Harvard Institute of Translational Immunology/ Helmsley Trust
Pilot Grants in Crohn’s Disease

Request for Applications: Filling Critical Gaps in our Understanding of the Mechanisms Underlying Crohn’s Disease
Due: February 23, 2011 at 12:00 noon ET

The Harvard Institute of Translational Immunology (HITI) is a newly-established collaborative effort which will bring together basic, translational and clinical investigators from across the Harvard community to develop interdisciplinary approaches for elucidating mechanisms of immune-mediated diseases. This knowledge will enable Harvard investigators to develop novel therapies, design immune-based assays to support clinical trials and improve diagnostic approaches to these diseases.

I. Rationale for the Pilot Grants
This RFA seeks innovative applications that will advance our knowledge of Crohn’s disease, a chronic inflammatory bowel disease with no known cure. Crohn’s disease can precipitate life-threatening complications and confers an increased susceptibility to colorectal cancer.

The topics for this RFA were inspired by suggestions from within and beyond the Harvard Community. Working with The Leona M. and Harry B. Helmsley Charitable Trust, HITI wishes to use this RFA to identify and support novel and interdisciplinary approaches related to critical aspects of Crohn’s disease pathophysiology. The primary goals of the RFA are deciphering the fundamental homeostatic mechanisms of microbe/epithelium/immune system interactions that are perturbed during the development of Crohn’s disease, and developing novel strategies to produce clinically valuable patient stratification. This RFA focuses on several innovative and challenging problems in the field of Crohn’s disease, solutions to which are likely to aggressively move the field forward. The goal of this RFA is to promote non-incremental advance in these critical areas.

Please read this RFA carefully as it contains important information about eligibility and review criteria. If you have any questions, please contact one of the individuals listed at the end of this announcement (section X).

II. Selected Approaches
Applications are invited that address the areas indicated below. The topics listed reflect community thinking about key gaps in our knowledge and possible approaches to addressing these issues. While feasibility will be a key factor in review of submissions, novel approaches and risk taking are encouraged.

1) Devising a novel in vitro intestinal epithelial cell culture system that will facilitate evaluation of mechanisms of Crohn’s disease
   • Engineered 3-dimensional constructs that faithfully capture the structure and function of the intestinal epithelium can bridge the gap between mouse models and clinical disease and are compatible with a high throughput strategy for assessment of pathophysiologic mechanisms and efficacy of drug candidates
   • Architecturally robust approaches incorporating other intestinal cell types, including cells of the immune system, that enable in vitro study of cellular-microbial interactions
2) Developing real-time readout systems that can interrogate the dynamics of microbiome, epithelial and immune cell interactions

- Creation of "reporter" constructs - bacteria, nanoparticles or nanocontainers - that can sense and record changes in key properties of, and interactions between, the microbiome and epithelial or immune cells
- Engineered constructs that preferentially colonize specific geographies of the gut, thereby providing highly informative real-time evaluation of gut physiology
- Advanced imaging technologies - either alone, or in concert with an engineered sensor - or use of miRNA or small molecule libraries to interrogate functional relevance/causality of aberrant biomarkers or functions in models of Crohn’s disease

3) Generating a creative and integrative analysis of the intestinal microbiome that moves beyond cataloging the luminal milieu

- Proof of concept in mice, or use of human organ-donor tissue, to define clinical approaches for undisturbed and geographically diverse sampling of the microbiome at the epithelial surface, the mucous layer and the lumen
- Mouse studies that characterize these geographically restricted microbial populations to determine their diversity, longevity and biological impact on mammalian cell function
- A systems biology approach to characterize complex interactions among the microbiome, the intestinal epithelium, and the associated immunological compartment
- Other novel approaches for deconstructing the complexity of the microbiome and providing unique perspectives on the symbiotic relationships between microbiota and intestinal cells

4) Formulating studies directed at the dynamic balance between injury and repair in the intestinal epithelium

- The role of cell metabolism - and its perturbation by endogenous or environmental inducers of cellular stress response pathways - both in epithelial cell injury and the subsequent repair process
- Investigation of other critical homeostatic functions - implicated or not by GWAS - which, if perturbed, increase the risk of inflammation and loss of epithelial barrier function
- The relationship between inflammation and predisposition to colorectal cancer, as it impacts Crohn’s patients directly, and as a means to better define the transition events between normal and neoplastic growth

5) Devising approaches to patient stratification that recognize the marked variability in their pathophysiology, genetics, and response to therapy

- Evaluation of early onset disease patients; integration of protective allele studies into GWAS of disease susceptibility; and identification and analysis of contributions of rare genetic variants to disease susceptibility
- More effective linkage of GWAS to mechanism, histology, patient disease status and response to therapeutics

III. Key Elements of the HITI/Helmsley Trust Crohn’s Disease Pilot Grant Program

- Any faculty member who holds a Harvard University faculty appointment regardless of type of degree or institutional appointment is eligible to be the Principal Investigator. All ranks of Professors, as well as Instructors, Lecturers, and HMS-appointed Research Associates are eligible to apply. If your appointment is not listed here, if you have questions about whether you are eligible to apply, or if you have any general questions about this RFA, please call 617-432-7550.
The principal goal of these grants is to support pilot studies that will lead to sustainable and innovative projects that will impact the lives of Crohn's patients.

HITI/Helmsley Trust Pilot Grants can range between $50K and $200K per application for one year depending upon the scope of the work. The majority of the awards will be in the range of $100K.

