Inflammatory Bowel Diseases, 2021, **27**, S1–16
https://doi.org/10.1093/ibd/izab230
Supplement Article

Research-Based Product Innovation to Address Critical Unmet Needs of Patients with Inflammatory Bowel Diseases

Gerard Honig, PhD,* Paul B. Larkin, PhD,* Caren Heller, MD, MBA,* and Andrés Hurtado-Lorenzo, PhD*

From the *Crohn's & Colitis Foundation, New York, NY, USA

Address correspondence to: Andrés Hurtado-Lorenzo, PhD, Vice President of Translational Research, Research Department, Crohn's & Colitis Foundation, 733 3rd Ave St 510, New York, NY 10017, USA (ahurtadolorenzo@crohnscolitisfoundation.org).

Despite progress in recent decades, patients with inflammatory bowel diseases face many critical unmet needs, demonstrating the limitations of available treatment options. Addressing these unmet needs will require interventions targeting multiple aspects of inflammatory bowel disease pathology, including disease drivers that are not targeted by available therapies. The vast majority of late-stage investigational therapies also focus primarily on a narrow range of fundamental mechanisms. Thus, there is a pressing need to advance to clinical stage differentiated investigational therapies directly targeting a broader range of key mechanistic drivers of inflammatory bowel diseases. In addition, innovations are critically needed to enable treatments to be tailored to the specific underlying abnormal biological pathways of patients; interventions with improved safety profiles; biomarkers to develop prognostic, predictive, and monitoring tests; novel devices for nonpharmacological approaches such as minimally invasive monitoring; and digital health technologies. To address these needs, the Crohn's & Colitis Foundation launched IBD Ventures, a venture philanthropy–funding mechanism, and IBD Innovate®, an innovative, product-focused scientific conference. This special IBD Innovate® supplement is a collection of articles reflecting the diverse and exciting research and development that is currently ongoing in the inflammatory bowel disease field to deliver innovative and differentiated products addressing critical unmet needs of patients. Here, we highlight the pipeline of new product opportunities currently advancing at the preclinical and early clinical development stages. We categorize and describe novel and differentiated potential product opportunities based on their potential to address the following critical unmet patient needs: (1) biomarkers for prognosis of disease course and prediction/monitoring of treatment response; (2) restoration of eubiosis; (3) restoration of barrier function and mucosal healing; (4) more effective and safer anti-inflammatories; (5) neuromodulatory and behavioral therapies; (6) management of disease complications; and (7) targeted drug delivery.

Key Words: anti-inflammatory, barrier integrity, behavioral therapy, biomarkers, complications, eubiosis, gut-targeted drug delivery, IBD therapies, mucosal healing, neuroinflammation, neuromodulation, precision medicine, preclinical development

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBDs) characterized by periods of remission and relapse.[1,2] Long-term observational studies indicate that IBD exhibits a very heterogeneous disease course, with some patients having more aggressive disease, characterized by continuously active disease or recurrent relapses and the need for treatment escalation.[3] Over half of patients may experience disease progression despite treatment, leading in some cases to irreversible bowel damage and complications such as strictures or fistulas.[3,4] Such outcomes are very difficult to treat once they develop, often require surgery, commonly recur after surgery, and dramatically affect the quality of life of patients.[5–7] Response to treatment is also variable; approximately 30%–40% of patients are primary nonresponders and 30% are secondary nonresponders to biologics, the most effective therapies available,[8–10] indicating an unmet need for new therapies to treat nonresponsive patients. In addition, clinicians lack validated and minimally invasive biomarkers for prognostication of disease course, prediction of treatment response, and monitoring of mucosal healing.[11] Therefore, patients and clinicians are in urgent need of novel and differentiated products ranging from disease-modifying therapies, which can induce sustained remission and prevent disease progression, to biomarkers with different contexts of use.

As highlighted in the *Challenges in IBD* publications, an initiative of the Crohn's & Colitis Foundation (hereafter, the Foundation), several translational gaps still remain to advance research and development (R&D) on innovative, differentiated, and effective solutions for patients,[12–15] including the: (1) identification of new therapeutic targets linked to IBD pathology so that treatments can be tailored to the biology of patients, enabling precision medicine; (2) discovery of drugs with new mechanisms of action (MoAs) to treat patients not responsive to current therapies; (3) development of drugs with improved safety profiles; (4) discovery and qualification of novel biomarkers to develop prognostic, predictive, and

Received for publications: May 18, 2021. **Editorial Decision:** August 10, 2021

monitoring tests; (5) development of novel devices providing a nonpharmacological approach to treatment, minimally invasive monitoring of intestinal inflammation and healing, and the targeted delivery of drugs; and (6) development of digital health technologies to harness the power of big data and real-world evidence towards improved care and quality of life (Fig. 1). The understanding of IBD pathogenesis, endotypes, and potential therapeutic targets has expanded dramatically in recent decades, moving beyond canonical systemic immune pathways to encompass mucosal immunology, the microbiome, and the nervous system (Fig. 2). Despite this, many of these well-recognized biological drivers of IBD are not directly targeted by any available therapy, nor by the vast majority of late-stage clinical programs, which primarily focus on suppression of inflammation (Fig. 3; Supplementary Table 1).

