Welcome from the Helmsley Board of Trustees

On behalf of The Leona M. and Harry B. Helmsley Charitable Trust, it is my pleasure to welcome you to the first program report of our IBD and Crohn’s Disease Program. Since 2008, seeking to confront these terrible diseases, the Trust has made major awards to the world’s top scientists and research institutions in the field. We are proud of the scope of our investments and the potential they hold, and are excited to tell you about them in this “year in review.” And while we are pleased with our efforts to date, we are not satisfied. We understand the work is complex and builds from insight to innovation to therapy, but the Helmsley Charitable Trust’s unwavering goal is to find a cure for IBD and Crohn’s disease. We look forward to working with all of our partners to make this ambitious objective a reality and to relieving the suffering of millions of patients and families worldwide.

About the Helmsley Charitable Trust

The Leona M. and Harry B. Helmsley Charitable Trust aspires to improve lives by supporting exceptional nonprofits and other mission-aligned organizations in the U.S. and around the world in health, place-based initiatives, and education and human services. Since 2008, when the Trust began its active grantmaking, it has committed more than $1.4 billion to a wide range of charitable organizations. For more information on the Trust and its programs, please visit www.helmsleytrust.org.

Growing the IBD Portfolio: 2009–2014

The Helmsley Charitable Trust IBD and Crohn’s Disease Program portfolio grew significantly in FY2014, with much of its new grantmaking—$46.3 million—focused on launching or expanding dynamic research networks.
Growth and Discovery: 2014–2015 in the IBD and Crohn’s Disease Program

Since 2009, the Helmsley Charitable Trust has authorized more than $185 million in grants to find a cure for IBD and Crohn’s disease and, while awaiting that outcome, to find better therapeutic and prevention strategies. The Trust’s funding supports leading research institutions around the world by bringing together scientists in new collaborations to study different facets of the disease and incorporate the latest technologies and most recent scientific insights into their work. More than 100 Helmsley-funded investigators are working in nine countries to understand how human genetics, the gut microbiome, and the immune system can cause and exacerbate IBD and bring those insights into the development of new treatments.

This past year was an exciting year for the program. The portfolio grew significantly, with much of its new grantmaking—$46.3 million—focused on launching or expanding dynamic research networks. These powerful partnerships bring together leading researchers and resources to pursue complex, critically important questions that can’t be addressed alone. They represent a central strategy that the Trust believes will yield the new knowledge we need to overcome Crohn’s disease.

In our 2014-2015 program year, we launched our first program Advisory Board (see inside back cover) to help shape the program’s direction ahead, review grant applications, and assist with program evaluation. In this “year in review,” we highlight the largest grants made this past year and the exciting, groundbreaking discoveries the Trust’s IBD/Crohn’s Disease Program continues to generate.
Very Early Onset IBD Consortium

In 2014, the Trust awarded more than $7.6 million to establish the Very Early Onset (VEO) IBD Consortium. The 10 member institutions that make up this consortium (funded through individual grants) are working toward treatments for IBD that strikes infants and young children. This condition is generally far more debilitating than adult-onset IBD and is sometimes fatal. Through international clinical collaboration, the Consortium hopes to improve identification of genetic variants and mechanisms that cause VEO IBD in order to develop state-of-the-art cell- and gene-based therapies. All consortium members have pledged to provide clinical data, DNA, or other biological samples from their patients.

The VEO IBD Consortium builds on an alliance between the international Early Onset Pediatric Inflammatory Bowel Disease Cohort Study (NEOPICS) and the Care-for-Rare Foundation. In October 2014, consortium members met in Toronto, Canada, to formally begin work on a VEO-IBD roadmap for research. The meeting was hosted by SickKids IBD Centre and NEOPICS and included presentations on:

• Children with Rare Diseases of the Immune System: Therapeutic Orphans or Pioneers of Individualized Therapy?
• Defining and Developing the Therapeutic Pipeline for VEO IBD: Boston, Toronto, and Munich Studies
• Developing an Intestinal VEO IBD Organoid Bank as a Tool for Research and Drug Discovery
• Immune Response in Macrophages as a Tool to Study VEO IBD

PROGRESS IN FIVE STAGES

The overarching goals of this project are to assess the role of recently identified genetic variants and networks associated with VEO IBD and identify potential targets for therapeutic intervention, and to develop cell and gene based therapies for VEO IBD patients.

