Research Report 2002

Crohn's and Colitis Foundation of Canada

Fondation canadienne des maladies inflammatoires de l'intestin

"This year, we invested $2.7 million in top-calibre Canadian research investigations. This investment reflects both the strength and excellence of the Canadian IBD research community, and the CCFC's strong commitment to finding a cure for IBD."

Michael J. Howorth
CCFC National Executive Director

Inflammatory bowel disease (IBD) affects more than 100,000 Canadian men, women and children. There is no known cause or cure.

The Crohn's and Colitis Foundation of Canada (CCFC) believes medical research is the key to finding a cure for these chronic digestive disorders. We have come to learn more about the fundamental biology of the intestine and IBD, thanks to intensive world-class research being conducted in Canada, much of which is sponsored by the CCFC.

The CCFC is the leading sponsor of IBD research in Canada

To date, the Foundation has invested more than $29 million in:

- 162 **Grants in Aid of Research** in university centres;
- The **Canadian IBD Network Tissue Bank**, facilitating the collection of IBD tissue and clinical data for collaborative research studies;
- The **CCFC IBD Network**, linking patients, clinicians and researchers across the country;
- The **CCFC Group Grant** program, supporting collaboration among IBD researchers across Canada;
- The **CCFC IBD Research Scientist Award**, assisting Canadian university-based investigators to conduct IBD research on an ongoing basis;
- The **"Innovations in IBD Research"** program, funding novel, less traditional research studies;
- **Laboratory equipment grants** to support young investigators establishing a career in IBD research;
- **Scholarships** to 154 summer students receiving training in IBD research;
- The establishment of the first **Canadian Chair in Intestinal Disease Research**;
- The funding of two world-class **intestinal disease research units** at McMaster University and the University of Calgary.

Leading the Search for a Cure

The CCFC's commitment to IBD research is stronger than ever. This year, we invested close to $2.71 million in research grants and initiatives. We are proud to report that we have nearly doubled our research funding since 1998/1999. This incredible growth is made possible by the thousands of CCFC members, volunteers, donors and sponsors who drive our fundraising efforts. Thanks to their contributions, the CCFC is the largest sponsor of IBD research in Canada.

Research Grants

The Foundation awarded nine new Grants in Aid of Research this year, signifying a $1.9 million investment. The grants cover a wide variety of research initiatives and represent the largest single-year investment in the Grants in Aid of Research program to date. We also continued our emphasis on the training of future IBD researchers, funding a new CCFC Finkelstein Fellowship and four new Summer Student Scholarships. In 2001/2002, the CCFC provided funding to more than 45 major medical research projects, fellowships and scholarships.

Canadian IBD Network Tissue Bank

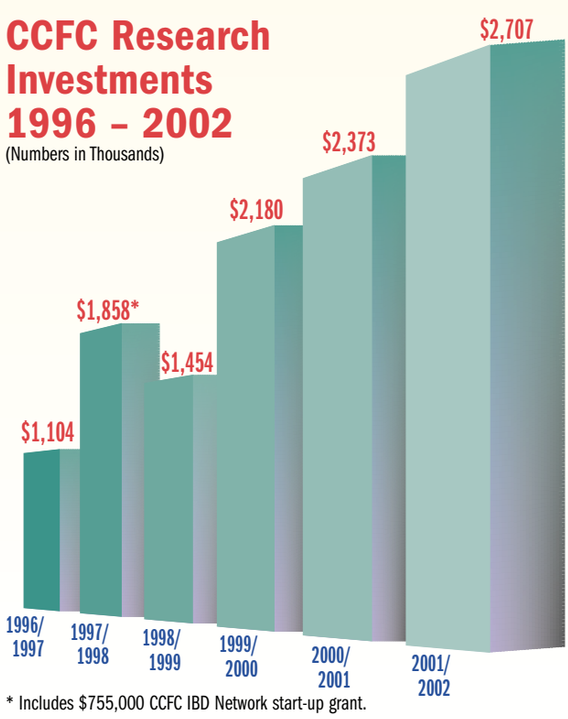
The Canadian IBD Network Tissue Bank enrolled a significant number of IBD physicians this year. As participants, these physicians submit tissue and data from patients who have been recently diagnosed with IBD. The materials and information will be used for innovative and large-scale research projects to be conducted through the CCFC IBD Network. In fact, the Foundation has announced two new studies to investigate the role of microbes as a causal factor in the development of IBD. These studies will use tissue and clinical data stored in the Tissue Bank to compare the microbes in newly-diagnosed patients to those of disease-free patients.

