obtained, researchers hope to devise novel therapeutics for existing cases and proactive therapeutic strategies to prevent the onset of IBD in identifiable high risk groups.

Response of neuroendocrine cells to intestinal inflammation

Kevan Jacobson — *B.C. Children's Hospital*

Understanding the mechanisms underlying the ability of intestinal inflammation to modify the organization and function of the enteric nervous system (ENS) is important. This study will analyze the neurobiological and functional consequences associated with enteric infection and chronic recurrent intestinal inflammation associated with IBD. The study's experiments will also increase the understanding of neural involvement in acute disease in chronic disease and neural involvement in ongoing symptoms post recovery. The use of probiotic bacteria in the study will allow researchers to begin to develop therapeutic interventions that may minimize the bacterial burden, as well as attenuate the intestinal disease and neurological consequences that might be associated with ongoing disease and genesis of ongoing symptoms.

Mucosal associated microflora and the development of Crohn's disease

Denis Otto Krause — *University of Manitoba*

Inflammatory bowel disease is hypothesized to be caused by a bacterial antigen that drives an inflammatory response in a genetically predisposed host. This means that there are probably bacteria that cause inflammation in the bowel in people that have a genetic defect in the cellular mechanisms that control inflammation. As yet we do not know which bacteria drive this inflammatory reaction. As it turns out, it is very difficult to unravel the bacterial species that are involved because most (70%) intestinal bacteria cannot be cultured. We propose to use molecular based methods that do not rely on cultivation to identify disease causing bacteria in genetically predisposed people.

Cellular protection by Interleukin-11 during intestinal inflammation

Mark J. Ropeleski — *Queen's University*

Certain intestinal epithelial proteins and regulatory pathways enhance epithelial functional integrity. The hypothesis of this study is that the intestinal epithelium can make proteins during physiologic and pathologic inflammatory stress in order to enhance cellular resistance to injury. This study will try to discover the mechanisms by which the cytoprotective cytokine Interlukin-11 protects the intestinal epithelium during pro-inflammatory stress as it pertains to the causes of Inflammatory Bowel Disease. Using an animal model of colitis as well as cells grown in culture, researchers will explore the effects of Interleukin-11 (IL-11), an anti-inflammatory cytokine that protects the epithelium in numerous models of intestinal injury and in particular, models of IBD. The long-term goal is to define new strategies for the maintenance of remission in IBD, and to develop therapeutic approaches that directly result in healing of the intestinal mucosa that have been damaged during inflammatory stress.

Functional roles of the Crohn's disease-related CARD15 protein

Katherine Siminovitch — *Mount Sinai Hospital*

Mutations in the CARD15 gene have been shown to be associated with Crohn's disease and CARD15 is now widely recognized as a Crohn's disease susceptibility gene. Variants of this gene have been shown to predispose to Crohn's disease in many diverse populations. This study will address several of the major gaps in current understanding of the function of CARD15. Researchers will define each of the steps that link a change in the CARD15 gene / protein to development of Crohn's disease, with the long range goal of developing improved therapeutic strategies for both preventing and treating Crohn's disease.

Mechanisms of Intestinal Susceptibility to Bacterial Pathogens: Implications for Inflammatory Bowel Disease

Bruce Vallance — *B.C. Research Institute for Children*

The exact mechanisms that lead to IBD are not known, however IBD may occur when the intestinal immune system of susceptible individuals is not able to recognize or control specific bacterial species, allowing the bacteria to infect intestinal tissues and cause chronic inflammation. This hypothesis was strengthened by the discovery that many Crohn's disease patients suffer a loss-of-function in the gene that encodes the NOD2 protein. NOD2 is a receptor that recognizes bacteria and is one of several receptors that trigger a host of inflammatory responses when they encounter bacterial or viral molecular patterns. Using the infectious colitis caused by the bacterial pathogen Citrobacter rodentium, the aim of this study will be to identify the basis for genetic susceptibility to a bacterial pathogen within the GI tract, as well as to determine the cell types that mediate the defect. As a result, this study will help to identify those individuals at risk of developing IBD, as well as clarify the type of microbes that can trigger chronic bowel inflammation.