To meet these ambitious research aims, the consortium is building on an existing worldwide network of children's hospitals to identify patients, and then use sophisticated laboratory and informatics techniques at elite research institutions to analyze the samples and provide new treatment options. A cohort of 400 infantile VEO IBD patients is being established and 600 relatives of the ill children are being recruited so that other factors leading to the disease can be considered. The scientists have organized their work into five research stages, which run in parallel as patients are recruited and samples are acquired. The five stages are:

1. **Phenotype and Genotype**
   Biological samples are collected from all patients for genetic, immunological, and functional studies in order to understand the critical causal pathways involved in VEO IBD.

2. **Discovery**
   Samples from patients for whom a previously recognized pathway is not identified will undergo microbiome analysis, whole exome sequencing, and other genetic analyses, and will be sent to the participating laboratories, where scientists can generate intestinal epithelial cell cultures, known as organoids, and stem cells for use in Stage 4.

3. **Computational Biology and Integrative Analysis**
   Data from Stages 1 and 2 are used to construct computer models of VEO IBD genes and associated networks. These networks can help define pathways responsible for VEO IBD and determine drug targets for Stage 5.
4. **Functional Studies and Experimental Validation Models**
   A variety of experimental tools and strategies are employed to validate genes identified as potentially causing IBD. These tools include organoids and stem cells developed in Stage 2, and various model systems such as humanized and conventional mouse models.

5. **Therapeutic Platform**
   Data generated during Stages 1-4 are integrated in a computerized exploratory platform to discover novel therapeutics for VEO IBD and may provide insights for adult therapies, as well.

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**LOOKING AHEAD**

In 2015, the members of the Very Early Onset Consortium are moving quickly to capitalize on the funding that allows laboratories to work together. Working groups focused on platforms to share results, gene discoveries, and challenging patient cases hold monthly webinars. Funding from the German Academic Exchange Service and the Harvard Stem Cell Institute will allow for training additional researchers to work on these rare manifestations of IBD and investigate potential lentiviral vectors of IBD to deliver future gene therapies. A meeting of the Consortium is planned for October 2015 in Munich.

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**At a Glance**

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<td>Care-for-Rare Foundation (Munich)</td>
<td>Christoph Klein, MD, PhD</td>
<td>Defining and Developing the Therapeutic Pipeline for VEO IBD: Munich Studies</td>
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<tr>
<td>Cedars-Sinai Medical Center (Los Angeles)</td>
<td>Dermot McGovern, MD, PhD</td>
<td>Computational Biology and Integrative Analysis for VEO IBD Therapeutic Pipeline Development</td>
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<tr>
<td>Children’s Hospital of Boston</td>
<td>Scott B. Snapper, MD, PhD</td>
<td>Defining and Developing the Therapeutic Pipeline for VEO IBD: Boston Studies</td>
</tr>
<tr>
<td>The Hospital for Sick Children (SickKids) (Toronto)</td>
<td>Aleixo M. Muise, MD, PhD</td>
<td>Defining and Developing the Therapeutic Pipeline for VEO IBD: Toronto Studies</td>
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<tr>
<td>Hubrecht Institute (Amsterdam)</td>
<td>Hans Clevers, MD, PhD</td>
<td>Developing an Intestinal VEO IBD Organoid Bank as a Tool for Research and Drug Discovery</td>
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<tr>
<td>Institute of Molecular Biotechnology GmbH (Vienna)</td>
<td>Josef Penninger, PhD</td>
<td>Novel Model Systems as a Tool to Study VEO IBD</td>
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<tr>
<td>Mount Sinai School of Medicine (New York)</td>
<td>Judy Cho, MD and Eric Schadt, PhD</td>
<td>Computational Biology and Integrative Analysis for VEO IBD Therapeutic Pipeline Development</td>
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<td>Stanford University (Palo Alto)</td>
<td>David Relman, MD</td>
<td>The Gut Microbiome as a Tool to Study VEO IBD</td>
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<td>University of Oxford (Oxford)</td>
<td>Fiona Powrie, PhD</td>
<td>Immune Response in Macrophages as a Tool to Study VEO IBD</td>
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<tr>
<td>Yale University (New Haven)</td>
<td>Ruslan Medzhitov, PhD</td>
<td>Exploring the Vulnerabilities of the Developing Intestinal System and its Role in VEO IBD</td>
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IBD Over Time Consortium

The Trust awarded a grant of $6.1 million in 2014 to launch the international IBD Over Time (IBDOT) Consortium. This consortium consists of three European institutions that are analyzing immune and microbial changes in Crohn’s disease patients after hematopoietic (bone marrow) stem cell transplantation. It is expected that this research will lead to innovative cell-based therapies that disrupt disease progression. Consortium members will share data and biospecimens from three existing cohorts of patients to investigate key mechanisms known to lead to disease development—namely, how the immune system interacts with the microbiome before, during, and after specific treatments. They will also pursue ways to heal intestinal lesions in patients with Crohn’s disease through “regenerative therapy.”

