Redefining Remission

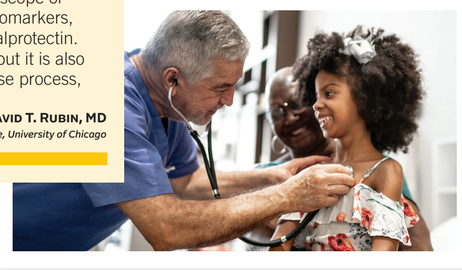
Why symptom relief isn't enough

People with inflammatory bowel disease (IBD) often assume that an absence of symptoms equals remission. While how someone feels and functions is critical, more than half of those in remission still have inflammation in their intestines, and this inflammation is associated with subsequent flares and disease progression, says David T. Rubin, MD, chair of the Crohn's & Colitis Foundation's National Scientific Advisory Committee (NSAC). "If we want to actually control the disease process, we need to pair symptom relief with measures of inflammation control."

That's exactly why getting more patients into "deep remission"—sustained relief of symptoms coupled with measurable proof that their intestinal wall is healthy and resolution of erosions and ulcers in the mucosal layer, the innermost layer of the intestines—is achieved. This is a key goal of the Foundation's new Strategic Plan, which is guiding our work through 2024. We're now approaching remission from all angles. Some highlights:

- **A Foundation-funded microbiome study** recently discovered that a specific strain of yeast is increased in the ulcers of Crohn's disease patients and may be a factor in why some of them don't heal.
- **Research from our Genetics Initiative** has revealed that a protein called PAI-1 is elevated in many IBD patients, and that it, too, may interfere with mucosal healing.
- **Our venture philanthropy program, IBD Ventures,** is currently funding the development of two novel drugs that promote tissue repair, as well as a biomarker-based blood test that aims to assess mucosal healing in a non-invasive manner.

"We have enough tools at our disposal now that we should not be managing people in crisis," says Dr. Rubin. "We should be getting them into deep remission, and the Foundation is leading the way."



"About 50–70% of people in symptomatic remission have persistent inflammation when you look with a scope or measure biomarkers, like fecal calprotectin. We want patients to feel well, but it is also necessary to control the disease process, so remission lasts."

—David T. Rubin, MD
Professor of Medicine, University of Chicago

Types of Remission

Remission is a term that many people with IBD think of as the absence of symptoms. However, remission can take different forms, depending on what is being observed:

- **Clinical remission:** Absence of symptoms. The patient feels well.
- **Biochemical remission:** Results of blood and stool tests are normal. Bloodwork shows that patient is not anemic and inflammatory biomarkers (such as C-reactive protein) are not elevated. Stool test shows that inflammatory biomarker calprotectin is not elevated.
- **Endoscopic remission:** A doctor performing an endoscopy (colonoscopy or sigmoidoscopy) does not see any signs of inflammation in the intestines.
- **Histologic remission:** No active inflammation is seen at the tissue level (when biopsies taken during a colonoscopy are examined under the microscope).
- **Deep remission:** Clinical remission (no symptoms) coupled with strong, objective evidence (currently in the form of biopsy results) that intestinal tissue is healthy.
- **Mucosal healing:** An absence of active disease seen during a colonoscopy (e.g., no ulcers, no bleeding). Aiming for mucosal healing lowers your risk of complications, such as strictures and fistulas.

Building a Stronger Defense

Understanding what weakens the intestinal wall is helping scientists figure out how to fortify it

A healthy gut wall has an important job: it provides a barrier that prevents damaging bacteria in the gut from reaching the intestinal tissue and the bloodstream, while still allowing nutrients to pass through. This barrier, also known as the mucosa, consists of a layer of cells called epithelial cells.

"The layer of epithelial cells needs to be joined together through structures called tight junctions. Imagine cementing a brick wall; if tight junctions are not properly assembled or are absent—which is often the case in IBD patients—bacteria can get through, resulting in inflammation and further mucosal damage," says Andrés Hurtado-Lorenzo, PhD, the Foundation's vice president of translational research.

While more research on many of these genes—most of which are not well understood—continues, Dr. Stappenbeck focuses on those that influence whether the gut mucosa can repair itself. His team's research determined that there is a genetic alteration that makes many IBD patients over-produce a protein called PAI-1 (plasminogen activator inhibitor). High levels of PAI-1 interfere with gut healing by inhibiting a clot-dissolving protein called TPA (tissue plasminogen activator).

"What can happen in IBD is that repair of gut ulcers does not progress properly because of excess PAI-1," says Dr. Stappenbeck. "If you can block PAI-1, then TPA can do its job of promoting the movement of cells over wounds to make it possible for normal tissue repair to continue."

"We're narrowing down the genes that are major players in IBD, which is paving the way for new treatments. We've already identified one target and found a compound that works; now, we're trying to perfect the molecule."

—Thad Stappenbeck, MD, PhD *Cleveland Clinic Foundation/Lerner Research Institute*

For the past decade, our Genetics Initiative has been dedicated to learning which genes play a role in determining who's vulnerable to IBD, including how increased or decreased production of these genes and their respective encoded proteins impacts the strength of the intestinal barrier. These efforts are already paying dividends from the discovery of hundreds of genes linked to IBD, says Thad Stappenbeck, MD, PhD, who is leading the Foundation's Genetics Initiative research at the Cleveland Clinic Foundation/Lerner Research Institute.