To address these research gaps and unmet patient needs, the Foundation's research portfolio expanded in 2017 with the creation of IBD Ventures, a venture philanthropy program[16,17] through which the Foundation supports R&D for novel product development in industry and academia. The program provides financial resources for the development of novel therapies, diagnostics, devices, and digital health solutions and provides opportunities for companies to access IBD Plexus®, an exceptional biorepository of IBD patient samples linked to clinical and molecular data.[18] IBD Ventures also provides opportunities to develop networks, knowledge, and partnerships through IBD Innovate®, the premier IBD innovative, product-focused scientific conference. As an extension to the IBD Innovate® conferences, this special issue presents, in a collection of primary articles, the diverse and exciting R&D that is currently ongoing in the IBD field to deliver innovative and differentiated products addressing critical unmet needs of patients based on new research concepts, technologies, and paradigms.

Here, we highlight the pipeline of new product opportunities currently advancing at the preclinical and early clinical development stages, and compare it to the late-stage clinical trial pipeline, reviewed in detail elsewhere.[19–21] We categorize and describe novel and differentiated product opportunities based on their predicted utility to address the critical patient unmet needs outlined in *Challenges in IBD*: (1) prognosis of disease course and prediction/monitoring of treatment response; (2) restoration of eubiosis; (3) restoration of barrier function and mucosal healing; (4) more effective and safer anti-inflammatories; (5) development of neuromodulatory and behavioral therapies; (6) management of disease complications; and (7) targeted drug delivery.[12-15] Examples discussed within each category, as well as additional examples, are listed in Supplementary Table 2.

Biomarkers for Prognosis, Treatment Response Prediction, and Monitoring

Advancing precision medicine to optimize therapy is an exciting and likely achievable goal to deliver improved outcomes in the IBD field by enabling more effective use of the interventions that are already available and targeting future therapies to those patients most in need and likely to respond. The increasing number of approved therapies for IBD, while a welcome development, creates challenges for patients and clinicians in that the disease course and response to a given therapy are highly heterogeneous and difficult to predict, particularly early in the disease course when there is still an opportunity for disease-modifying interventions.[11,13] Early, aggressive therapy with biologics (top-down treatment paradigm) is likely to be optimal for patients at high risk of moderate to severe and progressive disease; however, without validated biomarkers a top-down treatment paradigm could expose lower-risk patients, who might be able to stay in remission for decades using first-line therapy, to unnecessary risk and costs. Thus, improved tools for early stratification of patients likely to benefit from biologics, Janus kinase (JAK) inhibitors, or future therapies are urgently needed.[11]

Prognosis and prediction of treatment response

Ambitious natural history studies, such as Risk Stratification in Pediatric Crohn's Disease (RISK), have provided proof of the principle that prognosis using molecular biomarkers

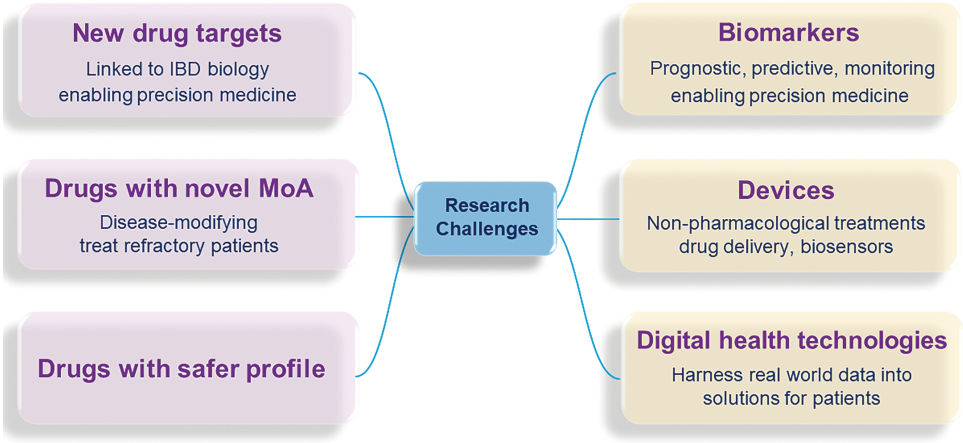

Figure 1. Translational research challenges and opportunities in IBD. Many gaps remain to translate research into solutions for patients. These include discovery of drug targets linked to IBD to tailor treatments reflecting the underlying pathways relevant to the patient's biology and to enable precision medicine. New drugs with differentiated MoAs and improved safety profiles are also required for disease modification and treatment of nonresponsive patients. Improving patients' outcomes also will depend on improved biomarkers for patient stratification and personalized treatments. Devices for nonpharmacological therapy, local drug delivery, and biosensors for continuous monitoring of inflammation are also needed. Digital health solutions based on analyses of real-world data can also contribute to improved health-care outcomes. Abbreviations: IBD, inflammatory bowel diseases; MoA, mechanism of action.

