Environmental Triggers Initiative
Request for Proposals

Psychological Stress in Inflammatory Bowel Disease: Signatures and Mechanisms

Program Guidelines
Effective June 30th 2017

Crohn’s & Colitis Foundation
National Office
Research & Scientific Programs 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.
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Key Dates

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Overview

The etiology of inflammatory bowel diseases (IBD) has been extensively studied. However, the causative factors are not fully understood. The importance of genetic susceptibility has been established in the last decade and genetic risk variants alleles have been identified, but lack of complete gene penetrance and rapid rise of IBD incidence in certain geographic regions, suggest that the interaction between genetic and environmental factors contribute to IBD. Several environmental risk factors including drugs (such as antibiotics), viruses, psychological stress, air pollutants, diet, and chemical exposure have been explored, but the data is still inconclusive.

In particular, there is increasing evidence that supports the role of psychological stress in the pathogenesis, susceptibility or exacerbation of IBD, as well as in the recurrence of flare-ups. This is, in part, explained by the emerging concept of the brain-gut axis, by which interactions between the central nervous system, the enteric nervous system, and the gastrointestinal tract regulate intestinal and brain function. However, the mechanism of how exposure to stress relates to IBD are not fully understood, nor have relevant metrics been developed to systematically evaluate the effects of stress as they may relate to IBD.

Recognizing the importance of environmental triggers in IBD, the Crohn's & Colitis Foundation (the Foundation) announces a new funding opportunity to promote innovative research focused on the role of environmental factors in IBD. **In particular, the present Request for Proposals will invite applications focused on the investigation of exposure to psychological stress and its possible role in IBD susceptibility, progression and relapse.** The Foundation supports basic and clinical research of the highest quality through various funding mechanisms. This RFP augments the current funding opportunities offered by the Foundation.
Program Guidelines

1. Scope

The Foundation is interested in elucidating a potential role of exposures to psychological stress in IBD susceptibility, exacerbation, progression and/or relapse.

Proposed studies must be based on clinically relevant observations made in patients and have high relevance and potential future impact for IBD patients, particularly as it relates to mitigating environmental triggers relevant to disease onset, progression, and/or relapse.

Projects will focus on the understanding of the role of exposure to psychological stress in IBD. One or two of the following thematic areas must be addressed by the project: A) identification of "signatures" that can be used as metrics of exposure to stress, and/or B) investigation of the mechanisms by which stress could lead to perturbations of biological processes known to play a role in IBD. Below is a description of the two thematic areas:

A. **Signatures:** Identification of "signatures" of exposure to stress and their correlation with relevant IBD clinical outcomes. These signatures are biological parameters that can provide a measurement or a potential biomarker of exposures to stress and reflect the functional, physiological and biochemical response to the exposure. Such metrics can include genetic, epigenetic, neuroimmunological, chemical, microbiological and other molecular signatures of the patient, which are associated with exposure to stress (e.g., chronic and/or acute) and can be found in correlation with clinical outcomes (e.g., initiation of disease and/or relapse). Examples of types of “signatures” include, but are not limited to, specific patterns of: 1) gene expression, 2) epigenetic modifications, 3) microRNAs, 4) microbial diversity, 5) neurotransmitters, neuropeptides, neuroendocrine factors, 6) metabolites, 7) neuroimmunological factors, 8) imaging signatures, and others. These studies are expected to be patient cohort based. Special consideration will be given to proposals including a normal control group in addition to well phenotyped and appropriately stratified IBD patient groups (e.g. Crohn's and colitis).

B. **Mechanisms:** Investigating the mechanism by which exposure to psychological stress can lead to perturbations of biological processes believed to play a role in IBD. Specifically, studies should focus on the elucidation of how exposures to stress could lead to alterations in IBD relevant functions and its relation to particular clinical outcomes. The proposals should include use of relevant model systems (animal models or patients) and must be hypothesis driven, based on clinically relevant observations in patients.

2. Eligibility

A. USA based and international applicants conducting active research in relevant areas are encouraged to apply. Applicants should describe how their prior experience will facilitate the achievement of the set goals. Experience conducting research related to the role of psychological factors and how the communication along the brain-gut axis may play a role in disease, is required. Previous experience in IBD research is preferred but not required.

B. All applications must include one senior investigator (PI) and one junior investigator (Co-PI). The funds should be used to acquire data that in addition to aligning with the scope of this initiative, will also serve to advance the junior investigator towards an independent research career. A
career development plan must be provided together with the research proposal and supported by recommendation letters from the department chairman. The PI and co-PI do not need to be at the same institution.

C. Individual or team applications will be accepted, but require at least one junior PI (Co-PI) in addition to the senior PI.

D. The Co-PI can be a postdoctoral fellow, who completed a minimum of 3 years of postdoctoral research, or a junior faculty member prior to receiving an independent R01 grant (or an equivalent award for international applicants).

3. Grant Funding Terms

One award will be granted for a maximum amount of $900,000 for a period of three (3) years ($300,000 per year). Specific milestones will be agreed upon project onset, and continuation of the funding after the first year is dependent on achieving the milestones. This award is inclusive of all overhead costs (up to 10%).

4. Submission Guidelines

A. The application should be structured as following (Appendix A for details):

   i. Executive summaries 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 (two page maximum, NIH format) of the PI and Co-PI.
   vii. Professional development plan for co-PI (postdoctoral fellow or 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 the chairman and collaborators.

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.