Inflammatory modulation of ion channels in DRG neurons enhances nociception in IBD

Stephen James Vanner — *Queen's University*

Pain is a major cause of ill-health in patients who suffer from IBD and pain can severely limit their quality of life. Current treatments include narcotics such as morphine, which have non-specific actions throughout the body. These non-specific actions include drowsiness, altered cognition, decreased energy levels, nausea and vomiting. In patients with active colitis, narcotics have the potential to precipitate life-threatening toxic megacolon. As a result, there is a great need for the development of effective agents to treat IBD pain that lacks these serious side effects. This study will examine the cellular mechanisms that underlie pain, specifically inflammatory pain. Its goal is to identify the key signaling events in inflammatory pain and to determine how they alter the "pain sensing" nerves. Ultimately, the goal is to identify targets on these nerves which could lead to a new class of selective pharmacological agents for the treatment of inflammatory pain.

Lipoxins as a Therapeutic Target in IBD

John Lawrence Wallace — *University of Calgary*

Evidence suggests that lipoxins (arachidonic acid products) reduce colonic inflammation. The goal of this study is to better evaluate the role of this group of lipid mediators in animal models of inflammatory bowel disease and provide a foundation for clinical studies which will help researchers understand the pathogenetic processes that lead to tissue injury and dysfunction. It will assess the production of lipoxins by the inflamed mouse colon at various stages of the inflammatory process. It will also examine the relationship between lipoxin synthesis and the severity of intestinal damage and inflammation, as well as examine epithelial barrier function. Interventional studies will be performed using a stable analogue of lipoxin A4 in order to determine if this agent can modulate the severity of colitis/enterocolitis in the two experimental models. We will perform dose-response studies and studies in which we utilize both preventative and curative treatment protocols. Finally, the study will attempt to identify the mechanisms of action of lipoxins in the intestine. The goal is to provide a solid foundation of information regarding the notion that lipoxins are a rational target for therapy of IBD, setting the stage for testing of this hypothesis in a clinical setting.

Crohn's and Colitis Foundation of Canada

Fondation canadienne des maladies inflammatoires de l'intestin

National Office
600–60 St. Clair Ave. E.
Toronto, ON M4T 1N5
Tel: 416-920-5035
Toll Free: 1-800-387-1479
Fax: 416-929-0364
Web Site: www.ccfc.ca
E-mail: ccfc@ccfc.ca

Registered Charity # 11883 1486 RR 0001

Crohn's and Colitis Foundation of Canada

Fondation canadienne des maladies inflammatoires de l'intestin

2004 2003

Research Report

"Each year, the CCFC increases its financial support into research toward finding the underlying causes of IBD, and, ultimately, the cure. It also initiates creative and innovative projects that bring together the finest medical minds specializing in IBD."

Dr. A. Hillary Steinhart,
Vice-Chair, Executive Council
CCFC IBD Research Institute

Inflammatory bowel disease (IBD) affects more than 170,000 Canadian men, women, and children. There is no known cause or cure.