The kickoff meeting for the IBDOT Consortium was held in September 2014 at the Hospital Saint-Louis in Paris, hosted by Dr. Matthieu Allez, head of the Department of Gastroenterology and Professor of Medicine, and attended by scientists from the three research centers that comprise the consortium. The gathering updated colleagues on the latest research relative to the consortium goals, refined study protocols, and shared methods that will lead to identifying normal and disease-promoting interactions between genetic factors, the immune system, and the microbiome.

PURSUING ISSUES IN IMMUNE RESPONSE, REGENERATIVE THERAPIES

Crohn’s disease starts in adolescence or early adulthood in the majority of patients, progressing to intestinal tissue damage over time. Accumulating evidence suggests that Crohn’s results from inflammation caused by an overzealous immune response to intestinal microbes or environmental factors in genetically susceptible individuals. The contribution of immune cells, known as T cells, to inflammation is suggested by their capacity to infiltrate tissues and produce factors known to cause inflammation, such as TNF (tumor necrosis factor).

Current management of Crohn’s relies on conventional immunosuppressant therapy or treatment with antibodies to TNF. These therapies fail in about 40% of patients. Among those who do respond, 50% stop responding in the first year of treatment. Recent studies using hematopoietic stem cell transplants to treat Crohn’s have yielded sustained drug-free remission for up to five years in 18 out of 22 patients. Some researchers hypothesize that this “resetting” of the immune system may explain these results, but the true mechanism of action is unclear. However, this outcome opens the door to the development and use of a whole range of innovative cell-based, regenerative therapies—the ultimate targets of this consortium’s research.
LOOKING AHEAD

In its first year of operations, the three participating laboratories in the IBD Over Time Consortium are focused on finalizing recruitment and patient protocols for stem cell patients and sharing of tissue samples. T-cell analyses from newly treated patients and detailed analysis of the major bacterial phyla in the first 25 patients are both underway.
SHARE Network

SHARE—Sinai-Helmsley Alliance for Research Excellence—is the largest and oldest research network in the Trust’s IBD and Crohn’s disease portfolio. In 2014, the program created a SHARE Steering Committee to better represent the individual projects and facilitate greater collaboration among its seven sites. Each site, plus a representative from the Data Management Center, is now represented on the committee. William Faubion, MD, of the Mayo Clinic serves as chair.

The SHARE Network facilitates the search for a cure by providing a formal structure capable of integrating and synthesizing the efforts of researchers from seven institutions throughout the country: Cedars-Sinai, Massachusetts General Hospital, Mayo Clinic, Mount Sinai Medical Center, University of Chicago, University of North Carolina, Chapel Hill, and Washington University—among the nation’s premier centers for the study of IBD and Crohn’s.

Utilizing $23.9 million in Helmsley Charitable Trust funding, this coordinated, multi-institution approach fulfills a critical need. There have been many advances in the identification of the genes responsible for increased risk of IBD. However, an understanding of how genetic disorders cause, modify, or increase the risk of developing IBD remains elusive. In large part, this stems from the fact that traditional single-center research programs examine genetic information without correlation with patient information, immunological, microbiological, and other pathobiological data.

SHARE enables the systematic analysis of a vast amount of data and information from a large and diverse patient base in the context of different patient subsets, including clinical phenotypes, response patterns to specific medical and surgical interventions, and disease course. Utilizing a systems biology platform, seven participating centers throughout the country consolidate resources, patient information, and experimental results.

Perhaps most significantly, the SHARE Network has created a space for targeted, controlled longitudinal studies focused on understanding and treating Crohn’s disease and colitis. Disease analysis is comprehensive and includes multiple, complementary approaches. These include patient sub-typing, clinical outcomes, epidemiology, pathologic features, genetics, microbiology, and immunology—tasks that are well beyond the capabilities and resources of any single research center.

In addition to creating the Steering Committee, in 2014:

- The SHARE Network implemented a number of initiatives to improve reporting and the network’s overall structure, including organizational flow charts for each of the multi-institutional projects and project dashboards.
- In March, representatives from the SHARE Network met during Digestive Disease Week (DDW) in Chicago.
- SHARE scientists have published nine papers, and four additional abstracts and manuscripts have been submitted for publication.
- SHARE investigators across the network have leveraged Helmsley-supported efforts to apply for eight additional grants, four of which have already been secured.
- As of November, SHARE had enrolled 4,512 patients into its research programs, one of the largest research databases of its kind.
LOOKING AHEAD

In 2015, the members of the SHARE research collaboration are focused on finishing the eight research projects funded over the past few years, including work on epigenetics, the role of Paneth cells in mucosal healing, piloting systems biology approaches to studying Crohn’s disease, and investigating rare presentations of the disease. In addition, SHARE’s bioinformatics leaders will, on behalf of the entire Helmsley IBD research network, lead a workshop at the NASA Jet Propulsion Laboratory to help bring “big data” architecture and analysis techniques to the study of IBD, first across SHARE and then in collaborating with other Helmsley-funded investigators.