The most exciting part of this work is that Dr. Stappenbeck's team has already identified, with support of the Foundation's IBD Ventures program, a compound that blocks PAI-1. This compound is gut-restricted, which means it remains in the gut and does not circulate in the bloodstream, avoiding potential adverse events linked to inhibition of PAI-1 in the blood. The team is currently in the process of refining and testing it and hopes to move to clinical trials within a few years. (See "On the Horizon: Drugs that Target Mucosal Healing," page 5.)

On the Horizon: Drugs That Target Mucosal Healing

Most IBD drugs suppress inflammation, which gives the gut a chance to heal itself—but that doesn't always end up happening, and some patients never reach remission. That's why the Foundation is currently supporting research looking at new investigational therapies that take a different approach by directly promoting mucosal healing.

One potential oral treatment is a drug that blocks the PAI-1 protein (discussed in "Building a Stronger Defense," page 4). Scientists at the Cleveland Clinic Foundation—the same group that discovered the role of PAI-1—are now using IBD Ventures funding to focus on drug discovery.

This translational work—which aims to turn laboratory discoveries into treatments that can be directly applied to patients—is a new approach for the Foundation, says Dr. Stappenbeck, who's heading up the project. "We have already discovered a lead compound that works in preclinical models, which is awesome. Now we're embarking on a series of experiments to perfect the molecule and make it more potent."

Another drug supported by the Foundation's IBD Ventures program is TP-317, which is a potential first-in-class oral therapy that's being developed by Thetis Pharmaceuticals. The active ingredient in it is Resolvin E1, a molecule naturally produced by the body to induce healing after an injury. The company's understanding of Resolvin E1's unique reparative mechanism in the intestines is supported by previous academic projects sponsored by the Foundation. Thetis hopes to move to clinical trials by 2022.

Can We Assess Mucosal Healing Without Invasive Biopsies?

Right now, the only way to know if a patient has achieved mucosal healing is to conduct an invasive endoscopy and biopsy of intestinal tissue. In the not-too-distant future, however, there might be a better way. A company called Glycominds, LLC, has developed a blood test that uses five unique biomarkers of inflammation and disease activity along with a proprietary algorithm (the ulcerative colitis response index, or UCRI) to monitor mucosal healing in ulcerative colitis.

Glycominds has already determined that their blood test is as effective as endoscopy/biopsy in identifying ulcerative colitis patients who have healed while taking anti-TNF medication—at least in a retrospective Belgian cohort of ulcerative colitis patients. Thanks to funding from IBD Ventures, the company is conducting a prospective multi-center U.S.–based trial that aims to validate their earlier findings, says Avi Dukler, PhD, managing director and president of Glycominds.

The study is now enrolling ulcerative colitis patients with moderate-to-severe disease who are starting or switching any anti-TNF drugs. Participants will receive the novel blood test several times throughout the study, as well as endoscopies and stool tests to measure fecal calprotectin (which checks for inflammation in the stool). Study results are expected by the end of 2022.

"The high bar that we're aiming for is to get rid of invasive endoscopies," says Dr. Dukler. "But even if we're able to just reduce endoscopies, that would be a very good thing."

Promoting Partnership for Better Care

Through IBD Qorus™, the Foundation's nationwide quality-of-care initiative, we're studying whether adhering to a treat-to-target strategy in practice will translate into helping more patients reach and sustain deep remission.

Treat-to-target works by having patients identify goals (or targets) for their care and then work closely with their healthcare provider to continuously evaluate progress toward these targets. In clinical trials, treat-to-target appears to help patients achieve mucosal healing. Through the collective efforts of participating care centers in IBD Qorus, we will be able to study the impact of treat-to-target in real-world practice settings for the first time.

"What we're doing with IBD Qorus is prompting patients to write down their own treatment goals before a visit. Patients work with their clinician to develop a treatment plan to help reach their goals, such as staying in remission," says Alandra Weaver, MPH, associate vice president of IBD Qorus. "My hope is that we will learn how to most effectively help patients and their providers communicate better and be clear on their goals, ultimately helping them track progress toward remission."

Help Us Change Lives

The innovative projects described in this edition of *Under the Microscope* are just a few of our endeavors designed to accelerate the pace of research and uncover new treatments and cures for Crohn's disease and ulcerative colitis. 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 contribute to the Crohn's & Colitis Foundation, please visit crohnscolitisfoundation.org/microscope.

CROHN'S & COLITIS FOUNDATION

The Crohn's & Colitis Foundation is the leading nonprofit organization focused on both research and patient support for inflammatory bowel disease (IBD). The Foundation's mission is to cure Crohn's disease and ulcerative colitis, and to improve the quality of life for millions of Americans living with IBD. Our work is dramatically accelerating the research process through our database and investment initiatives. We also provide extensive educational resources for patients and their families, medical professionals, and the public. **Learn more at crohnscolitisfoundation.org**

To become a monthly donor, please visit www.crohnscolitisfoundation.org/monthly.

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Under the Microscope

GROUNDBREAKING RESEARCH AND SUPPORT FOR PEOPLE WITH IBD
FALL 2021

A Path to Gut Healing

How we're working to bring more patients closer to the goal of sustained remission