A Patient-Centered Approach

What matters most to people with IBD? The answer drives everything we do.

Patient and caregiver support is at the center of everything we do. As the leading non-profit dedicated to combatting Crohn's disease and ulcerative colitis, we address immediate patient and caregiver needs by running support groups and providing educational resources. And we're equally dedicated to advancing science that will improve the quality of life for people with inflammatory bowel disease (IBD) and bring us closer to cures.

Guided by Challenges in IBD Research—an in-depth process that identifies current unmet needs and knowledge gaps in the IBD research field—we are prioritizing research that keeps patients at the forefront of our investment decisions. Our overarching goal: to tackle the most pressing patient needs. This includes identifying a wider range of therapeutics, providing more effective remedies for chronic abdominal pain, and enhancing doctors' abilities to predict which drugs will best help each individual patient.

"Despite recent advances, there is a great need to find new therapies for those still suffering, as well as new biomarkers, diagnostics, and research findings to optimize the use of treatments currently available," says Caren Heller, MD, MBA, chief scientific officer of the Crohn's & Colitis Foundation. "By focusing on filling these scientific gaps, we're driving innovation in areas that will improve quality of life for everyone with IBD."

Patients Urgently Need:
A Wider Range of Treatments

We are investing in the development of novel therapeutics.

A class of drugs called biologics is currently among the most effective treatment for IBD, yet they don't work for a substantial number of patients. Additionally, many users experience side effects or dislike that these medications must be administered via injection or infusion. It's crucial to seek out new ways to treat Crohn's disease and ulcerative colitis, which means approaching treatment from many angles.

In recent years, the Foundation has supported many projects that aim to uncover, develop, or advance new treatments. Some highlights from projects we have funded include:

- **Researchers at Vedanta Biosciences** developed a live biotherapeutic product that floods the gut with enough beneficial bacteria to out-compete harmful strains (such as Klebsiella pneumoniae) that increase inflammation in Crohn's.
- **Scientists at Artizan Biosciences** created an antibody that neutralizes toxins produced by specific harmful strains of gut bacteria present in IBD patients.
- **Johns Hopkins scientists** determined that an enzyme called GCPII is elevated in people with IBD with active inflammation and discovered a compound that inhibits it. (See page 5 for more info.)
- **Cleveland Clinic researchers** determined that a gene called PAI-1 was over-expressed in people with IBD and interfered with wound healing; this led to the discovery of a compound that blocks it.

The last example is the direct result of a unique partnership between the Foundation and the Cleveland Clinic, with the support of a leading provider of drug discovery services. As with many academic labs, the researchers at the Cleveland Clinic needed highly specialized drug discovery resources to take an amazing discovery—a new therapeutic target—and turn that information into a drug. Thanks to the arrangement we envisioned, set up, and have been managing, the collaboration led to novel PAI-1 inhibitors, which are being further refined to develop a compound that can eventually be tested in clinical trials with humans.

This model partnership has inspired our brand new **Therapeutics Incubator**, a program that will bring drug discovery expertise to other academic groups that have similarly impressive findings. The Incubator will accelerate the development of new drugs that treat IBD, as well as medications that address complications such as abdominal pain or fibrosis.

> We're dedicated to helping the 60% of IBD patients who don't respond to biologics or find that these drugs eventually fail them.

"A lot of academic groups discover new potential targets for treating IBD, but they don't have the funding or infrastructure to do drug discovery," says Andrés Hurtado-Lorenzo, PhD, vice president of translational research at the Crohn's & Colitis Foundation. "In the vast majority of cases, such findings get published in a medical journal, and that's it. We hope the Therapeutics Incubator will take the most promising targets and help turn them into new treatments."

Patients Urgently Need:
To Know Which Treatments Will Work for Them

We are funding research that advances precision medicine.

