IBD Therapeutics Incubator
(Discount discovery & development for novel IBD therapeutic targets)

Request for Proposals (RFP)

Program Guidelines & Policies

Effective July 20, 2022

Crohn’s & Colitis Foundation
National Office
Research Department
733 Third Avenue
Suite 510
New York, NY 10017

Contact:

Jean-Luc Tran, Director, Therapeutics Incubator
and
Dr. Andrés Hurtado-Lorenzo, Vice President, Translational Research & IBD Ventures

Email: ibdincubator@crohnscolitisfoundation.org

Last revision 7-4-2022
Key Dates

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFP Announcement</td>
<td>July 20, 2022</td>
</tr>
<tr>
<td>Request Therapeutics Incubator collaboration agreement for redline by</td>
<td>August 30, 2022</td>
</tr>
<tr>
<td>applicant’s institution, no later than</td>
<td></td>
</tr>
<tr>
<td>Deadline for submission of full proposal, including redlined</td>
<td>October 3, 2022</td>
</tr>
<tr>
<td>agreement</td>
<td></td>
</tr>
<tr>
<td>Project selection decisions</td>
<td>December 2022</td>
</tr>
</tbody>
</table>
1. Overview

The Crohn’s & Colitis Foundation (Foundation) is dedicated to addressing the unmet needs of patients with inflammatory bowel diseases (IBD) with the mission to find cures and improve the quality of life for IBD patients. The goal of this Request for Proposals (RFP) is to advance drug discovery research to create new therapeutic product opportunities from breakthrough academic research that has identified novel and differentiated potential drug targets for the treatment of Crohn’s disease and/or ulcerative colitis.

The therapeutics incubator represents an expansion of the Foundation’s IBD Ventures program. The IBD ventures program was launched in 2017 and consists of a Venture Investments arm that makes investments in companies and academic groups that already have a product development program and the infrastructure and knowledge to advance their existing product opportunities (e.g., a potential new therapy for IBD). In this case, we act as a more traditional investor to enable the company or academic researchers to advance the product development on their own, asking them to meet agreed-upon milestones. In contrast, under the IBD Therapeutics Incubator arm of IBD Ventures, the Foundation will partner with academic researchers and a specialized contract research organization (CRO) to provide drug discovery and development resources to generate a novel drug discovery preclinical package, which can be further advanced by larger venture investors and pharmaceutical/biotech companies into new therapeutic products to address medical unmet needs of IBD patients.

Specifically, this incubator-like mechanism enables the advancement of novel and validated drug targets, for which academic researchers lack adequate expertise or resources to advance them into drug discovery and development. In this incubator model, the scientific staff at the Crohn’s & Colitis Foundation, who have extensive drug discovery and development expertise, will take an active role in designing and leading the project(s), in collaboration with the academic applicant and CRO scientists. The R&D work will be mainly performed by the CRO, and if required, some of the research activities can be performed by the academic partner at their facility.

The Therapeutics Incubator mechanism has already advanced one proof-of-concept drug discovery project, demonstrating the feasibility of this approach. In this instance, The Foundation initiated a drug discovery campaign for a novel IBD drug target identified through the Foundation’s Genetics Initiative. This research was performed in partnership with an academic group at the Cleveland Clinic and outsourced to Evotec, a highly regarded drug discovery CRO. Using a rational drug design approach, novel gut restricted and potent drug-like compounds that bind and inhibit the target of interest were discovered and synthesized. The nominated lead compound has been now evaluated in two in vivo models of IBD, showing that oral administration of the compound ameliorates colitis and promotes mucosal healing. These positive outcomes, via the IBD Therapeutics Incubator, allowed the academic PI to raise follow-on funding by other institutions for further preclinical development and a new company creation. The Foundation is still working with this PI in specific preclinical development activities and maintains its involvement to help attract further investment from venture capital firms and big pharma.

This successful project is a clear demonstration that the IBD Therapeutics Incubator delivers tangible results by translating the finding of a potential IBD drug target with differentiated biology into a potent and gut-restricted small molecule therapeutic compound.
Therefore, with the IBD Therapeutics Incubator, the Foundation seeks to expand our ability to seize on the tremendous opportunities we see in academic research to expedite the identification and development of treatments to address pressing unmet IBD patient needs.

For further information about IBD unmet needs that can be addressed by new research-based products refer to our latest publication: Honig G, Larkin PB, Heller C, Hurtado-Lorenzo A. (2021). Research-Based Product Innovation to Address Critical Unmet Needs of Patients with Inflammatory Bowel Diseases. Inflamm Bowel Dis. 27(Suppl 2):S1-S16.