IBD 2002: Opportunities and Challenges in IBD

In May, 2002, the CCFC hosted a ground-breaking conference for leading IBD researchers from around the world. *IBD 2002: Opportunities and Challenges in IBD* featured discussions on the latest ideas and discoveries in several areas, including genetics; the application of new technologies in IBD research; the effect of bacteria or gut flora on immune regulation; and brain-gut interactions in the development of inflammation.

The conference was designed to help the Foundation identify new goals and directions for the CCFC's research programs. These recommendations will form the foundation for our future research initiatives.

It was evident from the discussions that researchers see the CCFC as the leader of IBD research in Canada. They unanimously endorsed the Foundation's Grants in Aid of Research program and encouraged the CCFC to expand its role in attracting new researchers to, and sustaining current ones in, the Canadian IBD research community.



* Includes $755,000 CCFC IBD Network start-up grant.

"IBD 2002: Opportunities and Challenges in IBD brought together leading IBD investigators from around the world to discuss new discoveries and advances in medical research in general and IBD specifically. These discussions formed the basis for specific recommendations regarding priorities and future directions for the research program of the Foundation that would aid in the effort to accelerate our search for the cure."

Dr. Ken Croitoru
CCFC Medical Advisory Council Chair

Recent Research Findings

Each year, the CCFC carefully invests in a number of promising research projects. The majority of these projects are conducted and funded over a three-year period. Here is what we learned from research projects completed this year:

A Genetic Role for Diminished Bone Density in IBD

Several factors, including corticosteroid use, are thought to contribute to IBD-related bone density loss. Genetics may also be involved in both the expression of the disease and bone loss. Drs. Gordon Greenberg, Lawrence Rubin and Mark Silverberg of the University of Toronto examined bone density in 410 IBD patients.

Thirty per cent of Crohn's patients who had never taken steroids had reduced bone mass at the start of the study. A similar number of non-steroid treated patients experienced relevant bone loss throughout the study. The hip was more affected than the lumbar spine – a pattern which may be associated with chronic inflammation. Their results support the idea that disease activity may be an important factor in bone density.

The researchers also examined some genetic factors that may impact bone loss, including tumour necrosis factor alpha (TNFα). This inflammatory agent may be a marker for patients with more aggressive Crohn's activity and thus are more prone to bone loss. Their preliminary investigation found TNFα was associated with reduced bone density in the femoral neck but not the lumbar spine.

In future, they will investigate additional genes as predictors of bone loss, and test the premises that disease activity is the key predictor of bone loss in Crohn's, and that corticosteroid use is the key predictor in ulcerative colitis.

Autonomic Nervous System in Experimental Colitis

Autonomic nerves control involuntary bodily function, such as gastrointestinal function and fever. Dr. Keith Sharkey of the University of Calgary looked at how the brain is involved in autonomic nerve response and whether that response leads to certain colitis symptoms.

An inadequate fever response increases susceptibility to infection. Dr. Sharkey examined fever response in colitis by introducing a bacterial product called lipopolysaccharide (LPS). The colitis model showed a reduced fever response to the LPS, while a healthy control model displayed the appropriate fever response. This is similar to the response to bacterial movement in colitis and may account for the body's diminished ability to fight off bacterial infection in IBD. The finding is consistent with the increased susceptibility to infection seen in IBD.