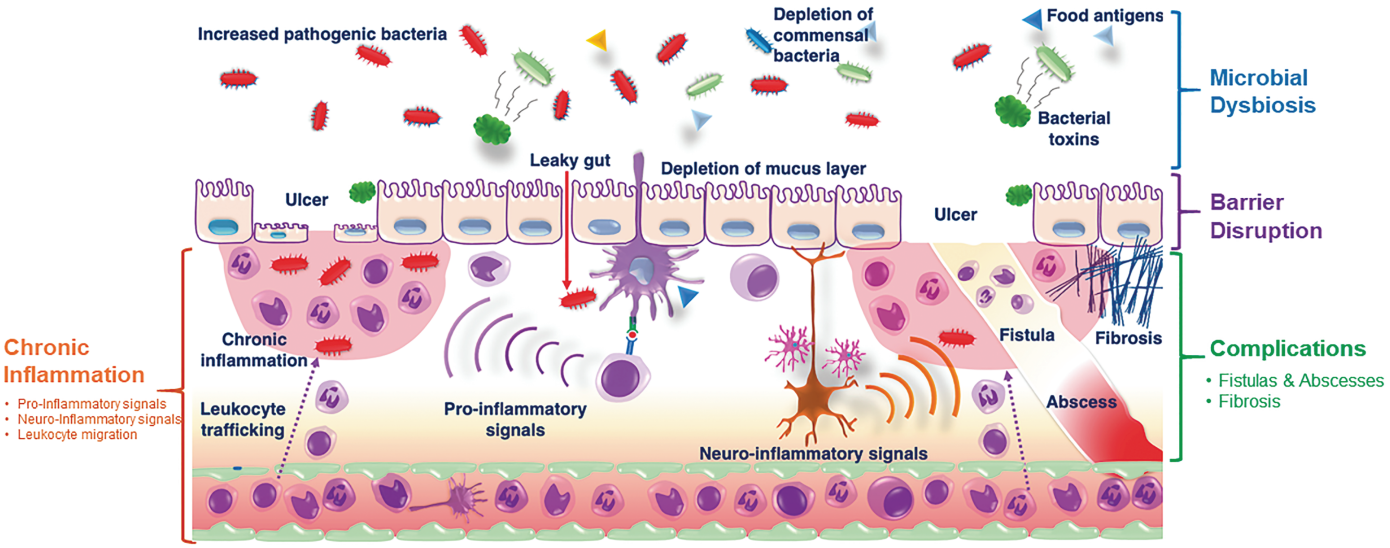

Figure 2. Multifactorial pathophysiology of IBD. Alterations of diverse biological mechanisms converge to drive the complex pathology of IBD. Depletion of commensal bacterial and overgrowth of pathobionts lead to deleterious microbial dysbiosis. Early loss of epithelial cell-cell interactions and depletion of the mucus layer lead to disruption of barrier integrity, resulting in enhanced epithelial permeability ('leaky gut') and paracellular translocation of luminal antigens (microbial, food-derived). Luminal antigens elicit an inflammatory response mediated by lymphocyte-derived proinflammatory signals and local neuroinflammatory signals, resulting in the continuous recruitment of leukocytes to sites of inflammation, chronic inflammation, and the concomitant erosion and ulceration of the mucosa. Penetration of ulcers into the submucosa results in complications like fistulas and abscesses. Sustained inflammation and activation of stromal cells also lead to fibrotic complications. Abbreviation: IBD, inflammatory bowel diseases.

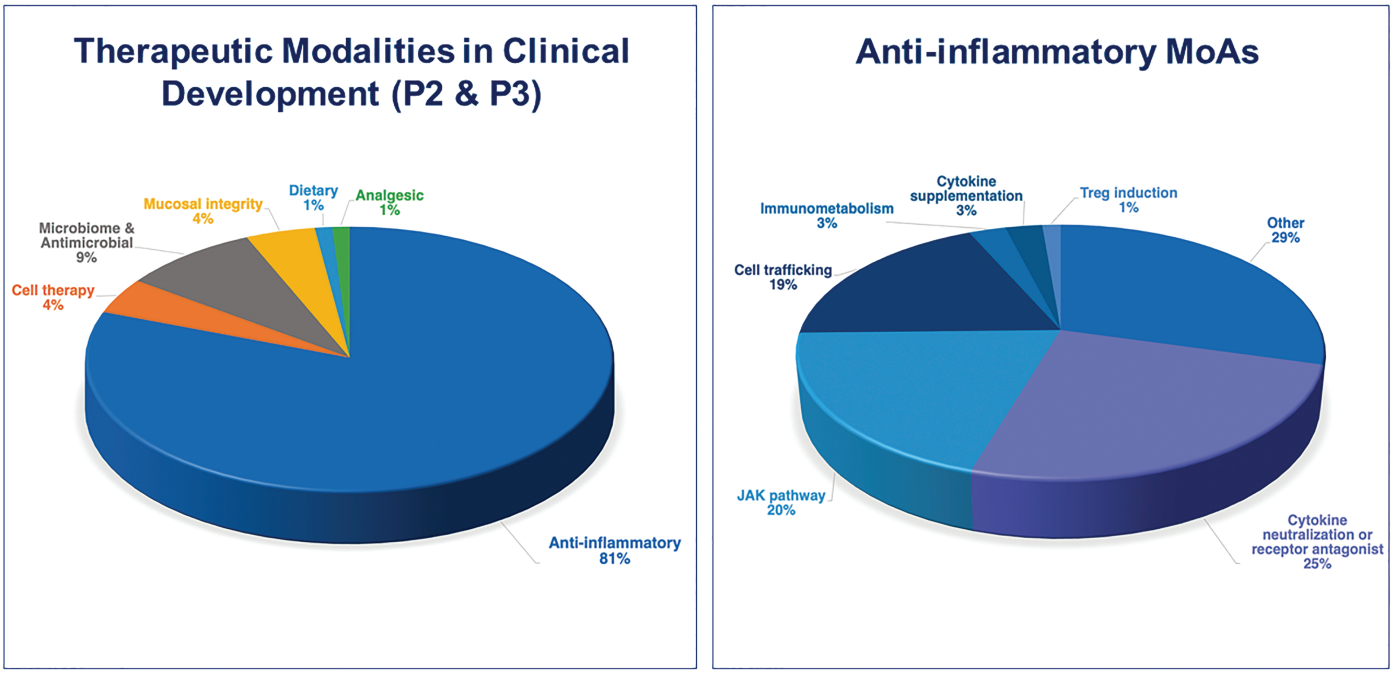

Figure 3. Mechanisms targeted in recent Phase 2 and Phase 3 clinical trials in IBD. All industry-sponsored Phase 2 and 3 trials initiated after April 24, 2016, and registered at ClinicalTrials.gov were included. The MoA was classified based on a literature search and sponsor's public statements. Each investigational drug was counted once per indication, even if multiple clinical trials were performed within that indication. Therapies approved by the FDA for the treatment of CD or UC were not included. Data, classifications, and trial listings are provided in Supplementary Table 1. Abbreviations: CD, Crohn's disease; FDA, Food and Drug Administration; IBD, inflammatory bowel diseases; JAK, Janus kinase; MoA, mechanism of action; UC, ulcerative colitis.