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<tr>
<td>Mount Sinai, Mass General, Cedars-Sinai, Mayo Clinic, University of Chicago</td>
<td>Sergio Lira, MD, PhD</td>
<td>Discovering Genes and Environmental Interactions</td>
<td>February 2012/36 months</td>
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<tr>
<td>University of Chicago, Mayo Clinic, Mount Sinai</td>
<td>Eugene Chang, MD</td>
<td>Identification of Aberrant Tissue Responses to Intestinal Microbes That Cause Ulcerative Colitis</td>
<td>February 2012/36 months</td>
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<tr>
<td>University of North Carolina at Chapel Hill and Washington University</td>
<td>Rodney Newberry, MD and Balfour Sartor, MD</td>
<td>Determinants of Early Postoperative Recurrence of Crohn’s Disease</td>
<td>February 2012/36 months</td>
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<tr>
<td>Mayo Clinic, Mass General, Cedars-Sinai</td>
<td>William A. Faubion, Jr., MD</td>
<td>Curing Crohn's Disease Requires an Epigenetic Approach</td>
<td>July 2013/36 months</td>
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<tr>
<td>Cedars-Sinai, Washington University, Mayo Clinic</td>
<td>Dermot McGovern, MD, PhD</td>
<td>Defining the Causes and Consequences of Changes in Paneth Cell Morphology in Crohn's Disease</td>
<td>July 2013/36 months</td>
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<tr>
<td>University of Chicago and Washington University</td>
<td>Bana Jabri, MD, PhD</td>
<td>Microbial-host interactions in UC patients with PSC</td>
<td>July 2013/36 months</td>
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<tr>
<td>Mount Sinai, Mass General, Cedars-Sinai, University of Chicago, University of North Carolina at Chapel Hill</td>
<td>Inga Peter, PhD</td>
<td>Systems Biology Approach to IBD</td>
<td>July 2013/36 months</td>
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<tr>
<td>Cedars-Sinai, University of Chicago, University of North Carolina, Mass General, Mayo Clinic, Mount Sinai, Washington University</td>
<td>Dermot McGovern, MD, PhD</td>
<td>Genetic, Serologic and Clinical Factors Associated with ‘Rare’ IBD Phenotypes</td>
<td>July 2013/36 months</td>
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**Israeli IBD Research Nucleus (IIRN)**

Funded in 2013, the Israeli IBD Research Nucleus (IIRN) held its first symposium in November 2014, bringing together scientists from five institutions.

Also in 2014, the Shaare Zedek Medical Center team launched a Helmsley-supported project titled “Population-based Analysis of IBD Using an Administrative Database from Israeli HMOs.” This effort will seek ways to overcome administrative, technical, marketing, and political barriers to studying IBD, create a merged database, and develop a powerful population-based method for exploring IBD in Israel using health administrative data from four HMOs. This work will enable ongoing assessment of incidence rates, cost of care, risk factors for the disease, and predictors of poor disease outcome. To date, all four HMOs have signed contracts to work on this project. Importantly, given the scope of this study, the Israeli Ministry of Health has already approved the IIRN’s use of the algorithm that identifies IBD patients from their HMO data.

By working in Israel, where IBD incidence is relatively high and where the health care system is conducive to population-wide studies, five IIRN teams— from Ben-Gurion University of the Negev and the associated Soroka Medical Center, Rambam Health Care Campus, Shaare Zedek Medical Center, Sheba Medical Center and the Tel Aviv Medical Center—are poised to gain insights into IBD that would be much more difficult to gain elsewhere. Researchers from these institutions contribute patients and samples to each other’s studies, making the data from each more powerful than they would be alone. The researchers also provide each other with complementary expertise.

IBD is chronic, complex, and cryptic. Therefore, interdisciplinary research encompassing genetics, microbiology, and immunology, with long-term follow-up of patients, retrieval of appropriate biological samples, and the completion of large epidemiological studies, are necessary to unravel the pathogenesis of these diseases.

IIRN research will aim to uncover correlations among symptoms and environmental factors, disease risk, quality of life outcomes and health economics-related issues. The IIRN team believes improved treatments will hinge on this research, which is providing answers to questions such as:

- Which patients are likely to have more serious disease trajectories?
- Who is likely to respond to drugs?
- What environmental factors are important drivers of the disease?
- And even, how does IBD affects patients and society at a psychological and economic level?