This project also identified certain brain cells (immune cells, and two types of glial cells) involved in autonomic nerve activation during colitis. This is the first time that brain cells have been shown to be directly involved in nerve response during colitis.

Complementary Medicine Use by IBD Patients in Canada

Complementary and alternative medicine (CAM) use by IBD patients is growing. Dr. Allan Best, of the University of British Columbia, and Drs. Robert Hilsden and Marja Verhoef, of the University of Calgary, examined CAM use among IBD patients, the types of CAM they are using and the perceived benefits.

Based on responses from 2,828 CCFC members with IBD, 47 per cent reported current or past CAM use. Of those, half were still using CAM at the time of the survey. The most common therapies were acidophilus (a beneficial bacteria, or probiotic), massage therapy, flax seed, meditation and naturopathy. Among the respondents who were currently using CAM, the most commonly reported benefits were a sense of well-being, improvement in symptoms, sense of control over the disease and improved energy level.

About 71 per cent of CAM patients said they had discussed it with their doctors. Forty-three per cent reported that their doctor was supportive of their use of CAM, while only 13 per cent felt their doctor was not supportive of their CAM use.

Mechanisms of Attenuation of Acute Phase Protein Gene Expression by TGFβ

Epithelial cells lining the intestine produce acute phase proteins (APP) in response to inflammatory signals. These proteins are increased in IBD. Dr. Claude Asselin of the University of Sherbrooke examined how these proteins are controlled by two anti-inflammatory agents, Transforming Growth Factor Beta (TGFβ) and butyrate.

TGFβ reduced the production of an APP gene called haptoglobin by down-regulating certain isoforms (types of protein) of a transcription factor (C/EBP) which is known to control intestinal cell inflammation. This is the first time these isoforms have been identified as targets of TGFβ.

Butyrate, a short-chain fatty acid, may help protect the epithelium during inflammation. Dr. Asselin's research has shown that butyrate reduced the production of haptoglobin by down-regulating these same isoforms. Butyrate also combined with other isoforms to induce another APP gene called serum amyloid A. The data suggests butyrate may be an important factor in gene expression and intestinal inflammation.

This research has provided valuable clues about the cause and progression of intestinal inflammation and it could lead to new ways of regulating inflammation.

Metabolic Bone Assessment in Children with IBD – A Prospective Study of Risk Factors and Basic Pathogenic Mechanisms

Osteoporosis is a significant complication of IBD and its treatments, particularly in childhood and adolescence when bones are growing. Drs. Anne Marie Griffiths and Gillian Hawker of the University of Toronto monitored bone density in newly-diagnosed children and adolescents to examine the frequency of bone loss, the impact on bone density following diagnosis and treatment; and the relationship between bone density and bowel inflammation.

Bone scans (taken before IBD treatment started) revealed a decrease in bone mineral density among young Crohn's patients compared to healthy peers. In contrast, the bone mineral density of children with ulcerative colitis was similar to healthy peers. Follow-up examinations one year later indicated improvements in bone formation but it was still not at a normal level. Overall, Crohn's patients had lower bone mineral density than their healthy peers.

To examine the relationship between bowel inflammation and low bone density, the researchers introduced serum from the newly-diagnosed, untreated Crohn's patients to an animal bone model. They found that bone formation was reduced. However, when they blocked inflammatory mediators in the serum, which were at elevated levels, the changes in bone formation were partly prevented.

The researchers suggest bone scanning for young patients to identify those who should be receiving treatment to delay or prevent osteoporosis.

Nitric Oxide Synthesis by Intestinal Epithelial Cells

Epithelial cells line the inside of the intestine and defend against harmful substances that can cause inflammation. They do this by secreting water to flush away the substances. In inflammatory disease, this secretion is impaired. Dr. Wallace MacNaughton of the University of Calgary examined whether nitric oxide plays a role in decreased water secretion.

