



IBD ^{CHALLENGES IN} Research

UPDATE ON PROGRESS AND IMPORTANT FUTURE GOALS FOR CCFA RESEARCH

Lay Summary

The Crohn's & Colitis Foundation of America (CCFA) has invested over \$180 million in inflammatory bowel diseases (IBD) research since 1967. Since 1990, CCFA has brought together thought leaders in IBD every four to five years to update the Foundation's scientific strategic plan called "Challenges in IBD Research." At this meeting, experts review the research progress that has been made over the past five years and then recommend areas of research focus over the following five years. These meetings allow basic (laboratory) and clinical (patient care) researchers to come together to identify and prioritize research questions that are important across both areas. This goal is identify ways to move important research findings from the bench to the bedside. "Challenges in IBD Research" provides a "roadmap" for all of CCFA's research programs.

The last Challenges document was published in 2008. This paper described what advances had taken place in basic and clinical research from 2004-2008, and provided goals for the next five years. The important research findings during this time period were 1) identification of genes for IBD, 2) better understanding of the relationship between the immune system and the bacteria in the gut (microbiome), 3) better understanding of how the innate immune system helps to keep stability in the lining of the gut (mucosal homeostasis), and 4) the discovery of cells that drive and regulate immune responses.

This document also identified important goals for CCFA research from 2008-2012. These goals included 1) the development of better tools to identify genes associated with IBD, 2) the development of better tools for gut bacterial (microbiome) analysis, 3) better understanding of the association between genetic markers and response to medical therapy, and 4) improvement in the medications available to treat IBD.

In June 2012, the new "challenges" work group evaluated progress since the last document. The following basic science advances were identified:

- Rapid progress in identifying genes for both Crohn's disease (CD) and ulcerative colitis (UC), with over 160 genes found to date.
- Improved technology for DNA sequencing and bioinformatics (application of statistics to biology) has allowed researchers to describe many aspects of the bacteria in the gut and how they interact with the immune system. These tools have allowed for identification of individual species and groups of bacteria that may be involved in inflammatory bowel diseases (IBD). These bacterial communities are more complex in their interactions and biochemistry than previously thought.
- The interaction of the gut bacteria (microbiota) and cells in the adaptive immune system has been shown to play a role in the development of Th17 and regulatory T cells.
- New functions of certain innate immune cells have been discovered, as have new innate immune cell types (such as lymphoid cells (ILCs)).



Significant advances in clinical research also occurred:

- Large studies have been initiated to see if there are clinical or biological tests that can predict treatment outcomes or risks in pediatric IBD patients (examples include the “RISK” Stratification Study and the Predicting Response to Standardized Pediatric Colitis Therapy study [“PROTECT”]).
- Registries that include patients from multiple centers throughout the United States have been started to determine whether there are complications of medical therapies used in the treatment of pediatric IBD.
- Large studies have provided a better understanding of the risks and benefits of medical and surgical therapies in certain groups (one example is the Pregnancy in IBD and Neonatal Outcomes study [“PIANO”] which follows women with IBD during pregnancy, and then follows the babies born to these mothers).

Based on these advances, leading researchers developed a new set of research goals for CCFA in 2012 and beyond. The researchers reviewed eight separate research focus areas including 1) epidemiology and the role of environmental factors, 2) IBD diagnoses, 3) optimizing medical therapy, 4) genetics, 5) microbiome, 6) adaptive immunity, 7) innate immunity, and 8) epithelial cell biology. After review of these individual areas, researchers identified global issues important to all areas of IBD research that would advance the ultimate mission of CCFA: to cure Crohn’s disease and ulcerative colitis and to improve the quality of life of children and adults affected by these diseases.

Summary of Global Priorities

- Identify tools (including genetic, immunologic, microbial, tissue expression, and clinical profiles) that will predict the aggressiveness of CD or UC, whether complications will develop, and how individual patients will respond to particular therapies.
- Understand how environmental factors enhance the risk or progression of IBD through effects on microbial, epigenetic, immunologic, and mucosal barrier influences.
 - Studies on the role of diet in the development and progression of IBD are needed.
- Determine which environmental triggers initiate, maintain, and/or reactivate disease.
- Further understand the interactions (cross-talk) between genes, microbiota, epithelial cells, and innate and adaptive immune responses that may influence the stability of the gut lining versus the development of inflammation.
 - Determine cellular pathways for communication with the microbiota.
 - Define cell types and the pathways associated with gut stability versus inflammation, with an ultimate goal of finding new therapies targeting these pathways.
- Determine the best treatment approaches using studies that directly compare medical therapies (comparative effectiveness studies).

To carry out this research agenda, the following resources are needed:

- Centralized infrastructure for maintaining biological samples and data.
- Long-term prospective studies of pediatric and adult IBD patients where biological specimens (including tissue biopsies, blood and stool) are collected throughout the course of their diseases.
- Infrastructure to recruit and follow patients from childhood to adult life.
- Access to data and specimens collected prior to and following treatment with established and new medical therapies.
- Improved tools for measuring disease activity in IBD.
- More specific laboratory tools including humanized mice and lineage specific models for mechanistic research.
- Availability of new methodology for improved cell lines and freshly isolated mucosal cells.
- Implementation of a series of workshops to improve IBD research methodology and promote integrative multidisciplinary approaches and resources.

Since 1990, there has been remarkable progress in our understanding of IBD development and of specific targets for new therapies in IBD. However, further strides are clearly needed. CCFA has played a central role in advancing this research. Through development of the ambitious research goals outlined in this document, CCFA has again led the effort to further the understanding of IBD. CCFA is keen to advance this research agenda in 2012 and beyond.