Toward this last question, in 2014 researchers at Ben-Gurion University of the Negev completed an analysis of 137 patient questionnaires that revealed how Crohn’s disease affected their work lives, as well as their education and socio-economic status.
## Lead Institutions – IIRN

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<tr>
<td>Ben-Gurion University of the Negev</td>
<td>Shmuel Odes, MD</td>
<td>Socio-economic Impact of Crohn’s Disease on the Israeli Population</td>
<td>March 2013/36 months</td>
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<tr>
<td>Rambam Health Care Campus</td>
<td>Yehuda Chowers, MD</td>
<td>Personalizing and Tailoring IBD Drug Therapy</td>
<td>March 2013/36 months</td>
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<tr>
<td>Shaare Zedek Medical Center</td>
<td>Dan Turner, MD, PhD</td>
<td>Population-based Analysis of IBD Using Administrative Database from Israeli HMOs</td>
<td>March 2013/36 months</td>
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<tr>
<td>Sheba Medical Center</td>
<td>Rami Eliakim, MD</td>
<td>Monitoring of Crohn’s Disease Patients at Risk for Imminent Flares and Future Complications</td>
<td>March 2013/36 months</td>
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<tr>
<td>Tel Aviv University</td>
<td>Iris Dotan, MD</td>
<td>Understanding the Pathogenesis of Crohn’s Disease: Predicting Disease Behavior and Response to Therapy</td>
<td>March 2013/36 months</td>
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### LOOKING AHEAD

Throughout 2015, IIRN scientists will continue their joint investigations. In a study of response to medications for Crohn’s disease, researchers at Rambam Health Care Campus are investigating changes in immunology among patients who do and do not respond to front-line therapies. At Sheba Medical Center, a study to test the ability of capsule endoscopy to evaluate patients and predict the risk of disease complications and flares continues to enroll patients. And at Shaare Zedek Medical Center, researchers continue to fine-tune a unique database of patient records from Israel’s four health insurers to assess incidence of IBD, risk factors, and predictors of poor outcomes.
Broad Institute of MIT and Harvard: Genetics, Exome Projects

In 2014 the Trust awarded nearly $9.9 million to the Broad Institute of MIT and Harvard to support whole exome sequencing from 20,000 individuals, identify genes that confer either strong risk or protection from IBD, and evaluate potential therapeutic targets.

Broad scientists hope the exome project reveals new therapeutic targets for IBD, spurring the development of new treatments. This project has far-reaching potential, as all information generated from it, including raw and processed genetic data and analyses, will be made available to the entire scientific community to maximize the impact on functional research and therapeutic development in IBD.

In addition, the exome research is using existing patient data and samples to explore infantile IBD cases likely to harbor a heavier genetic load of IBD risk variants, including severe protein-coding mutations that are less frequently seen in adult patients. Scientists will also be able to research IBD in people from Latino, East Asian, and African American ethnicities, three groups that were not widely surveyed in previous studies.

This grant complements an existing large research program to study genetic differences between Crohn’s disease patients and healthy individuals to understand how IBD is caused and maintained in the body.

Looking Ahead

The Broad Institute’s two Helmsley-funded projects on IBD are proceeding swiftly in 2015. The host genetics grant will continue to study the role of cell death (autophagy) in the development of Crohn’s disease, and the exome project is well on its way to sequencing 20,000 IBD samples to identify the full spectrum of IBD-relevant rare variants throughout the genome.

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<tr>
<td>Broad Institute of Harvard &amp; MIT</td>
<td>Ramnik Xavier, MD, PhD</td>
<td>Novel Therapeutic Approaches for Crohn’s Disease</td>
<td>October 2013/36 months</td>
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<tr>
<td>Broad Institute of Harvard &amp; MIT</td>
<td>Mark Daly, PhD</td>
<td>Using Proteins and the Exome to Impact IBD</td>
<td>August 2014/36 months</td>
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<tr>
<td>Crohn’s and Colitis Foundation of America</td>
<td>Herbert “Skip” Virgin, IV, MD, PhD</td>
<td>CCFA Genetics Initiative</td>
<td>July 2012/24 months</td>
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<tr>
<td>Crohn’s and Colitis Canada</td>
<td>Ken Croitoru, MDCM, FRCP(C)</td>
<td>Genetic Environmental Microbial (GEM) Project Acceleration and Analysis</td>
<td>September 2013/48 months</td>
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CCFA Genetics

The Crohn’s and Colitis Foundation of America (CCFA) received a second $1.5 million Helmsley Trust grant in 2014 to support the CCFA Genetics Initiative, which culminated in 2014. This initiative has taken on a study of complex genetic traits to determine how genes exert their influence on the biology of health and disease and interact with environmental triggers for these diseases. To approach the enormously complex and unexplored set of data, the initiative provided a cross-disciplinary and multi-investigator collaborative platform, with research taking place primarily at Massachusetts General Hospital and Washington University.