2. Scope

The Foundation is seeking proposals from academic researchers who have discovered and validated novel potential therapeutic targets for the treatment of IBD. Applicants will focus their proposals on providing convincing experimental evidence to support the nomination of a novel and differentiated therapeutic target for IBD, that warrants a drug discovery campaign within the Foundation’s IBD Therapeutics Incubator.

A successful drug target that can be a candidate for the IBD Therapeutics Incubator should meet most if not all the following criteria:

1. **Addressing an unmet need in IBD (required).** May include an improved and less toxic therapeutic approach; improved treatment of mild to moderate, moderate to severe, unremitting, refractory, and/or recurrent disease; therapeutics for complications; induction of mucosal healing; prevention and/or restoration of barrier damage/dysfunction.

2. **Linked to human IBD (required).** Demonstration that the drug target is altered in IBD patients. Targets that are uniquely linked to Crohn’s disease and/or to ulcerative colitis are encouraged.

3. **Novel and differentiated mechanism of action (required)** from those targeted by current therapies.

4. **Validated (required).** Demonstration that genetic or pharmacological modulation of the target, in \( \text{in vivo} \) and/or \( \text{ex-vivo} \) models of IBD, ameliorates or exacerbates colitis, and/or biological processes known to drive IBD.

5. **Druggable (required).** Experimental or theoretical demonstration that the target will bind with high affinity to a drug (e.g., available tool compounds, antibodies), resulting in modulation of the target’s functional signaling (biomarkers change) and a therapeutic effect.

6. **Available screening assays (desired not required).** These could include biochemical, enzymatic, cell-based assays, etc.

7. **Available tool compounds or antibodies (desired not required)** that regulate target activity and that can be used as controls for \( \text{in vivo} \) and \( \text{in vitro} \) efficacy studies.

8. **Available biomarkers (desired not required).** In particular, pharmacodynamic biomarkers, target engagement biomarkers, and patient stratification biomarkers.

9. **Favorable safety profile (desired not required).** Data supporting that therapeutic modulation of the target may not be associated with adverse side effects. Data can be derived from genetic knockout or transgenic models of the target. If available, non-GLP toxicology studies with tool compounds are also acceptable.

Overall, it is expected that proof-of-concept validation experiments should have been performed by the applicant demonstrating that the proposed target is novel, differentiated from available options in the clinic, and linked to human IBD biology. Such preliminary data may include pharmacological or genetic manipulation of the target or related biological pathway in a relevant \( \text{in vitro} \) or \( \text{in vivo} \) model. Insights
derived from human data (such as the quantification of the target and/or relevant biomarkers in clinical samples) are encouraged. Demonstration of a well-designed assay to screen candidates and assess *in vivo* target engagement is also encouraged. At this stage, fundable activities by the Therapeutics Incubator may include optimization of screening assays (miniaturization, etc.), high-throughput screening, rational design of candidates through medicinal chemistry and/or protein engineering approaches and others (see examples of relevant R&D activities below).

If the applicant’s proposed therapeutic target is selected, the incubator’s scope of work (SOW) will consist of drug discovery activities tailored to selected drug target(s) and it will be designed in collaboration with the Foundation’s scientific staff, the CRO, and the academic applicant. Depending on the level of development of the proposed drug target, approaches could include, hit identification via HTS or rational drug design, hit to lead identification, lead optimization, and others as shown below. Once the SOW is defined, in collaboration with the Foundation, the academic applicant and the CRO, milestones with clear Go / No Go decisions will be defined and evaluated at six-month intervals. The budget will be also determined at that point and depends on what activities to reach the milestones are required and where the research takes place.

Potential Areas of Focus:

- Novel and differentiated targets uniquely linked to Crohn’s disease and/or to ulcerative colitis are encouraged
- Restoration of barrier function and induction of mucosal healing by different modes of action. For instance:
  - Restoration of cell-cell junctions
  - Anti-apoptotic
  - Epithelial restitution/wound healing
Antimicrobial defense (e.g. defensins regulation)
- Treatment of complications – structuring (fibrostenotic) and penetrating (fistulizing) disease
- Regulators of neuroinflammation relevant to the gut function
- Others

Therapeutic modalities
- Small molecules
- Large molecules

Examples of Relevant R&D Activities:
- Screening assay development (biochemical, enzymatic, cell-based, etc.)
- Rational drug design
- Library screening
- Hit identification
- Hit to lead
- Lead optimization
- Target engagement assays
- Medicinal chemistry
- In vitro efficacy (cell-based)
- In vivo efficacy (IBD animal models)
- DMPK
- PK-PD
- PD biomarker identification
- Dose range finding
- Exploratory non-GLP toxicology

3. Eligibility

Applications from a team with the relevant expertise are required, with one lead Principal Investigator (PI) and at least one Co-PI.