IV. Overview of Application and Review Processes
A five page complete application (see section VI) will be due, February 23, 2011. The reviewers will score the applications and choose applicants for a second phase of evaluation, which consists of an interview with the Pilot Grant Review Committee. These interviews will allow the Pilot Grant Review Committee to assess the proposals in depth and make the final funding decisions.

V. Timeline for the Grant Submission and Review

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<td>December 16, 2010</td>
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<tr>
<td>Applications Due</td>
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<td>Interview Invitations</td>
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<td>Interviews</td>
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<td>Funding Decisions Announced</td>
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Applications must be submitted online on the Harvard Catalyst website at http://catalyst.harvard.edu/services/hitifunding/crohns.html.

VI. Organization of the Grant Application

1. Project title
2. Category (selected from the five subject headings in section II)
3. Abstract (maximum of 250 words)
4. Administrative documents
   The following administrative documents should be uploaded as a single PDF via the webform (found at the url listed above):
   a) For each institution that will receive funds (in the case of collaborations), the following forms must be completed:
      i. PHS 398 Face Page, to be signed by institutional official.
      ii. PHS 398 Form Page 4: Detailed budget for one year. Refer to section IX for allowable costs. (If more than one site will share the budget, the combined total should not exceed $200,000.)
      iii. Narrative Budget Justification.
      iv. If the effort is collaborative in nature, provide a brief statement describing the work to be performed at each institution (2-3 sentences).
   b) PHS 398 Biographical Sketches for the PI, co-investigators and significant collaborators.
   c) Letter from the PI's department verifying appointment title.
5. The scientific proposal (uploaded as a separate PDF via the webform).
   The scientific proposal is limited to five pages, not including references. You must use Arial font, size 11, single-spaced, with 0.7 inch margins. Include the following sections (suggested lengths in parentheses):
   a) Introduction (1 page)
      Describe the scientific background for your grant application. Critically evaluate existing knowledge; explain how your pilot proposal relates to gaps in current knowledge; and
specifically discuss how your project has the potential to impact health of individuals with Crohn’s disease.

b) Project Details (2 ½-3½ pages)
Describe the specific aim(s) that will be completed in the funding period. For each aim, provide the experimental details, and delineate an approximate timeline for the activities related to that aim, including realistic milestones with which to judge progress of the project. Preliminary data is not required, but can be included if it speaks to feasibility. Please describe contributions from each member of the team (if the project is collaborative in nature) in the design and execution of the proposed experiments.

c) Future Plans (½ page)
Describe how you propose to extend and fund your project past the year of HITI support. Provide an overview of the future experimental plan (experimental details are not necessary). If the grant itself is not translational in nature, you must describe, in a clear and compelling fashion, how you would proceed in the following year to create this transition.

d) References (limit to 1 additional page)

e) Appendix material is not allowed. All figures should be included in the body of the application.

VII. Main Review Criteria
The critical qualities of successful applications will be innovation, feasibility and impact. Specifically, applicants should address the following questions in their proposals:

- Does the proposal provide a novel approach to an identified problem/obstacle in Crohn’s research, or does it identify a new topic of research? If successful, how will the results impact on Crohn’s patients?
- Is the project focused and achievable, and does it have a high potential to secure future extramural funding?
- Do the investigators have the requisite skills and experience to carry out the project successfully?

VIII. Interview
A critical feature of our application process is the interview, where the applicant and his/her collaborators will be asked to present and discuss their work. Investigators receiving the best scores on their submitted applications will be invited for an interview, and only a subset of those interviewed will be funded. We will inform the Principal Investigators as to whether they have been selected for an interview, and, if so, when they should expect their interview to be held.

If your project requires IRB or IACUC approval, you will need to have submitted your protocol(s) to the relevant board(s) in advance of the March 30 – April 1 interview. Additionally, either an approval letter or a statement by the review committee indicating that all necessary information has been supplied by the applicant must be provided at the time of the interview in order to be considered for funding.

IX. Funding
Funding decisions will be announced on April 11, with an intended award date of April 15. The maximum period of award is 12 months, starting on the effective funding date. The maximum amount to be awarded per application is $200,000, direct costs. Indirect costs are not allowed. Salaries and fringe for scientific staff, but not administrative personnel, are permissible. Budgeting for travel and computers is not allowed; equipment requests will be granted only if the equipment is shown to be vital to the specific goals of the project. Note that the funding cannot be released until all applicable human and animal subject protocols have been approved and copies, with approval
letters, sent to HITI. While initial awards will be for a period of one year, this does not rule out the possibility that continuing support may become available. It is imperative that projects commence on or near the listed start date, since it is unlikely that no cost extensions will be considered. It is anticipated that up to 10 pilot grants will be funded in this cycle.

X. Additional Information
Inquiries about the application process should be directed to Amy Webber, Research Navigator Coordinator, Harvard Catalyst (617-432-7550); HITI_Crohns@catalyst.harvard.edu.

Inquiries into scientific/research areas should be directed to David Beller, PhD, Program Director, HITI (617-432-2280); david_beller@hms.harvard.edu. Dr. Beller will be available to discuss the appropriateness of proposed submissions to this RFA.

Inquiries relating to financial or grants management areas should be directed to Lucy Kolessin, Director of Finance and Research Administration (617-432-7804); lucy_kolessin@hms.harvard.edu.