is feasible in IBD, even early in the disease course, and that early intervention with biologics in high-risk patients, which could be supported by an improved prognosis, has the potential to prevent fistulas and improve long-term outcomes.[11,22,23] Tests for prognosis of a severe disease course in IBD have incorporated serological tests for antibodies against microbial antigens, genetic testing, and multivariate risk assessments.[11,24,25] To date, these tests have not been widely adopted, potentially due to concerns regarding cost-effectiveness[26] and accuracy. A recent addition to the available testing regimen

is PredictSURE IBD, a blood-based test intended to support early prognosis of whether a patient will experience severe disease in both CD and UC, which received a Conformitè Europëenne (CE) mark in 2019. This test uses a quantitative polymerase chain reaction (qPCR) panel to detect a gene expression signature associated with CD8+ T cells, with the goal of identifying patients who will require treatment escalation over the subsequent 18 months in order to select them for earlier aggressive therapy.[27] With the support of the Foundation, the performance of this test is being assessed in a US validation study[28] and is being evaluated in parallel for the potential to improve outcomes through biomarker-informed treatment in a interventional trial in the United Kingdom.[29]

To address predictions of the risks of specific disease outcomes, such as complications, and the likelihood of responses to specific therapies, we applied machine-learning classifiers to develop novel prognostic and predictive models based on gene expression features from mucosal ileal biopsies collected at the time of diagnosis within the RISK study, resulting in compact candidate biomarker panels with improved performance for the identification of pediatric patients at high risk of developing specific complications, as well as patients likely to respond to anti–tumor necrosis factor alpha (anti-TNFα) therapy. In partnership with LifeArc, a venture philanthropy organization, we have initiated development of clinical qPCR tests based on these results.[30] Other researchers have pursued microbiome biomarkers,[31–33] as reported by Busquets and colleagues in this issue (submitted for publication).[34]

Noninvasive monitoring

Close monitoring of disease activity and treatment monitoring can improve outcomes, but is limited by current methods of assessment, which are invasive or imprecise.[11,14,35–38] Blood-based protein panel tests to monitor inflammation and healing have been developed for CD[39] and for UC.[40] The Ulcerative Colitis Response Index, a novel panel of blood neutrophil markers developed by Glycominds, accurately detected mucosal healing in UC patients treated with biologics.[40] With the support of IBD Ventures, the company is performing a clinical validation study in the United States. Novel medical devices offer additional opportunities for noninvasive monitoring, such as a wearable inflammation sensor[41] that is currently being evaluated for continuous monitoring of inflammation in UC patients and ingestible robotic capsules for imaging and sampling, as described in this issue by Papalia et al (in press)[42] and Yau et al (in press).[43]

Restoring Eubiosis

While the roles of the gut microbiome in nutrient absorption and pathogen resistance have been well known for many years, the role of an individual's microbiome composition in risks and progression of specific diseases, particularly IBD, has greatly advanced in recent years.[44] Inflammatory bowel diseases onset and progression are characterized by altered composition and function of the microbiome (dysbiosis; Fig. 2), leading to a pathogenic immune response, and microbes can trigger or ameliorate colitis in experimental models,[45,46] thus restoring a healthy host-microbiome relationship (eubiosis) is a promising therapeutic approach for the treatment of IBD.[46] Trials of fecal-derived microbiota transfer (FMT) to induce remission in UC provide a clinical proof of principle for this concept,[47,48] while also illustrating the limitations of FMT, including intensive protocols and variable efficacy, highlighting the need for more targeted, controlled, and patient-friendly interventions.[46]

A number of important patient needs may potentially be addressed though microbiome-targeted interventions, and there is the potential for a precision medicine approach through testing for the presence of specific microbiome factors to identify the patients likely to respond to interventions targeting those factors. As the mechanisms of action would be orthogonal and distinct from anti-inflammatories, combination therapy—for example, for the maintenance of deep remission following induction with an immunosuppressive agent—is promising.[45,46] Most microbiome-based interventions may be expected to have a relatively benign safety profile, as they are typically gut-restricted and avoid global immunosuppression.[46] These therapies may thus also be appropriate for early and/or mild-to-moderate IBD, for which few industry-sponsored trials have been performed (Fig. 3; Supplementary Table 1). Additional unmet needs that could be addressed include pouchitis[49] and prevention of recurrence following surgery.[46,50] Potential for the treatment of chronic abdominal pain has also been proposed.[51] However, despite intense interest in this field, relatively few microbiome-based interventions other than antibiotics have progressed to the clinic to date (Fig. 3; Supplementary Table 1).