- **Proposal in scope of the RFP (see section 2)**
  - PI must be a senior faculty member (Professor, Head of Research, Associate Professor, etc.) with relevant expertise in IBD biology and therapeutic target discovery.
  - Co-PI(s) must be an academic researcher with relevant expertise that is complementary to PI’s expertise, and could include medicinal chemistry, assay development, IBD biology, *in vivo* pharmacology, etc. and who is at any level of the academic professional track.
  - PI and Co-PIs must be employed by a non-profit research institution. International applicants are eligible to apply and there are no geographical restrictions regarding research site location(s).
  - Applications are strongly encouraged from diverse teams of applicants that include women, underrepresented racial and ethnic groups, individuals with disabilities, and/or individuals from disadvantaged backgrounds.
4. Terms & Conditions Key Points

The IBD Therapeutic Incubator requires a collaborative agreement with selected academic researchers, the Foundation, and a CRO/CROs to identify and develop new IBD therapeutic drug product opportunities to attract pharmaceutical and venture capital partnerships for further development and commercialization. The Foundation will lead the project selection and oversight, working with the IBD Ventures Scientific Review Committee and other ad hoc reviewers. The Foundation will also lead the planning and execution of the research project(s) utilizing additional advisors as required.

The focus of the RFP will be selection of novel, validated and differentiated drug targets to advance through the IBD Therapeutics Incubator.

We anticipate investing up to $1,500,000 over a three year period per project to discover and develop therapeutic drug opportunities for each selected therapeutic target candidate. While most of the budget will be used to fund activities at the selected CRO, in certain instances funds could go to the academic investigator and institution to support one or more research activities defined within the scope of work, which are not available at the CRO.

Roles of the key participants in the IBD Therapeutic Incubator program:

- **Academic researcher/investigator:** Provides the drug target, related background intellectual property (background IP), including know-how, available screening assays, etc., and other expertise, to enable the research and development (R&D) work that will be performed at the CRO. All relevant established assays and study protocols that are available at the applicant’s laboratory will be transferred to the CRO once the agreement contract is signed to avoid delays and re-invention. If required, the institution could be funded to perform experimental work which cannot be provided by the CRO.

- **Crohn’s & Colitis Foundation:** Will lead the scientific, operational, and contractual aspects to advance the projects, fund milestone-dependent R&D at the CRO and possibly at research institution, and act as the client of the CRO.

- **Contract research organization (CRO):** Will perform all experimental drug discovery research leading to the identification of drug candidates and the generation of novel IP (Resulting IP). The CRO will also have the capabilities to perform preclinical development work in support of IND enabling studies if the project advances to that stage and the funding is available. The CRO will be a fee-for-service contractor and have no ownership of the Resulting IP. The CRO will assign ownership of Resulting IP to the Foundation.

The Foundation will assign ownership of the Resulting IP to the academic researcher/investigator’s institution and receive a percentage of the net royalty income received by the institution if the Resulting IP is licensed and/or commercialized. The institution will lead efforts to prosecute the Resulting IP and to out license the Resulting IP, in consultation with and support from the Foundation. If this is not successful within three years and/or there is a cessation of reasonable efforts by the institution to develop a commercial IBD therapeutic product from the Resulting IP, the funding agreement will allow the Foundation to have the option, but not the obligation, to lead commercialization efforts into a potential IBD marketed drug, through another venture
capital, venture philanthropy or pharma partner, with the institution retaining an increased share of the net royalty income. Any other IP developed by institution through use of the Resulting IP that is commercialized also would be subject to receipt by Foundation of a share of net royalty income.

The Foundation has developed an agreement template that is anticipated to be acceptable for most academic institutions. If interested in applying to this RFP, applicant should request the collaboration agreement for review by the applicant’s institution. Redline (if any) to this agreement will be assessed as part of the application review process.

Please request the Therapeutics Incubator collaboration agreement template no later than **August 30, 2022**. This will allow sufficient time for applicants to have their respective technology transfer office and/or legal departments review it before the proposal submission deadline (October 3rd, 2022).

