how best to treat them, is a pressing need. In children with Crohn's disease, boys and girls differ in disease severity and growth failure. That is, female patients tend to have more severe clinical disease but don't suffer from growth failure, while male patients tend to have less severe clinical disease and suffer from growth failure. Understanding the reasons for these differences could provide new clues on the reasons for disease severity and growth effects of IBD, and how better to treat them. This project tests whether sex hormones (estrogen in females, testosterone in males) act differently on the function of hormones controlling growth (growth hormone itself, Insulin-like Growth Factor-1 [IGF-1], and the pathway linking them). This project will study 90 pediatric Crohn's patients under the age of 17, matched to a control group of patients with short stature alone (unrelated to Crohn's disease), and determine whether disease activity affects growth hormone/IGF-1 levels, and how this affects growth in kids with Crohn's.

Also include a brief glossary of any scientific terms included in your lay summary.

Scientific summary of the Project

Summary should provide a clear, concise overview of the proposed work, including the background, objective, or hypothesis and its supporting rationale; specific aims of the study for general scientific audience.

Budget Period Detail

Start and End Dates

Specify date on which you expect to start this project. Enter dates for 3 years in 1 year increments.

Complete the e-form total budget.

The budget requested per year may not exceed $300,000 inclusive of indirect cost (Direct costs: $272,500; indirect costs: $27,500).

Budget Summary Detail

The total budget request for year 1 must not exceed $300,000 inclusive of 10% indirect cost. Salaries are capped at NIH limits. The total budget for 3 years is $900,000 inclusive of 10% indirect costs (Direct costs: $817,500; indirect costs: $82,500). Justification of the budget for the 3 year period must be provided.

Current and Pending Financial Support

Please provide information on additional ongoing funding that currently supports this research project.

Organization Assurance

Human/Animal Studies Approval/Recombinant DNA

All activities involving human subjects or vertebrate animals must be approved by an appropriate institutional review board (IRB) or equivalent prior to the start date of award. Indicate with "Yes" or "No" response, and if yes indicate date of approval and attach approval in that Attachments Section.

Copies of the IRB approval should be provided to the Foundation's Research Department. If approval is not available at the time of application, provide a date of anticipated approval. **This approval must be received before the start date of the approved grant.**

Upload Attachments

Cover page
Describe background and expertise of the PI, Co-PI and the relevant investigators, and the role/ tasks to be performed by each investigator

Research Plan/Protocol (Required)

The description of the proposed research project must include the following items in sufficient detail to permit evaluation of the scientific merit of the study. *This cannot exceed 10 pages, single spaced. The page limits distribution indicated below are included as a guideline and not required.*

- Overall objectives and specific aims (no more than 1 page)
    - Briefly outline the general scientific objectives
    - Describe concisely and realistically what the specific research described in this application is intended to accomplish. Specifically outline Aims for year 1, year 2 or year 3, goals, 6 months interval milestones and timelines. State any hypotheses to be tested.

- Background -including preliminary data (no more than 3 pages)
    - Outline the previous work in the area by others, and the preliminary data or previous studies by the investigator(s). Enough preliminary data should be included in the application to demonstrate that the project is feasible and that the investigator is likely to complete the project successfully in the duration of the grant. Provide evidence that supports clinically relevant observations made in patients
- Detailed description of methods and materials to be used (no more than 5 pages)
    - Provide a detailed discussion of the experimental design, procedures, and materials to be used to accomplish the specific aims.
    - Describe protocols, including methods for new techniques, and explain the advantages over existing methodologies.
    - Discuss the kinds of data expected to be obtained and the means by which data will be analyzed and interpreted.
    - Justify the use of any animal models (i.e., choice of species, number used, etc.).
    - Discuss potential difficulties and/or limitations of the proposed procedures and alternative approaches to achieve aims.
- Significance and relevance of the proposed research to Crohn's disease and/or ulcerative colitis (no more than 1 page)
- Justify the significance of the results of this project to the understanding of the etiology, pathogenesis, therapy, and prevention of IBD. Specifically identify the gaps this project is intended to fill.
- Facilities available to carry out the proposed studies (one or two paragraphs)
    - Describe the facilities available, including square footage, equipment, animal care facilities, and other environmental factors. Pay particular attention to those items required for successful completion of this proposal. Include a description for each facility to be involved.
- References (no more than 2 pages)
    - Literature citations should be listed in this section, at the end of the Research Plan. ***These are not counted as part of the 10 page limit.

Formatting the Application

Applicants must adhere to the following instructions in completing the proposal sections that make up the electronic version of the application.

1. *Please remember to insert your name in the header on each form in the attachment section.*
2. *Font size: Use 11 point Times New Roman or 10-point Arial as the minimum font size for the text of the application. A 9-point Times New Roman or 8-point Arial font type may be used for figures, legends, and tables.*
3. *Single-spaced text is acceptable, and space between paragraphs is recommended.*
4. *Margins: The margins of your text should be at least 1" inch on all sides, unless a form with different margins is supplied in the Application Templates or Forms.*

Timeline and Milestones (1 page)

Timeline for completion of project (Gantt chart or similar format): List of milestones projected for every six months of the project period.

Milestone-driven budget summary table (1 page)

Summary of expenses broken down by specific aim / milestone. When Foundation funding would be supplemented by additional funds from another source applied towards project objectives (cost sharing), such funding may be indicated (in a separate column). Project related overhead may be included in proposed Foundation funding but must not exceed 10% of total funding provided.

Biosketches for Key Personnel

Biosketch (NIH format) for PI and Co-PI (required) and additional key personnel (optional).

Letters of Collaboration

Attach supporting letter(s) (optional).

References/ Appendices (optional)

Uploaded reference material may include, but not limited to:

1. Article references
2. Abstracts
3. Original Pictures
4. Other Letters of Support

Human and/or Animal Approvals- Optional

Upload IRB approvals for human and animal research

Signed Signature Pages

This document is generated by the PDFs and Signature Pages module after submitting all the forms and uploading all the required documents. Module PDFs and Signature Pages is located on the navigation bar on the left hand side.

Validate

Click *Validate* to check for any missing REQUIRED information or files. All missing required information will be listed on the screen.

PDFs and Signature Pages

Click *Print Signature Pages* to be signed by the applicant and the organization officials. Upload the signed document on the Upload Attachments module.

Click *Print Signature Pages and Attached PFD Files* if you would like to save the full application for your records. Do not upload the full application with the signed signature pages in Upload Attachment module.

Submit

Only the primary PI is authorized to submit the application.