Anti-inflammatory consortia

One approach is to shift the overall composition of a dysbiotic, proinflammatory microbiome towards a healthy state by transferring a consortium of bacteria isolated from healthy individuals, which then colonize the gastrointestinal (GI) tract, stably engraft, and shift the ecology of the recipient's microbiome (Fig. 4). The 2 most advanced programs in this regard are SER-287 (Seres Therapeutics) and VE-202 (Vedanta Biosciences). SER-287 is a spore fraction preparation derived from donor feces, consisting primarily of Firmicutes, a large group of bacteria that are depleted in UC and predicted, based on FMT studies, to exert beneficial effects on mucosal homeostasis via the production of bioactive metabolites.[52] SER-287 is intended to recapitulate therapeutic actions of FMT in a safer and more controlled product. In a Phase 1b study in mild-to-moderate UC, engraftment of donor bacteria, shifts in microbiome composition, and preliminary efficacy were observed, leading to a Phase 2b study that did not meet its efficacy enpoint.[53, 54] Another consortium approach is exemplified by VE-202, a defined consortium of cultured bacteria. This consortium was constructed based on an *in vivo* screen for strains capable of inducing polarization of regulatory T cells (Tregs) in the colon,[55, 56] potentially through shifts in the colonic short-chain fatty acid metabolism.[57]

Decolonization of pathobionts

Eradication of the pathogenic bacteria that overgrow in IBD is another approach. Pathobionts can be present but kept in check by the microbiome in healthy individuals, but can transition into a pathogenic state when the microbiome is disrupted, such as in IBD.[58] IBD patients are at marked increased risk of infections from bacteria that proliferate in a dysbiotic or inflamed gut environment; however, in addition to known gut pathogens that that proliferate in a dysbiotic gut environment, such as *Clostridioides difficile* (C. difficile),[59] certain Enterobacteriaceae species, such as adherent-invasive *Escherichia coli* (AIEC) and *Klebsiella pneumoniae*

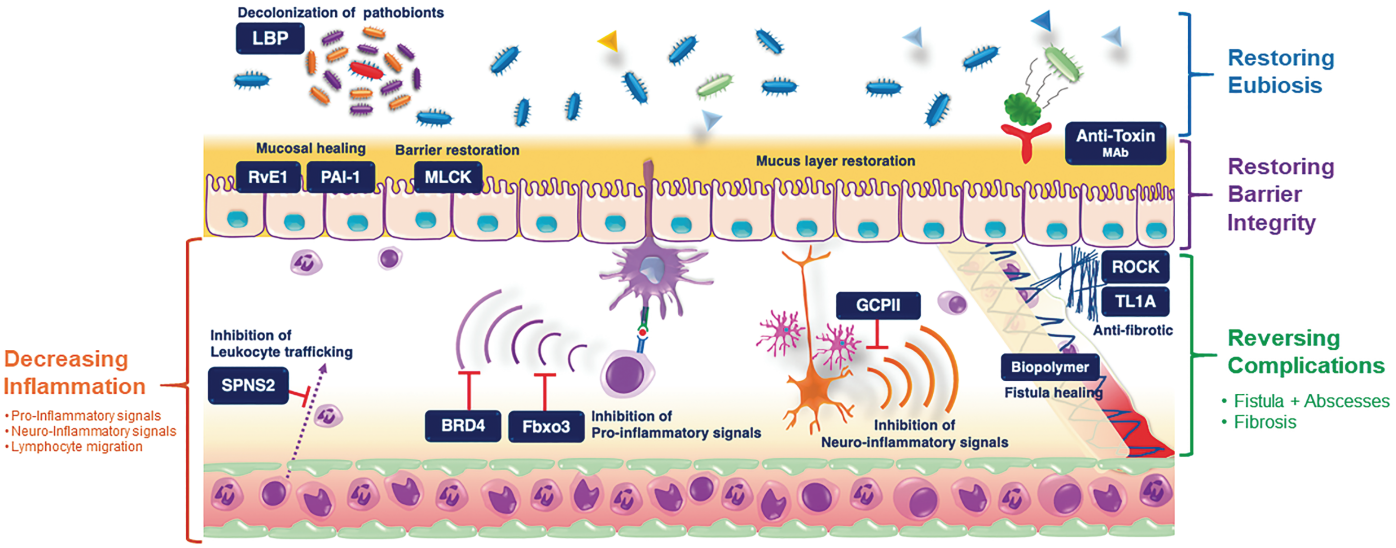

Figure 4. New potential therapeutic targets for IBD with differentiated MoAs. The diversity of IBD pathological mechanisms represents an opportunity for novel treatment approaches. Examples of therapeutic candidates in preclinical development include LBPs, which restore eubiosis by decolonizing pathobionts and repopulating commensal microbiota. Supplementation of RvE1 and inhibition of PAI-1 induce enterocyte proliferation and mucosal healing. An inhibitor of MLCK prevents its trafficking to TJs, avoiding barrier junction damage. A neutralizing MAb against IgA-coated bacteria-derived toxins can also prevent barrier damage. Inhibitors of SPNS2 abrogate leukocyte trafficking to sites of inflammation. BRD4 and Fbxo3 antagonists inhibit proinflammatory mediators, and an inhibitor of GCPII may abrogate local neuroinflammatory signals. Opportunities for treatment of fibrotic complications include neutralizing anti-TL1A monoclonal antibodies and inhibitors of ROCK. Programmable biopolymers are in development to enable tissue reconstruction and healing of the fistula tract. Abbreviations: BRD4, bromodomain-containing protein 4; GCPII, glutamate carboxypeptidase II; IBD, inflammatory bowel diseases; IgA, immunoglobin A; LBP, live biotherapeutic product; MAb, monoclonal antibody; MLCK, myosin light chain kinase; MoA, mechanism of action; PAI-1, plasminogen activator inhibitor–1; ROCK, rho-associated coiled-coil-containing protein kinase; RvE1, resolvin E1; TJ, tight junction.