The investigators’ overarching hypothesis is that deregulated pathways contribute in specific ways to Crohn’s disease and ulcerative colitis and will provide an entry point for novel approaches to therapy and diagnosis of each disease.

To date, CCFA’s Genetics Initiative Core Team has reviewed and prioritized IBD gene candidates, identified coding variants that confer risk, and initiated studies of genes and proteins to link genetics to function and mechanism. These are first steps toward providing diagnostic and treatment information carefully tailored to an individual patient’s genes and disease strains.

An important result of their analysis of unique IBD proteins is the implication of unsuspected pathways that act in specific cell types in IBD pathogenesis. This led to the discovery that a gene involved in the process of autophagy is associated with Crohn’s and that the proteins produced by this gene regulate epithelial cell secretion of antimicrobial peptides.

As the project wrapped up late in 2014, representatives from the Helmsley Charitable Trust and from the initiative attended a second annual face-to-face meeting in Boston. In all, the CCFA Genetics Initiative demonstrated the wide-ranging benefits of an integrated, cross-disciplinary team of researchers working together on a related set of scientific issues.

CCC Genetic Environmental Microbial (GEM) Project

The GEM (Genetic Environmental Microbial) Project is a research study recruiting individuals at high risk for Crohn’s disease, such as family members of Crohn’s patients, from around the world, in order to identify its causes or triggers. It is the world’s largest study investigating these triggers, and the only study currently underway designed to obtain subjects before they become ill and in sufficient numbers to provide the statistical power that may provide clues to what sets off Crohn’s. The focus for GEM in 2014 was bringing on new sites to enroll patients.

The GEM Project has already recruited more than 3,500 asymptomatic first-degree relatives through 36 recruitment sites in Canada, the US, and Israel. Centralized and regional infrastructures and processes (i.e., database, biorepository, processing labs, etc.) for the work are well-established. GEM has also developed 12 sites and a centralized sample processing center in the United Kingdom. In addition, discussions are underway with major academic institutions in France, Miami, FL, and Southern California. Each of these sites would serve as the hub for a regional recruitment effort for siblings of persons with Crohn’s disease. In 2015, Mount Sinai in New York will also begin contributing to this important project. GEM is a project of Crohn’s and Colitis Canada.

LOOKING AHEAD

Building on positive outcomes of the Trust’s earlier grants, the 2014 renewal grant will fund continuation and expansion of research into more than 20 genes potentially involved in the onset or continuation of inflammation associated with Crohn’s disease and ulcerative colitis.
CCFA Microbiome

Building on the work begun under the CCFA Gut Microbiome Initiative, the Trust awarded a $6.6 million renewal grant to CCFA in 2014 to continue microbiome research and expand the microbiome project consortia. This three-year project involving almost 30 scientists from nine institutions will identify how microbes in the human gut are activated in conjunction with genetics and diet and translate those findings toward developing new IBD treatments.

The majority of scientists in the project are working to identify pathways that can be manipulated to help people either maintain a healthy digestive system or alleviate inflammation in the gut. A smaller group will validate microbial targets and initial lead molecules suitable for pre-clinical drug studies. A third group will investigate how diet can help or hinder individual components of the gut microbiome, as well as potentially alter the structure and function of different microbes that are important to digestion.

Identifying which of these microbial products are key to IBD and establishing which can be effectively targeted should offer new ways to treat and ultimately cure Crohn’s disease and ulcerative colitis.

The key deliverables of the project are:

- Six validated targets of microbial products/pathways;
- Two biologically validated lead molecules (“hits”) for the targets, which will be presented for prospective biopharmaceutical development; and
- Dietary interventions validated for targeting microbial products and pathways in IBD.

A March 2014 issue of *Cell Host & Microbe* featured a key study from the initiative, which found, among other things, that antibiotic usage in children with Crohn’s disease could be counterproductive because these drugs cause a loss of beneficial microbes and an increase in pathological ones.