To request the full agreement template and any further information and clarification of the therapeutics incubator terms & conditions please contact Jean-Luc Tran at ibdincubator@crohnscolitisfoundation.org

5. How to apply

Interested investigators should submit full proposals and accompanying documentation by **October 3rd, 2022**. Proposals will be evaluated competitively based on the alignment of the proposed therapeutic target with the scope (Section 2) of the program and the feasibility of success of the project.

All applications should be submitted through the proposalCENTRAL portal at the following URL: [https://proposalcentral.altum.com/](https://proposalcentral.altum.com/)

Please refer to Appendix A for complete instructions on the application process.

6. Application Review and Selection Criteria

The proposals will undergo peer review by a multidisciplinary review committee including experts in IBD biology and industry scientists who are experts in drug discovery and development, and it will be evaluated based on the following criteria:

**The scope:** The proposal should align with the scope of the Therapeutics Incubator RFP (section 2).

In summary, proposed drug targets should meet most if not all the following criteria:

1. Addressing an unmet need in Crohn’s disease and/or ulcerative colitis (required)
2. Linked to the biology of Crohn’s disease and/or ulcerative colitis (required)
3. Novel and differentiated mechanism of action (required)
4. Validated in preclinical proof-of-concept studies (required)
5. Druggable target (required)
6. Available screening assays (desired but not required)
7. Available tool compounds or antibodies (desired but not required)
8. Available biomarkers (desired but not required)
9. Favorable safety profile (desired but not required)
Clinical and translational relevance to IBD: The drug target and its mechanism of action should be based on an established link to IBD. The translational potential of the project will have an impact on IBD patients’ quality of life by addressing unmet medical needs. Drug targets uniquely linked to Crohn’s disease and/or to ulcerative colitis are encouraged.

Research team & environment: The factors to be considered are complementary expertise of the PIs and the collaborators, personnel expertise, and infrastructure to support R&D activities if required. The PI must show a successful track record of achievements in advancing the scientific understanding of IBD biology and pathogenesis, drug target discovery and validation, expertise in a variety of models of IBD pathology.

Background IP and research tools: Description of all knowledge regarding the drug target and related screening assays, tool compounds and other relevant research tools that are available by the time of project initiation.

7. Oversight & Reporting

Once a drug target(s) of interest is selected, drug discovery and development milestones and SOW will be defined by the Foundation in collaboration with the academic PI and CRO. Advancement of the project will be evaluated with periodic teleconferences every two to three weeks (CRO scientists and program manager; academic PI, and Foundation scientists) to assess the achievement of the preestablished milestones, decide on next steps, and to troubleshoot when experimental problems emerge. Outcomes are captured in detailed slide decks, updated every two to three weeks, and through a final scientific report produced by the CRO. Because the Foundation is the client of the CRO, all final scientific and operational decisions are taken by the Foundation.

Overall progress of the research and milestone achievement will be evaluated every 6 months by a specialized review committee and Foundation scientific staff. Foundation will make informed Go/No Go decisions based on the input from these review/oversight meetings.

The academic PI will be required to submit an annual progress report via Proposal Central using the Foundation’s progress report template. This report summarizes the main progress achieved by the research at the CRO and/or the PI’s laboratory (if applicable). An annual financial report is also expected if PI receives funding to conduct some aspects of the research.

9. Contact Information

For more information and questions please contact

Jean-Luc Tran, Director, Therapeutics Incubator and Dr. Andrés Hurtado-Lorenzo, Vice President, Translational Research & IBD Ventures at: ibdincubator@crohnscolitisfoundation.org
APPENDIX A: Full Application Submission Guidelines

General information
The full application is due on October 3, 2022.
The application should be submitted to proposalCENTRAL at: https://proposalcentral.altum.com

Paper copies of the application are not accepted.

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 “Grant opportunities” on the far right of the page and select Crohn’s & Colitis Foundation under “Filter by Grant Maker” drop down menu on the upper left of the page.
c. Locate the “Therapeutics Incubator” 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.

Application Instruction: ProposalCentral.
The Full Application form will include the following fields:
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 instructions on how payment will be transferred to your institution and should not include information on the Investigator. This is required even if the institution has received Foundation funding in the past.