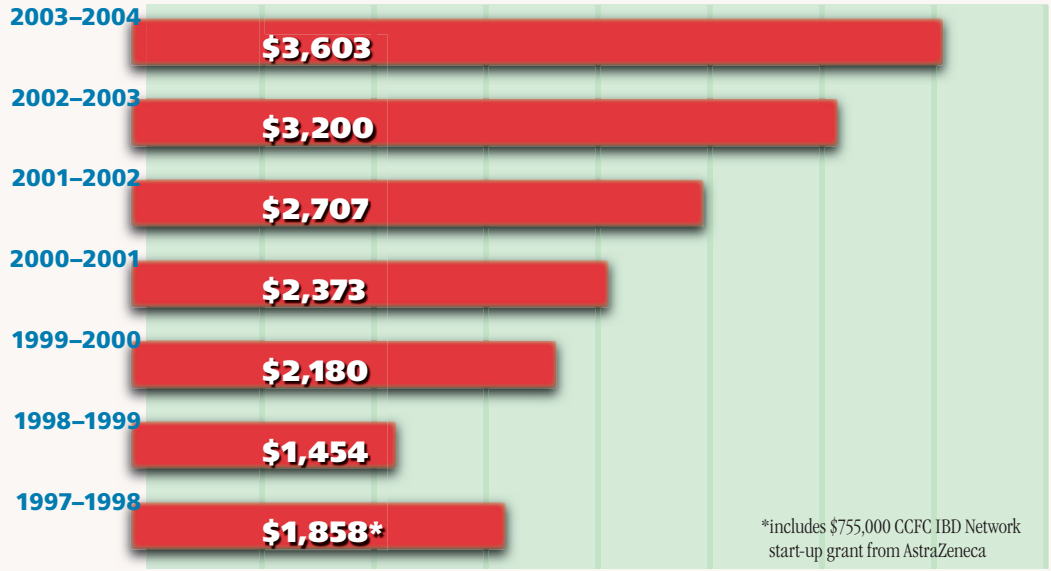
Celebrating breakthroughs in the search for a cure

This is the 30th anniversary of the Crohn's and Colitis Foundation of Canada (CCFC). We have a lot to celebrate. Thanks in part to funds provided by the CCFC, this year researchers isolated the gene associated with the development of Crohn's disease. However, there is a lot more work to do. Other exciting projects funded by the Foundation are devoted to isolating the bacterial antigens associated with IBD, studying the intestinal immune systems of individuals susceptible to IBD and the most effective ways to treat the physical pain caused by IBD.

In the past year alone, the CCFC has invested over $3.6 million dollars funding both ongoing and brand new research projects. That brings its total to over $35 million dollars over the history of the Foundation. Here are some examples of how CCFC donations have been invested:

CCFC Research Investments: 1997-2004

(Numbers in thousands)



Research Initiatives:

GEM Project

In the spring of 2004, the Executive Council of the CCFC IBD Research Institute met with other top Canadian researchers to develop the design, nature and scope of the "GEM project," a multi-disciplinary study of the Genetic, Environmental and Microbial causes of IBD in humans.

CCFC IBD Research Institute

In the summer of 2003, the CCFC announced plans to invest more than $25 million in IBD research in the first five years of the Institute. Here are some of its projects:

Major Expansion of the CCFC Research Grants

Following an increase from $75,000 to $125,000 in 2003, in 2004 the CCFC's Grants in Aid of Research will increase from $125,000 to $150,000 per annum for up to three years. Our Grants Review Committee normally oversees the peer review of 15-20 grant proposals per year. This year, however, we received an unprecedented 29 proposals. Clearly, the word has spread among IBD researchers that the CCFC Grants in Aid of Research Program is among the most esteemed in Canada. That means the Foundation attracts world-class researchers who can only expand our knowledge into the disease. Thanks to the contributions of CCFC members and sponsors, 10 new projects will be conducted this year to carry us closer to finding a cure.

Epidemiological Study to Assess the Incidence and cost of IBD in Canada

In 2003, the CCFC funded a major epidemiological study led by Dr. Charles Bernstein of the University of Manitoba to study the burden of Crohn's disease and colitis to the country in terms of health care costs, time lost from work due to illness, etc.

Expanding Personnel Awards

The CCFC is expanding the sponsorship of the brightest medical students, encouraging them to pursue careers in IBD research.

Canada's First Clinical Trials Consortium

In the spring of 2004, the CCFC invested in the formation of a network of the best clinical trial specialists in Canada who will work together to find new approaches and treatments for IBD.