(KP) species, are expanded in many IBD patients and can drive colitis in preclinical models due to exacerbation of proinflammatory dysbiosis and effects on mucosal integrity.[45,60] Decolonization of multiple pathobionts (Fig. 4) has been observed in FMT trials,[61] stimulating the development of therapeutic consortia. With the support of IBD Ventures, Vedanta Biosciences is using *in vitro* screening for direct inhibitory effects on specific pathobionts, *in vivo* studies in pathobiont-driven colitis models, and insights from FMT trials to develop a bacterial consortium (referred also as a live biotherapeutic product) for CD (Fig. 4).[62] Consortia of lytic bacteriophages are another approach that takes advantage of the narrow kill spectra of bacteriophages and their ability to overcome antibiotic resistance,[63] which limits traditional antibiotics. Intralytix is evaluating a preparation of phages against AIEC in a Phase 1/2a trial of AIEC-positive CD patients; the impact of the intervention on AIEC carriage will be assessed, illustrating the potential for microbiome biomarkers for both stratification and pharmacodynamics.[60] BiomX is advancing a phage consortium against KP, and also evaluating bacterial carriage as a patient stratification biomarker.[64,65] Finally, pharmacological inhibition of FimH, a cell-surface virulence factor used by AIEC to adhere to the gut wall, is a promising approach,[66–68] as exemplified by sibofimloc, a small-molecule FimH inhibitor that is being evaluated by Enterome in a Phase 2 trial for prevention of postoperative recurrence in CD.[69]

Bacterial toxin neutralization

Targeting other microbiome-derived factors beyond FimH, such as toxins or metabolites, is another exciting direction for IBD drug discovery. Bezlotoxumab, the first Food and Drug Administration (FDA)–approved antibody therapeutic targeting a microbial factor, neutralizes *C. difficile* toxins, providing a proof of principle for neutralization of a microbe-derived toxin in a GI disease.[70–72] One of the limiting factors in furthering this concept beyond well-known pathogenic factors has been the challenge of identifying rare but functionally important bacterial strains and virulence genes using metagenomic sequencing. Artizan Biosciences is leveraging immunoglobin A (IgA)–sequencing, a technology that enables targeted isolation and characterization of immunogenic bacteria,[73,74] in multiple IBD patient cohorts in order to identify pathogenic IgA-coated microbes in specific IBD subpopulations. With the support of IBD Ventures, Artizan is also developing therapeutics that neutralize toxins secreted by IgA-coated pathogenic bacteria (Fig. 4). Additional microbiome-targeted programs are described in Supplementary Table 2.

Restoration of Barrier Integrity and Mucosal Healing

Tightly bound epithelial cells (enterocytes) create a barrier that prevents the translocation of luminal microorganisms and food antigens into the submucosa.[75,76] Epithelial cells are bound together by protein structures known as tight junctions (TJs) and adherens junctions (AJs), which create an impermeable seal that limits the leakage of luminal content.[77,78] Goblet cells provide an additional defense by secreting mucin to create a mucus layer, which prevents the invasion of luminal bacterial into the inner tissue,[79] and Paneth cells, which secrete antibacterial peptides called defensins.[80]

Clinical evidence has shown that irrespective of the extent of disease activity, increased intestinal permeability, due

to mucosal barrier dysfunction, is a biological hallmark of IBD and a predictor of onset, relapse, and complications.[81–84] Barrier integrity defects leading to increased permeability and persistent mucosal erosion in IBD include impaired structures and functions of TJs and AJs, decreased goblet cells and mucin production, a reduced mucus layer, impaired production of defensins, increased epithelial apoptosis, and defective transition from inflammation to proliferation (Fig. 2).[85–87]

Despite the positive correlation between the use of biologics and improvement of mucosal healing, likely as an indirect effect of controlling inflammation,[88] mucosal damage can persist in some patients in apparent clinical remission.[89] These observations have led to the implementation of the therapeutic approach known as treat-to-target, in which objective measures such as mucosal healing and deep remission are desired goals.[11,90,91] In fact, achievement of mucosal healing has been shown to be linked to improved clinical outcomes compared to incomplete healing.[91,92] With these goals in mind, new therapeutic modalities that directly restore barrier function and induce mucosal healing are currently being pursued by several biotech companies and academic groups. Some examples of promising approaches, including lipid mediators, cell proliferation inducers, anti-apoptotics, and TJ and AJ restoration, are highlighted below.

Lipid mediators

Thetis Pharmaceuticals (TP), with the support of IBD Ventures, is developing TP-317 for the treatment of IBD. TP-317 delivers resolvin E1 (RvE1) to the GI tract. Resolvin E1 is a lipid derived from omega-3 fatty acids and is an endogenous molecule that restores mucosal homeostasis by resolving inflammation and promoting healing without overt immunosuppression.[93–95] Supplementation of RvE1 *in vivo* promotes intestinal mucosa wound repair by increasing cellular proliferation and migration (Fig. 4).[95] Another lipid target currently pursed as mediator of mucosal repair is prostaglandin E2, which regulates epithelial growth and repair.[96] Prostaglandin E2 is rapidly inactivated by nicotinamide adenine dinucleotide (NAD+)-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH). Inhibition of 15-PGDH restored colonic ulcers in experimental colitis.[97] Rodeo Therapeutics (recently acquired by Amgen) developed proprietary small-molecule 15-PGDH inhibitors for induction of tissue regeneration and mucosal repair and healing in IBD.