Enable other Users to Access the Proposal: Add personnel who 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.
Co-PI(s), PI, and Key Personnel: Add the roles and the contact information for Co-Principal Investigator (Co-PI) and key personnel whom you would like to include in this application.
Lay Summary
The Foundation has instituted a Stakeholder Reviewer Program, in which selected lay patients or caregivers participate as voting members of the various review committees. The Lay Summary should provide a clear, concise overview, in lay language, of the proposed drug target biology and mode of action, how the target could be used to develop novel therapies for IBD and how it could provide a differentiated approach compared to available therapies or improve the current practices in IBD management. In addition, please provide a brief impact statement describing the potential of the proposed therapeutic target to impact IBD healthcare. Also, include a brief glossary of any scientific terms included in your lay summary. Please note that a lay summary that is not written using lay language could affect the score provided by the Stakeholder Reviewer.

Scientific Summary of the Project
The Scientific Summary should provide a clear, concise overview of the proposed therapeutic target, including the background of the target’s biology, mechanism and mode of action of the potential therapeutic approach, target validation studies, types of samples and/or the model systems (in vitro and/or in vivo) that could be transferred to the CRO and support the Therapeutics Incubator drug discovery efforts, expected outcomes if the proposed drug target is chosen for the Therapeutics Incubator program and the translational potential of the study. Please include references and upload a Cited References document as an attachment.

Relevance to IBD
Re-state, what population of IBD patients the study will potently benefit (Crohn’s disease/ Ulcerative colitis). Explain the relevance of the therapeutic target for the treatment of IBD, the differentiation of the proposed therapeutic modality and mode of action compared to currently available therapies and the unmet need that the proposed therapy will address. Explain how the proposed therapeutic target is aligned with the scope of this RFP.

Current and Pending Financial Support
Please provide information on additional ongoing funding that currently supports research related to the proposed therapeutic target.

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/IACUC) 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.

Human and/or Animal Approvals: Upload IRB/IACUC approvals for human and animal research

Upload Proposal (Attach document or fill directly in ProposalCentral):

- Applicant expertise and resources related to proposed therapeutic target
  Describe background and expertise of the PI, Co-PI and the relevant investigators, and the role/ tasks that could be performed by each investigator if required. These include lab capabilities, in vitro models, in vivo models, screening assays, bioanalytic assays, medicinal chemistry, bioinformatics, compound libraries, etc)
- **Background and rationale of therapeutic target:** Description of the current understanding of the biology of the proposed target and its role in IBD pathogenesis and why the researcher believes it should be a drug target. Description of the intended therapeutic modality to modulate the target (small molecule, large molecule, agonist, antagonist, etc.) will be also useful.

- **Describe how target addresses an unmet need in IBD (required).** May include improved and less toxic therapy; improved treatment of severe, unremitting, refractory, and/or recurrent disease; therapeutics for complications; induction of mucosal healing; prevention and or restoration of barrier damage/dysfunction.

- **Describe how target is linked to human IBD (required).** Demonstration that the drug target is altered in IBD patients.

- **Describe how the target is novel and has a differentiated mode of action (required) from those targeted by current therapies.**

- **Describe target discovery and validation studies (required).** Demonstration that genetic or pharmacological modulation of the target ameliorates or exacerbates colitis or IBD biological processes.

- **Describe druggability of the target (required).** Experimental or theoretical demonstration that the target will bind with high affinity to a drug (e.g., available tool compounds, antibodies), resulting in modulation of the target’s function and a therapeutic effect. Describe the intended drug’s mechanism of action (e.g., agonist, antagonist, inhibitor, activator, etc.).

- **Describe available screening assays (desired not required).** These could include biochemical, enzymatic, cell-based assays, etc.

- **Describe available tool compounds or antibodies (desired not required) that regulate target activity and that can be used as controls in in vivo and in vitro efficacy studies.**

- **Describe biomarkers to support therapeutics development (desired not required).** Available / and or potential biomarkers based on literature In particular pharmacodynamic biomarkers, target engagement biomarkers, and patient stratification biomarkers.

- **Facilities available to perform research if required** (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 that could support research activities related to the proposed drug target. 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.

- **Biosketches for Key Personnel**
  - Biosketch (NIH format) for PI, Co-PI, and additional key personnel (optional).

- **References/ Appendices (optional)**
  - Uploaded reference material may include, but is not limited to:
    - Pitch deck focused on proposed drug target
    - Article references
    - Abstracts
    - Other Letters of Support

- **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 are located on the navigation bar on the left-hand side.

By signing and submitting your proposal the applicant agreed to and understood the IBD Therapeutics Incubator terms

**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.