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<tr>
<td>Crohn’s and Colitis Foundation of America</td>
<td>Jonathan Braun, MD, PhD</td>
<td>Establishing Validated Targets and Lead Molecules for Microbiome-Based IBD Therapy</td>
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IBD Plexus

In February 2015, the Trustees approved a grant to the Crohn's and Colitis Foundation of America (CCFA) to implement IBD Partners, now called IBD Plexus. This initiative will accelerate high-impact IBD research by creating a platform to provide scientists and clinicians with integrated scientific, medical, and patient-reported data. Within three years, databases and biobanks will be combined or built with clinical information on more than 30,000 Crohn's and colitis patients, along with genetic and microbial profiles from 7,000 patients who will be followed over time.

Later this year, CCFA will publicly unveil the initiative in a coordinated campaign to introduce the new resource to patients and their families, practitioners, and researchers.

The initiative is designed to connect the historically separate and parallel processes of a) basic outcomes and translational research to understand and validate disease mechanisms; b) patient support, engagement, and education; and c) clinical care and quality improvement. The resulting platform will be used by scientists in academia and industry, as well as by doctors and nurses who treat IBD patients. When in full operation, it will be the largest IBD dataset of its kind in the world. The project has been supported with planning grants from the Helmsley Charitable Trust, as well as support from the Patient-Centered Outcomes Research Institute (PCORI), industry, and CCFA.

The implementation of the IBD Plexus initiative is well underway, with significant components in progress. In addition to entering into contracts with vendors for large data management and biobanking, a research team has been appointed and a staffing model has been developed. The research team consists of Jim Lewis of the University of Pennsylvania as Chief Plexus Scientist, Mike Kappelman from the University of North Carolina at Chapel Hill as Associate Chief Scientist for Patient Powered Research, and Rick Duerr at the University of Pittsburgh as Associate Chief Scientist for Translational Research. The staffing model being developed will ensure that the initiative maintains the needed research team members and that it includes experts in applied clinical informatics, translational bioinformatics, and drug discovery and biomarkers.

Finally, CCFA kicked off the first IBD Plexus Industry Affairs work group meeting. The goals of this work group, which includes representatives from numerous pharmaceutical and nutrition companies, are primarily to inform the design and operations of IBD Plexus, develop a guiding roadmap for future industry-specific initiatives, and champion the project within each member's organization.

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<th>Grantee</th>
<th>Principal Investigator</th>
<th>Project Title</th>
<th>Start Date/Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn's and Colitis Foundation of America</td>
<td>Caren A. Heller, MD, MBA</td>
<td>CCFA IBD Exchange Planning Grant</td>
<td>December 2012/12 months</td>
</tr>
<tr>
<td>Crohn's and Colitis Foundation of America</td>
<td>Caren A. Heller, MD, MBA</td>
<td>IBD Partners Transition and Integration Phase Grant</td>
<td>July 2014/Six months</td>
</tr>
<tr>
<td>Crohn's and Colitis Foundation of America</td>
<td>Caren A. Heller, MD, MBA</td>
<td>IBD Partners Implementation Phase</td>
<td>February 2015/36 months</td>
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</table>
Multidisciplinary Teams

Helmsley-supported funding—established at Harvard University, Mount Sinai Medical Center, the Tel Aviv Sourasky Medical Center, and the Weizmann Institute of Science—is allowing multidisciplinary teams of researchers to test new scientific questions about the cause and progression of IBD. In 2014, the Trust awarded $3.5 million to the Weizmann Institute of Science and $3.4 million to Tel Aviv Sourasky Medical Center.

The Weizmann Institute of Science in Israel is developing two complementary IBD model systems that investigate the contributions of patient-specific microbiome compositions and susceptibility genes in the development of IBD. One model system will utilize a unique technology developed at the Weizmann Institute known as the multi-compartment cell culture device. The other will be germ-free mice that are “humanized” with patient microbiota to mimic specific subsets of IBD. This project will serve as a proof of concept that a combination of in vivo and ex vivo model systems can depict the interplay of genetic and microbial factors in IBD. If the two models successfully work together, a broad range of projects to identify causes of, and potential new therapies for, IBD will be possible.

At Tel Aviv Sourasky Medical Center, researchers are building on a project studying pouchitis to uncover disease-causing pathways in IBD. Pouchitis, a unique inflammation that develops in about half of ulcerative colitis patients who undergo a partial resection of the bowel and the creation of a “pouch” to hold waste materials, presents a unique opportunity for research into how IBD develops. Because having the surgery is a necessary precondition for developing pouchitis, researchers have the ability to study the onset of the condition in human beings and human tissue and use the information to better understand the origins of IBD. More than 260 pouch patients—about 70 percent of all such patients in Israel—are being treated at Tel Aviv Sourasky, offering scientists there the potential to make a significant and major contribution to medicine’s understanding of IBD and the development of Crohn’s disease.