Cell proliferation inducers and/or anti-apoptotics

Glucagon-like peptide 2 (GLP2) stimulates crypt cell proliferation and decreases apoptosis, leading to enhanced barrier function and reduced inflammation.[98,99] The GLP2 analogue teduglutide is approved to treat short bowel syndrome but has shown limited efficacy for IBD, likely due to the short plasma half-life.[100] Novel, long-acting GLP2 receptor agonists generated at the California Institute for Biomedical Research demonstrate >10-fold increases in half-life and superior *in vivo* efficacy compared to teduglutide.[101] A new target for mucosal healing is the plasminogen activator inhibitor–1 (PAI-1), a serine protease inhibitor of fibrinolysis that regulates the coagulation cascade[102] and was found to be highly expressed in the mucosa of IBD patients with active disease and those who are nonresponsive to anti-TNFα therapy.[103] Inhibition of PAI-1 activity ameliorates colitis and crypt hyperplasia.[103] The proposed MoA involves the proliferation of wound-associated epithelial cells, which are the primary single layer of repair cells that migrate across the damaged mucosa.[103] In collaboration with the Foundation's research team, Thaddeus Stappenbeck and colleagues at the Cleveland Clinic are developing novel, potent, and gut-restricted PAI-1 inhibitors for the treatment of IBD (Fig. 4).

Restoration of AJs and TJ

Genetic variants of the C1orf106 gene decrease stability of its encoded protein and confer an increased risk of UC.[104,105] C1orf106 maintains the barrier function by promoting the stability of AJ via regulation of the ubiquitination and degradation of cytohesin-1,[106] a regulator of protein trafficking.[107,108] In the absence of C1orf106, cytohesin-1 levels are elevated, leading to increased recycling of the junctional proteins E-cadherins and decreased stability of AJ. High-throughput screening is ongoing for small molecules that increase the stability of C1orf106 to restore the integrity of the epithelial barrier in IBD.[106] Myosin light chain kinase (MLCK), which is upregulated in CD, is another potential target; it is a central regulator of intestinal epithelial TJs and has been proposed as a mediator of TNFα-induced barrier dysfunction.[109] A novel small molecule (Divertin) has been rationally designed to prevent the translocation of MLCK to TJs and restore barrier function, while preserving the kinase activity that is necessary for other biological processes (Fig. 4).[110] Additional targets are listed in Supplementary Table 2, including proteinase-activated receptor-1, as reported in this issue (Motta et al, in press).[111]

Efforts focused on direct restoration of barrier function and wound healing are resulting in exciting advances and warrant consideration for further development into clinical-stage products. Currently, the pipeline of clinical trials evaluating the efficacy of drugs that target MoAs related to the direct restoration of barrier integrity or wound healing, as opposed to indirect mucosal healing as a result of immunoregulatory effects, remains scarce. Among Phase 2 and Phase 3 clinical trials initiated in the past 5 years, only 4 trials directly target barrier integrity restoration, compared to 75 anti-inflammatory trials (Fig. 3; Supplementary Table 1). While a focus on barrier integrity has merit for drug development, clinical development challenges will need to be addressed, including whether barrier permeability measures should be used as an endpoint in addition to endoscopic healing[112] and whether barrier integrity therapies would be effective as stand-alone treatments or should be used in combination with other therapies.[113–115] In conclusion, while experimental and clinical evidence suggest that barrier dysfunction may be a primary underlying defect leading to paracellular translocation of luminal antigens and elicitation of chronic inflammation in IBD (Fig. 2), will therapies with this MoA represent a *bona fide* disease-modifying treatment to induce deep remission and avoid disease progression?

Improved Anti-Inflammatories

Though currently marketed anti-inflammatories have enabled enormous advances in the management of IBD, significant opportunities for improvement remain. Here, we discuss next-generation anti-inflammatories that could address unmet needs, including a lack/loss of response to available therapies and a lack of effective, disease-modifying therapies with

an improved safety profile. Drug delivery innovations, which could also provide improved anti-inflammatories based on established MoAs, are discussed in Targeted Drug Delivery section. Small-molecule anti-inflammatory drug discovery for IBD is reviewed in further detail within this issue by Zhou and colleagues (in press).[116]

Cytokine neutralization and supplementation

Anti-cytokine monoclonal antibodies are used for a wide variety of inflammatory diseases, including IBD. Products focused on the same targets as approved therapies, but with potential advantages, such as lower immunogenicity, could add value, but improved efficacy or safety compared to approved products may be challenging to demonstrate.[117] Several groups are targeting additional proinflammatory cytokines; these targets are supported by the published literature, often including data from non-IBD diseases and disease models, and have been reviewed in detail elsewhere.[118–121] Interleukin (IL) 17 neutralization has shown strong efficacy in other inflammatory indications, but worsened outcomes in an IBD trial.[122] The mechanism of this remains unclear, but is an important reminder that suppression of cytokines can have unexpected consequences, and that despite the commonalities across multiple inflammatory diseases, they are distinct entities.[123,124] Loss of response to anti-TNFα therapy may be driven by Oncostatin M,[125,126] the target of a neutralizing antibody program.[127,128] Supplementation with immunoregulatory cytokines is also conceptually appealing for IBD, though efforts in this arena have not yet been successful, potentially due to pleiotropic effects.[129] Significant development efforts have focused on IL-10,[130–132] transforming growth factor β,[133,134] and IL-22, which may restore epithelial integrity.[135] The larger point is that inflammation may evolve over the course of disease and that agents that neutralize a single cytokine may lose effectiveness over time, potentially requiring monitoring of disease activity and combination therapy to overcome treatment resistance.