Funding National and International collaborations through a new CCFC Group Grant Program

With this program, the CCFC intends to dedicate itself to subsidizing collaborative multi-disciplinary health research in Canadian research institutions. In 2004, grants of up to $150,000 per year for three years will be available to groups of up to three collaborators.

Sponsoring Symposia with a focus on IBD research in Canada and abroad

The Foundation will sponsor a Satellite Symposium focusing on IBD at the upcoming World Congress of Gastroenterology in Montreal.

The Canadian IBD Network Tissue Bank

The Canadian IBD Network Tissue Bank has proven invaluable in facilitating the collection of IBD tissue and clinical data for collaborative research studies.

Research Grants

Thanks to the generosity of its supporters, the CCFC has funded ten new research projects in 2003-2004, for an overall total of more than 180 Grants-in-Aid-of-Research over the past 30 years. Here is a list of the new research projects :

The Effect of nerve growth factor and probiotics in models of intestinal inflammation.

John Bienenstock — *McMaster University*

The international medical research community generally agrees that IBD probably has a genetic background and that an abnormal response to relatively normal conventional microflora in the intestine is responsible for the inflammatory changes. Probiotic organisms which are normal commensals of the GI tract can have significant beneficial effects in the prevention of the onset of colitis, although the mechanism of action of these organisms is not clear. Despite this deficiency, various probiotic organisms appear to be effective in human disease. This may be due to the stimulation of nerve growth factor (NGF) which has unusual anti-inflammatory properties. This study will explore and possibly determine whether NGF is involved in the mechanism of action of probiotics in down regulation of inflammation in these models. Through these studies we may be able to identify new targets for novel therapeutic approaches in IBD.

Prebiotics (non-digestible food ingredients) and experimental colitis

Levinus "Leo" Albert Dieleman — *University of Alberta*

Research in animal models of colitis as well in patients with IBD has shown that several specific gut bacteria are crucial for the development of disease. Besides disease-inducing bacteria, there are also bacteria that are beneficial for the host, called probiotic bacteria. Administration of the probiotic bacteria Lactobacilli and Bifidobacteria can prevent colitis development in experimental colitis, as well as in ulcerative colitis and pouchitis. Prebiotics are non-digestible oligosaccharides which occur naturally in various foods. Since they can stimulate the growth of these probiotic bacteria in the gut, they offer promise for emerging new therapies of IBD directed towards changing the intestinal bacteria and their function. This grant will focus on testing the efficacy of two promising prebiotics in two different rodent models of chronic intestinal inflammation. It will also investigate protective immune and non-immune mechanisms in these colitis-susceptible hosts. The results of these studies will lay the foundation for a therapeutic trial using dietary therapy such as prebiotics in patients with IBD.

The Archaeal Microbiota In Inflammatory Bowel Disease (IBD)

W. Ford Doolittle — *Dalhousie University*

Microbial causes are proven or suspected for most if not all chronic inflammatory disease, including arthritis, chronic gastritis, as well as lower GI inflammatory disease, including ulcerative colitis and Crohn's disease. Host genetic factors such as the NOD2 gene (CARD15) and variations in type and level of antimicrobial peptides, as well as an absence of protective flora, all likely contribute to these complex diseases. No single microbe, however, has unequivocally been proven to cause IBD, though the majority of gut microbes have never been cultured. This study will be the first to test a conjecture that archaea play a role (as causative or protective agents) in Crohn's disease and ulcerative colitis, in the first truly comprehensive assessment of archaeal diversity in inflammatory bowel disease patients. Researchers hope to determine which archaea are present in the bowel flora and associated tissues of healthy individuals, and whether there is a difference in diversity and prevalence of archaea between patients with inflammatory bowel disease and healthy individuals; whether there are such differences between patients with these two conditions, and whether there are such differences between different tissues and locations within patients. On the basis of the information