Collaborative Projects

In addition to these grants, the Helmsley Charitable Trust launched a Collaborative Pilot Research Grant Initiative at the IBD Network’s inaugural meeting in 2013 that led to the award of three, one-time $50,000 grants in early 2014. These awards went to projects at:

- Shaare Zedek Medical Center and Broad Institute of MIT and Harvard, where researchers are exploring whether manipulating the microbiome can be effective in inducing remission in acute severe pediatric ulcerative colitis using a combination of four antibiotic regimens and fecal microbiota transplantation.

- The University of Chicago and Washington University, where scientists are collaborating to develop an experimental system using organoids generated from epithelial cells that will improve the ability of IBD investigators to understand the underlying defects that trigger and/or exacerbate IBD.

- The University of North Carolina at Chapel Hill and Harvard Medical School, where investigators are seeking to avoid some of the potential side effects of steroid use by testing the use of hydrogel particles as a method of administering steroid therapies to patients with Crohn’s disease who develop inflammation of the upper gastrointestinal tract.
<table>
<thead>
<tr>
<th>Lead Institutions – Intramural Research</th>
<th>Principal Investigator</th>
<th>Project Title</th>
<th>Start Date/Term</th>
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<tr>
<td>Harvard College</td>
<td>Laurence Turka, MD</td>
<td>Pilot Grants Program in Crohn’s Disease</td>
<td>May 2012/42 months</td>
</tr>
<tr>
<td>Shaare Zedek Medical Center</td>
<td>Dan Turner, MD, PhD, Ramnik Xavier, MD, PhD</td>
<td>Manipulating the Microbiome in Acute Severe Pediatric Ulcerative Colitis by Antibiotics and Fecal Microbiota Transplantation: A Randomized Pilot Clinical Trial</td>
<td>January 2014/12 months</td>
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<tr>
<td>Tel Aviv Sourasky Medical Center</td>
<td>Iris Dotan, MD</td>
<td>Pouchitis: A Key to Understanding Crohn’s Disease</td>
<td>October 2014/36 months</td>
</tr>
<tr>
<td>University of Chicago</td>
<td>Bana Jabri, MD, PhD, Thaddeus Stappenbeck, MD, PhD</td>
<td>Understanding the Underlying Defects that Trigger or Exacerbate IBD</td>
<td>January 2014/12 months</td>
</tr>
<tr>
<td>University of North Carolina at Chapel Hill</td>
<td>Hans Herfarth, MD, PhD, Jeffrey M. Karp, PhD</td>
<td>Optimization of a Novel Inflammation Activated Drug Delivery System Using Hydrogel Microparticles</td>
<td>January 2014/12 months</td>
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<tr>
<td>Weizmann Institute of Science</td>
<td>Benjamin Geiger</td>
<td>Creating a Laboratory for the Study of Immunology and Inflammation</td>
<td>January 2013/12 months</td>
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<tr>
<td>Weizmann Institute of Science</td>
<td>Benjamin Geiger</td>
<td>Creating Experimental Models to Aid in IBD Therapeutics Discovery</td>
<td>October 2014/24 months</td>
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Research Training Awards

In 2014, the Trust awarded $4.3 million to 18 individual investigators as part of the ongoing Research Training Awards program at the Crohn’s and Colitis Foundation of America (CCFA). Six of these Helmsley-supported scientists have already gone on to leverage an additional $1 million in National Institutes of Health funding.

Fourteen of the awards are Research Fellowship Awards, “first phase” grants that support investigators new to the field of IBD research and require them to spend 90 percent of their time working on their research grants over three years. Ten awards are Career Development Awards, “second phase” grants awarded to investigators who have completed at least two years of IBD-related research, and that require them to spend 80 percent of their time working on their research grants over three years. Past recipients of these training awards have gone on to leverage nearly $257 million in funding from NIH.

LOOKING AHEAD

CCFA’s training awards are intended to encourage the development of individuals with research potential to help them prepare for a career of independent basic and/or clinical investigation in the area of IBD. Research Fellowship Awards support investigators new to the field of IBD research with at least two years of post-doctoral training. Career Development Awards fund investigators with five to 10 years of post-doctoral training. Both awards also provide mentoring to the awardees while allowing them to dedicate their time and energy to IBD research.

Recipients are required to spend 90% and 80% of their time, respectively, working on their research grants.

At a Glance

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<thead>
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<th>Lead Institutions – Research Training</th>
<th>Project Title</th>
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<tbody>
<tr>
<td>Crohn’s and Colitis Foundation of America</td>
<td>2015 CCFA Research Training Awards</td>
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</table>
**IBD and Crohn’s Disease**

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- Walter Panzirer

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