



Crohn's and Colitis
Foundation of Canada

Fondation canadienne des
maladies inflammatoires
de l'intestin



*The Crohn's and Colitis Foundation of Canada - Vertex Pharmaceuticals
Sponsored Research Program*

Request for Proposals

I. Background and Purpose. The Crohn's and Colitis Foundation of Canada (the "CCFC") and Vertex Pharmaceuticals ("Vertex") are pleased to announce the establishment of the Crohn's and Colitis Foundation of Canada-Vertex Pharmaceuticals Sponsored Research Program (the "Program"). Through this Program, the CCFC and Vertex will support research initiatives in the area of Crohn's disease and colitis research.

Subject to execution of a written mutually agreeable sponsored research agreement among the CCFC, Vertex, and the Institution of selected investigators (a "Definitive Agreement"), Vertex and CCFC will together sponsor up to three (3) 2-year research projects commencing January 1, 2012.

This Request for Proposals describes the specific fields of research for which proposals are sought, as well as details related to the application process and funding arrangement. Letter of Intent and Detailed Proposal templates required for application are provided in the appendices. The application process and scientific review process will be managed by the CCFC, and projects which meet the criteria for funding will be selected by the CCFC and Vertex.

II. Program Eligibility

1. Who may apply?

Any scientist employed by a Canadian academic institution or other medical research non-profit institution (each, an "Institution"), who is eligible under the policies of their Institution to participate.

2. Eligible Research Fields

Despite the clinical benefit achieved with current standard of care therapeutics, multiple unmet medical needs remain for both Crohn's disease (CD) and ulcerative colitis (UC) patients. Results of genetic association studies completed in the past several years have identified ~100 disease susceptibility loci for CD and/or UC that are defining the pathogenesis of these diseases and provide a molecular framework for selection of new therapeutic targets for drug discovery research. Combined with a personalized medicine paradigm, matching drugs designed to impact specific disease pathways with selection of patients carrying a specific genetic defect may result in maximal benefits in disease management.

Vertex research efforts are currently focused on the inflammatory aspects of CD and UC, with projects targeting Th1 and Th17 cell functions, cytokine and chemokine receptor signaling, inflammatory cell migration, ROS generation and inflammatory cell mediated tissue injury. Since these projects primarily

address acquired immunity, we are interested in exploring collaborative opportunities on other elements of IBD pathogenesis to identify new targets and further diversify a research platform for discovery of novel IBD therapies.

To meet this objective, the following areas have been identified for research proposals:

A. Innate immune mechanisms in bacterial recognition & clearance

Polymorphisms in genes for NOD2, ATG16L1 and IRGM have been associated with loss of function defects, resulting in diminished recognition and clearance of intracellular bacteria by epithelial cells and macrophages, altered antigen processing by dendritic cells, and dysregulation of the NOD/TLR signaling network.

Research proposals are being sought that may address the following:

- Identification and functional characterization of innate inducers or negative regulators of autophagy and NOD2 activation
- Inter-regulation and maintenance of homeostasis within the NOD2 and TLR signaling networks

B. Adherent invasive E coli (AIEC) in Crohn's disease

AIEC are emerging as potential virulent strains of commensal bacteria associated with pathogenesis of ileal / ileocolonic CD. AIEC strains have been isolated from ~35% ileal lesions from CD patients compared to ~5% of healthy subjects and are characterized by their strong adherence to intestinal epithelium and replication within mucosal macrophages. The compliment of virulence factors AIEC utilize has not been fully defined, but the strains all share an ability to invade cells by an endocytic process, resist bactericidal mechanisms and replicate in acidic phagolysosomes.