Which patients will respond well to a specific drug? Right now, it's mostly a guessing game, which can result in months of delay as patients and their medical teams use trial and error, waiting sequentially for each new medication to work. But our dedication to precision medicine—in which treatments are tailored to individuals—is poised to change that. One crucial step is identifying biomarkers, which are biological characteristics that can be used to identify subsets of people who are most likely to respond to a particular therapy.

Soon, it may be possible to match a patient to the right biologic with a simple blood test. In a new Foundation-supported study, published in *Cell Host & Microbe*, researchers at the Broad Institute of MIT and Harvard created "multi-omic" patient profiles. These profiles—which include information about patients' genes, proteins, and metabolites (bacteria byproducts)—have the potential to accurately predict whether a patient will respond to specific classes of available biologics.

The scientists discovered that IBD patients who respond to certain biologic drugs have unique microbial signatures that could potentially be used to match patients to one of three commonly used types of biologic therapies. Says Hurtado-Lorenzo, "Being able to predict which patients will or won't respond to certain drugs and figuring out how to optimize care is crucial."

Patients Urgently Need:
To Determine Why Their Gut Isn't Healing

We are leading research that explores the connection between a common yeast and gut ulcers.

Thanks to Foundation-funded work, researchers at the Cleveland Clinic Foundation recently discovered that *Debaryomyces hansenii*, a yeast found in many cheeses and processed meats, is present in areas of inflamed small intestine of many Crohn's disease patients. What's more, they determined that introducing this type of fungus into animals with experimentally induced intestinal wounds stops healing these damaged areas. The scientists published their findings in *Science*.

"The significance of our study is that we found a potential infectious component for Crohn's disease," says Thad Stappenbeck, MD, PhD, who led the research. "Targeting this infection may be a viable approach to treat the disease or develop diet-based prevention strategies, which are greatly needed as current therapies fail in about 50% of our patients."

Patients Urgently Need:
Safe and Effective Abdominal Pain Relief

We are supporting new studies exploring pain mechanisms and potential remedies for chronic abdominal pain.

For many people with IBD, abdominal pain is a constant companion, and the currently available remedies aren't always helpful and can be harmful. Non-steroidal anti-inflammatory drugs (NSAIDs) can cause gut bleeding, and opioids—the strongest pain medications on the market—are addictive and often exacerbate gastrointestinal distress by leading to constipation.

To address patients' pressing needs for reliable relief, we recently launched the Chronic Abdominal Pain in IBD initiative. We are now funding three studies that may help answer some key questions about the underlying biology of this pain and patients most likely to suffer from it.

> Our goal: to get answers— and relief—for the 30% to 50% of IBD patients who struggle with chronic abdominal pain.

Can there be abdominal pain in the absence of intestinal inflammation?

It's easy to understand why flares can be painful. Yet, about half of patients who go into remission (no longer have evidence of intestinal inflammation) continue to struggle with chronic abdominal pain. To understand why, we need to know what's going on in the gut and in the brain, which is where pain sensations are processed.

Using a grant from the Foundation, Qasim Aziz, PhD, an expert in neurogastroenterology at Queen Mary University of London, will recruit 300 IBD patients for this study. He will follow them for several years to compare what's happening in the brain, intestines, and microbiome when pain resolves after a flare versus when it becomes chronic.

Is there a connection between enzymes and chronic abdominal pain?

Barbara Slusher, PhD, director of Johns Hopkins Drug Discovery Program, has been studying an enzyme called GCPII for more than 25 years. She has already determined that levels of this enzyme are dramatically higher in IBD patients with inflammation. Thanks to funding from our IBD Ventures program, she has also discovered a drug-like inhibitor of GCPII, which is currently in the pre-clinical development stage.

Now, using a grant from our new pain initiative, Slusher will attempt to determine whether GCPII stays elevated in people with chronic abdominal pain. Her hypothesis is that GCPII increases during an IBD flare and makes neurons more excitable, and that these neurons remain activated even after the inflammation has abated. She will be tapping into data from IBD Plexus, the Foundation's large data platform with a linked biobank, in addition to studying about 120 patients at Johns Hopkins.