Some epithelial cells are programmed to respond to specific secretion agents and trigger the secretion of chloride ions when appropriate. Chloride in turn triggers water secretion. In this study, the secretion was impaired by inducible nitric oxide synthase, an enzyme which produces nitric oxide (NO). NO blocks chloride secretion by epithelial cells. Chloride secretion was restored to proper levels by inhibiting NO synthase. Inhibiting NO synthase also prevented the movement of the bacteria into the intestine during and after inflammation.

This research improves understanding of the barrier function of the epithelium and provides new avenues for possible treatment.

Permeability and Crohn's Disease

The delivery of antigens or harmful substances to the gastrointestinal tract through an abnormally 'leaky' or permeable small intestine is believed to be a major factor in the development of Crohn's disease.

Dr. Jon Meddings of the University of Calgary looked at intracellular factors that control inflammation and may control leakiness of the gut. A major factor is a complex called NF kappa B, which can increase the release of inflammatory signals when activated. This project indicated that activation of NF kappa B increased leakiness of intestinal cells. This leakiness could be inhibited or prevented by limiting the activation of NF kappa B. Overall results showed a close connection between abnormal permeability and abnormal inflammatory responses.

The project has provided valuable information about permeability factors in Crohn's disease and may ultimately contribute to better predictive factors and possible prevention of disease relapse.

Regulation of Intestinal Epithelial Barrier Function by GLP-2

Glucagon-like Peptide 2 (GLP-2) is a growth hormone secreted by intestinal cells. It regulates intestinal growth and the permeability of the intestinal cell lining which serves as a barrier against potentially harmful substances. Dr. Mary Perdue of McMaster University studied the effects of GLP-2 on the permeability, or leakiness, of this cell lining.

GLP-2 was used in two conditions that feature increased permeability: food allergy and stress. In both cases, GLP-2 reduced the penetration of potentially harmful substances into the intestine by reducing the permeability of the cell lining. In the case of the food allergy, the hormone also reduced inflammation, and ion secretion, which causes diarrhea.

The results suggest that GLP-2 is a promising potential therapy which could regulate or decrease intestinal permeability, accelerate bowel healing and prevent relapse of inflammation.

Role of GLP-2 in the Treatment of IBD

The intestinal hormone Glucagon-like Peptide 2 (GLP-2) helps repair and regenerate intestinal cells. Current therapies for IBD reduce inflammation but do not affect intestinal growth. Dr. Patricia Lee Brubaker of the University of Toronto examined whether GLP-2 alone or in combination with 5-ASA or corticosteroids, could stimulate intestinal growth.

GLP 2 alone increased small intestinal growth, and significantly reduced the colon damage caused by colitis in a mouse model. The combination of GLP-2 with 5-ASA plus corticosteroids further increased the effectiveness of GLP-2, but the combination of GLP-2 and corticosteroids alone actually decreased the effectiveness of GLP-2.

The results suggest that GLP-2 may be a new approach for the treatment of patients with IBD when used in combination with 5-ASA and corticosteroids.

Role of Poly ADP-Ribose Polymerase in Modulating Epithelial Permeability and Inflammation

Oxidative stress is a process in which molecules (called free radicals) attack and destroy cells, including those in the intestine. It is believed to contribute to the intestinal permeability, or leakiness, seen in IBD. Dr. Karen Madsen of the University of Alberta examined an enzyme called poly-ADP-ribose polymerase (PARP), which plays an important role in whether a cell dies or repairs itself during oxidative stress and, therefore, whether the intestinal barrier remains intact or breaks down.

The results showed PARP was involved in the breakdown of the intestinal barrier. The enzyme was found in increased amounts in IBD. Inhibiting PARP improved intestinal barrier function, reduced secretion of immune system proteins that cause inflammation and decreased inflammation.

The results improve understanding of intestinal barrier function breakdown and may lead to treatments to repair the damaged barriers, especially during inflammatory "flare-ups".

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