Research proposals are being sought that may address the following:

- Comparative genetic studies of AIEC strain virulence factors
- Investigation of potential drug targets associated with AIEC translocation, infection, or replication in epithelial cells and macrophages
- Systems biology approaches to elaborate microbial and host pathways at the transcriptome / proteome / epigenetic level which regulate interaction, adaptation and survival of AIEC in host epithelial cells or macrophages
- Development of mouse models to assess the hierarchy of infective virulence mechanisms and colitogenic potential of AIEC strains with emphasis on validation of models for in vivo efficacy studies
- Evaluation of biofilm formation, localization of AIEC colonies in mucosal tissue, and correlates with polymorphisms in autophagy and NOD2 genes

C. Epithelial barrier permeability and epithelial repair/restitution

A number of polymorphisms have been identified in genes that could affect epithelial cell functions and epithelial barrier integrity. These include genes associated with ER stress (ORMDL3, XBP1),

the extracellular matrix (ECM-1, LAMB1), ion transport (SLC26A3, SLC22A23, P-gp), microtubule organization, adherens junction and tight junctions (HNF4A, CHD1, CEP72, TPPP). However, functional defects associated with these polymorphisms and potential roles in altering trans-cellular, para-cellular permeability, regulation of tight junction integrity, or trans-epithelial leukocyte migration remain poorly defined.

Proposals comparing the role of wild type and genetic variants in the following processes would be of interest:

- Inflammatory mediator (TNF α /IL-1 β /IFN γ) signaling and trans-epithelial leukocyte migration
- Regulation of tight junction integrity and altered trans- and/or para-cellular permeability
- Regulation of intestinal epithelial repair mechanisms (restitution) and/or epithelial-myofibroblast interactions (physiological and pathophysiological fibrosis)
- Epithelial cell differentiation, proliferation and regulation of Paneth cell or crypt stem cell function.

III. Funding. Up to \$CAD100,000 per year for up to two (2) years.

IV. Review and Selection Process. This Program will use a two-stage application process described as follows.

1. Letters of Intent. Initially, each applicant will submit a brief, non-confidential summary of the proposed research (a “Letter of Intent”), with a one-page project synopsis, using the Letter of Intent form provided in Appendix A. The Letter of Intent will briefly describe the research objectives, an overview of proposed studies, and will highlight the biomedical relevance. The level of detail should be no greater than that of an abstract submission for publication at a public conference. Based on the Letters of Intent submitted, the CCFC and Vertex will select up to ten (10) projects for a second round of application. To maximize the chances of success, the Letter of Intent should succinctly address the following:

A. Background and Significance.

- (i) Need and Significance (highlighting the novelty, risk and potential benefits of the project).
- (ii) Briefly describe recent research directly relevant to the proposal, including others in the field and, in particular, your own work.

B. Proposed Research Plan.

- (i) Specific Aims and Objectives
- (ii) Total support amount requested.

C. Investigator Information.

- (i) Identify co-investigators
- (ii) Curriculum vitae (in brief) for each investigator
- (iii) Relevant publications/manuscripts (no more than five (5) citations) for each investigator

2. Detailed Proposals. The second stage of application requires that applicants, who are selected from the first round of Letters of Intent, submit a detailed research plan (up to six (6) pages, as guided by the format defined in the Detailed Proposal form provided in Appendix B) and a simple budget, brief biographical information on any co-investigators. Detailed Proposals may contain confidential information and provided the confidential information is identified as “confidential,” the CCFC and Vertex will treat such information as confidential. The Detailed Proposal should provide greater detail than in the Letter of Intent, including the following:

A. Background and Significance

- (i) A more formal connection of the proposed project to the furtherance of Crohn’s disease and colitis disease, diagnosis, or treatment understanding, including a concise relevant literature review.
- (ii) Unlike the Letter of Intent the Detailed Proposal is a confidential document, so in submitting a Detailed Proposal, investigators are invited to elaborate more on their recent research that has relevance to the proposal.

B. Proposed Research Plan.

- (i) Specific objectives, and for each objective provide an estimate of the cost and time required for completion.
- (ii) Describe the milestone criteria that will be used to determine if the specific objectives have been achieved.
- (iii) Describe key risks (beyond the control of the investigator) that could potentially jeopardize the successful attainment of objectives.