5. Application Review

Applications will undergo peer review by a multidisciplinary review committee designated by the Foundation. The review committee will evaluate the proposals based on the following criteria:

A. Full alignment with the scope for this RFP (Section 1):
   i. Hypothesis derived from patient based observations.
   ii. Identification in patients of metrics (signatures) of exposure to stress and/or
Mechanisms of how stress affect IBD related biological functions in patients or experimental animal models.
Correlation of identified signatures and mechanism with disease outcomes.
Priority will be given to studies including a normal control group in addition to the IBD group(s).

B. Approach and project strategy (sufficient preliminary data, goals, experimental plan and alternative strategies)

C. Feasibility of success (Demonstration of capabilities, personnel and infrastructure to conduct the proposed study, organizational resources, collaborators)

D. Investigators’ background and expertise (Demonstration of prior professional achievements in the field relevant to the proposed study, expertise in IBD research is preferred but not required, publication track record)

E. Professional development of the junior investigator (co-PI) and mentorship plan of the senior investigator.

6. Progress Oversight
The investigators will be required to provide an annual progress report and convene with the members of the review committee annually to present and discuss their findings and the strategy of the ongoing study. These face to face oversight meetings with the committee will be scheduled before the end of each budget year. Expenses related to these meetings will be covered by the Foundation and they do not need to be included in the project's budget. In addition to this in person meetings, teleconferences at months 6, 18 and 30 will be scheduled to evaluate 6 months intervals interim progress. This teleconferences will include the review committee and Foundation staff in addition to the PI and Co-PI of the project.

7. 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

8. Contact Information
For additional information please submit your queries to:
Nataly Shtraizent, NShtraizent@crohnscolitisfoundation.org
Appendices

Appendix A: Policies and Instructions for Electronic Application

General information

The full application is due on October 2, 2017. **Access to the electronic version will be closed by 8:00 pm EST.** Note: No supplemental materials will be accepted after the submission deadline unless requested by staff for administrative purposes or requested by the reviewers for clarification.

All applications should be submitted to proposal central at: [https://proposalcentral.altum.com/](https://proposalcentral.altum.com/)

**Paper copies of the application are not accepted.**

To start the application process follow the steps below:

A. 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.

B. Once you are a registered user, please click on “grants 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.

C. Locate the “Environmental Triggers - Psychological Stress” announcement and click “Apply now”.

D. 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.

E. 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**

RFP Guidelines 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.

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 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 your time (in percentages of full time effort) is allocated in your current position at this institution.

Summary
Lay Summary
The Foundation has instituted a Stakeholder Reviewer Program, in which selected lay IBD patients or caregivers 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 Stakeholder Reviewers will be able to evaluate your application. The lay summary should include the following information:

- What question will this project attempt to answer?
- Why is this question important to IBD?
- What is the study design?
- How do the hypothesis and specific aims fit with Foundation’s scientific priorities?
- 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?

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.

Relevance of the Project to IBD
Provide a description of how this project is explicitly related to IBD and how it will promote both research and the Crohn's & Colitis mission.

This statement will be evaluated as part of your application as well as used to inform the Foundation's National Board of Trustees and the general public of the nature of this work; therefore, do not include proprietary or confidential information.

Pointers:
- This section must be written in language that is easily understandable to a 6th-7th grade reader.
- Define all scientific terms; Words like “pathogenesis” or “cytokines” might be common words to you, but not necessarily to lay persons.

Discipline:
Please select all categories that best describe the area of your expertise

Scope
Please select all categories that best describe the scope of the proposed studies, which are relevant to the thematic areas of the program.

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

Budget Summary Detail
The total budget request for three years may not exceed $900,000 including indirect cost (Direct costs: $817,500; indirect costs: $82,500). Justification of the budget must be described.

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. Applications exceeding the page limit may not be reviewed.

- 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.

- Timeline for completion of project and the list of milestones projected for every six months of the project

- 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 environmental factors in 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.
• Pertinent References (no more than 2 pages)  
  o 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:

  • Please remember to insert your name in the header on each form in the attachment section.
  • Font size: Use 12 point Times New Roman or 11-point Arial as the minimum font size for the text of the application. A 10-point Times New Roman or 10-point Arial font type may be used for figures, legends, and tables.
  • Single-spaced text is acceptable, and space between paragraphs is recommended.
  • Margins: The margins of your text should be at least 1” inch all around, unless a form with different margins is supplied in the Application Templates or Forms.

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

PI Biosketch and Co-PI Biosketch
A short biosketch (two page maximum, NIH format) for each faculty participant

Professional development plan
Required for co-PI (postdoctoral fellow or junior faculty)

Letters of Collaboration
Attach supporting letter(s).

Chairman letter of support
Required

Mentorship plan
Required for co-PI (postdoctoral fellow or junior faculty)

References/ Appendices- Optional (part of Attachments section)
Uploaded reference material may include, but not limited to:
  • Article references
  • Abstracts
  • Original Pictures
  • 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 PDF 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.

SPECIAL INSTRUCTIONS

Special Instructions for Foreign Applicants
Complete budget request must be in U.S. dollars - We will NOT convert.

Please be aware that you should give more details than you might be accustomed, especially in the areas of background material and preliminary data, experimental design, and available facilities, budgetary items (particularly percent of effort and salary requests for key personnel). We suggest that you reach out to the Foundation to discuss. Please send your inquiries by email Nataly Shtraizent: NShtraizent@crohnscolitisfoundation.org or call 646-943-7461.