Which bacteria are responsible for producing dangerous fats in the gut?

At McMaster University in Canada, Premysl Bercik, MD, PhD, has been studying lipids (fats) in the guts of people with IBD and in those with irritable bowel syndrome (IBS), a condition that's characterized by unexplained abdominal pain. He has already determined that a subset of patients with IBD or IBS (or both) have high levels of specific lipids in the gut.

These fats are generated by gut bacteria in response to certain foods. If Bercik and his colleagues can pinpoint which bacteria are responsible, people with high levels might be able to reduce or eliminate pain simply by making dietary changes.

"Getting more patients into remission is an important goal, but if half of the patients in remission still have debilitating pain, that's not a great outcome," says Gerard Honig, PhD, director of research innovation for the Crohn's & Colitis Foundation. "The research we're supporting will help improve our understanding of chronic abdominal pain and move us toward better solutions."

Foundation Award Recipient Advances Bacterial-Based Treatment

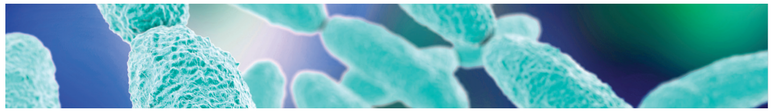
Weston Whitaker, PhD, then a postdoctoral fellow at Stanford University, was selected by the Foundation in 2015 as one of our Research Fellowship Award recipients. Within a year, he used our grant plus other funding to create a platform that enables scientists to program microbes to deliver specific therapeutic molecules to the gut. Shortly after, he left Stanford to form Novome Biotechnologies.

In late 2021, Novome entered into a multiyear, multimillion-dollar research collaboration and licensing agreement with biotech company Genentech. Genentech is now using Novome's proprietary platform to discover, engineer, and develop bacterial strains that can directly deliver treatment to the intestinal tract.

"We're proud to have supported this work," says Michael Osso, president and CEO of the Crohn's & Colitis Foundation. "We took a risk by funding a project at such an early stage, and it is paying off."

You Are Not Alone.

We provide access to online and in-person support groups, a peer-to-peer support program, a residential camp for children with IBD, and much more. Visit **crohnscolitisfoundation.org/community-support** to find out how we can help you.



Help Us Change Lives

The innovative projects described in this edition of *Under the Microscope* are just a few of the many ways we are working to accelerate the pace of research and uncover new treatments and cures for Crohn's disease and ulcerative colitis as quickly as possible. While our ultimate vision is a world without IBD, we're equally committed to helping patients who are struggling with the physical and emotional toll of living with IBD right now—but we can't do any of it without your help.

Help create a better tomorrow for those suffering from IBD by making a gift to the Crohn's & Colitis Foundation today. To make a contribution to the Crohn's & Colitis Foundation, please visit **crohnscolitisfoundation.org/microscope**.

Leave a Legacy of Giving

You can help to strengthen the vision and commitment of the Crohn's & Colitis Foundation by including the Foundation in your estate planning. As a member of the Founders Society, you will be listed in our Impact Report and receive inside information and updates on our mission advancement and research progress.

If you're interested in making a planned gift or have questions regarding planned giving and the Founders Society, please contact Susan Carriker at **scarriker@crohnscolitisfoundation.org**.

Or visit **crohnscolitisfoundation.org/freewill** to access a free tool that will help you make a will in 20 minutes so you can easily leave a legacy gift to the Foundation.

CROHN'S & COLITIS FOUNDATION

Under the Microscope

GROUNDBREAKING RESEARCH AND SUPPORT FOR PEOPLE WITH IBD SPRING 2022

Patient Needs Drive Foundation-Funded Research

Our people-first focus is guiding research and uncovering surprising treatment solutions.

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