C. Third Party Resources. Identify prior, current and pending sources of support to your lab related to the proposed project.

V. Timeline and Deadlines.

- September 15, 2011: Deadline for submission of Letters of Intent to CCFC
- September 29, 2011: Announcement of finalists
- October 27, 2011: Deadline for submission of Detailed Proposals to CCFC
- December 15, 2011: Announcement of Sponsorship recipients
- January 1, 2012: Earliest eligible start-date of Sponsorship

VI. Other Requirements: Terms and Conditions of the Sponsorship.

1. Collaborators. Proposals including up to two co-investigators (“Co-Investigators”) at the same or different Institutions will be considered, but all investigators must be individually eligible. If Co-Investigators are listed, the investigator (“Contact Investigator”) who will be primarily responsible for communication with the CCFC and Vertex must indicate that all Co-Investigators have consented to the collaboration concept insofar as is outlined in the proposal and to the provision of their names and details in the proposal document. Inclusion of Co-Investigators in the Detailed Proposal, will constitute consent that the Co-Investigators will comply with all Program requirements. Funding will only be assigned to

the Contact Investigator. The Contact Investigator must indicate in a Letter of Intent all concurrent submissions of separate proposals that list the Contact Investigator as a Co-Investigator. Funding of studies supported by third parties, other than the investigator's non-profit Institution or the Canadian government, generally will be rejected.

2. Reporting. Subject to the terms of the Definitive Agreement, investigators will provide periodic progress reports and meet with the CCFC and Vertex on a regular basis throughout the duration of the funding period.

3. Publication. Subject to the terms of the Definitive Agreement, publication of funded research results will not be restricted, except as needed to comply with a short pre-disclosure period for all research publications and presentations resulting from the funded work

4. Funding of Supplies. Subject to the terms of the Definitive Agreement, requests for funding of "supplies" should generally be limited to a maximum of 15% (before application of any indirect costs) of the total requested funds. Requests for funding of capital equipment purchases generally will be rejected.

VII. Submission of Proposals.

Electronic versions of the Letters of Intent must be (1) submitted via email to @ccfc.ca and be clearly identified as a proposal for the Crohn's and Colitis Foundation of Canada-Vertex-Pharmaceuticals Sponsored Research Program, and (2) received no later than September 15, 2011.

The Application Form contains additional instructions for the preparation and submission of the Letters of Intent and Detailed Proposals. Applicants are required to adhere to all formatting stipulations in submitting their applications.

Please only provide the specifically requested materials. Additional materials such as letters of support, updates on publications, updates on other support received, letters confirming academic appointment, reprints, etc., will not be reviewed.

VIII. Contact Information. For additional information on the Program and the application process, please contact your liaison:

Rohini Soni
Chief Research Officer
Crohn's and Colitis Foundation of Canada
416-920-5035 ext. 214
rsoni@ccfc.ca

IX. Legal Terms and Conditions. This document is a request for proposals in respect of the Program and is not a tender. Neither the RFP nor the submission of any Letters of Intent or Detailed Proposals in response to the RFP will, in any way whatsoever, create a binding agreement between CCFC, Vertex and any applicant. For clarity, this RFP is not intended to be an offer to enter into a bidding contract with applicants, including a Definitive Agreement, and no agreement of any kind will exist between any applicant and CCFC or Vertex until a Definitive Agreement if any, has been formally

executed by the Institution of a selected applicant and CCFC and Vertex. Notwithstanding any other provision of this RFP, CCFC and Vertex may, in their sole discretion, accept or reject any or all Letters of Intent or Detailed Proposals. CCFC and Vertex may accept any Letter of Intent or Detailed Proposal in whole or in part. CCFC may elect to cancel this RFP process at any time before the end of the RFP process but, for clarity, before execution of a Definitive Agreement. After a cancellation of the RFP process, if any, CCFC may subsequently advertise or call for new submissions for the same or different subject matter of this RFP with the same or different participants.