JAK inhibition

Nonresponse to biologics provides theoretical justification for the development of anti-inflammatories that can inhibit multiple cytokine signaling pathways at once. The only approved therapy that fits this description for IBD, other than steroids that are not suitable for chronic use, is the oral JAK inhibitor tofacitinib. Given safety concerns, which may limit doses[136] in achieving optimal efficacy,[137,138] a variety of next-generation JAK inhibitors are in development. These seek to improve on tofacitinib in a variety of ways, including increased selectivity among JAK family members and gut-restricted delivery.[116] Similar to JAK inhibitors, inhibitors of the E3 ubiquitin ligase Fbxo3, such as those being developed by Koutif Therapeutics with IBD Ventures support, interfere with another signaling pathway involved in cytokine signaling by impacting degradation of TNF receptor–associated factor proteins (Fig. 4).[139,140] Epigenetic targets also have the potential to impact a variety of downstream mediators. For example, various inhibitors of bromodomain and extraterminal motif (BET) proteins have been developed and show potential for controlling inflammation.[141] However, toxicity and limited efficacy have limited enthusiasm to date, leading researchers at the University of Texas to develop, with support from IBD Ventures, next-generation inhibitors of BET family member bromodomain-containing protein 4 with improved selectivity and potency (Fig. 4),[142,143] as reviewed in this issue (in press).[116] Signal integration and propagation via the inflammasome provides another opportunity to impact multiple inflammatory mediators.[144, 145]

Leukocyte-trafficking inhibitors

As an alternative to targeting specific inflammatory-signaling molecules or inflammatory-signaling cascades, there are also a variety of approaches focused on the leukocyte-trafficking aspect of inflammation.[146] The role of integrins in the biology of leukocyte trafficking is well described, providing several potential targets in addition to the approved therapy in this category, vedolizumab (which binds the α4β7 integrin). While integrins are well-validated therapeutic targets,[147,148] several integrin programs have been terminated recently, including etrolizumab, due to limited efficacy,[149] and ontamalimab, which was advanced to Phase 3[150–153] but was terminated for commercial reasons.[154] Assets from the Phase 3 trials of ontamalimab are being made available to the research community via IBD Plexus.[155] Efforts to develop improved integrin-targeting therapies could pursue different elements of the signaling pathway or seek to improve on existing products: for example, by utilizing a small molecule to enable oral dosing.[116,156]

The other prominent pathway where approved drugs target leukocyte trafficking is the sphingosine 1-phosphate (S1P) signaling pathway, with several drugs approved for other indications and ozanimod, recently FDA-approved for the treatment of moderate-to-severe UC.[116] Next-generation strategies targeting S1P signaling include efforts by researchers at New York University, supported via IBD Ventures, to target sphingolipid transporter 2 (SPNS2), an S1P transporter that contributes to S1P gradients in lymph but not in blood, to avoid cardiovascular side effects (Fig. 4).[157,158] In addition to leukocyte trafficking agents that target pathways validated by the use of approved drugs, there are a variety of other targets that may be useful targets for modulating cell trafficking. Chemokines are a clear example, including chemokine receptor type 9 and CXC4 chemokine receptor type 4, as reviewed in this issue.[116]

Treg modulation

Tregs are recognized as playing critical roles in maintaining immune homeostasis, and their dysfunction is thought to contribute to IBD; thus, restoration of Treg activity or function has received significant attention.[159,160] Autologous transplantation of expanded Tregs is 1 approach.[161–163] Interleukin 2 can stimulate Tregs through a high-affinity receptor isoform, although engagement of a lower-affinity isoform at higher concentrations is proinflammatory.[164–166] In order to improve the therapeutic window, multiple groups have developed IL-2 mimetics with increased Treg specificity,[164,167–169] including PT101, which was reported to upregulate Tregs in a recent study of healthy subjects.[170] The induction of antigen-specific immune tolerance has the potential for a more targeted intervention addressing disease etiology and avoiding broader immunosuppression; contemporary approaches do not necessarily rely on identification of causative autoantigens.[171–174] Preclinical approaches

include antigen-coated nanoparticles[174,175] and antigen-directed metabolic ablation.[176]

Neuromodulatory and Behavioral Therapies

Altered neuronal signaling has long been recognized as a driver of multiple GI pathologies, notably disorders of gut-brain interaction such as irritable bowel syndrome (IBS).[177] Although the underlying biological mechanisms are yet to be fully elucidated, multiple lines of evidence indicate that targeting such processes may be an effective and mechanistically differentiated therapeutic strategy in IBD.[178] This strategy can comprise pharmacological interventions, but also "bioelectronic medicine,"[179] in which novel medical devices are used to stimulate or inhibit specific neurons or neuronal processes. Modalities such as cognitive behavioral therapy (CBT) also have significant potential to empower patients to control pathological brain processes, such as central sensitization, that increase risks of chronic pain and other negative outcomes in IBD.[51] Digital therapeutics integrated with telemedicine approaches have the potential to broaden patient access to behavioral therapy.

Modulation of neuroinflammatory signals in the gut

Local neuroglial circuits are highly sensitive to inflammatory factors and can be triggered to sustain inflammation or drive chronic visceral pain and dysmotility even after the inflammation subsides. Glutamate carboxypeptidase II (GCPII) is a regulator of glutamatergic excitatory neurotransmission that has been extensively studied as a drug target for neuroinflammatory conditions.[180] Both GCPII expression and activity were shown to be increased in inflamed tissues in IBD, and inhibition ameliorated colitis in multiple models.[181–185] With IBD Ventures support, researchers at Johns Hopkins Drug Discovery developed novel, gut-restricted GCPII inhibitors as investigational IBD therapeutics. While the specific cellular mechanism of therapeutic action is still under investigation and may involve both epithelial and neuroglial processes, the potential to directly inhibit aberrant neuronal excitation in IBD is a highly differentiated and exciting approach (Fig 4).

Modulation of autonomic function

The autonomic nervous system regulates local and systemic immune responses. Modulation of specific autonomic pathways, such as the vagus nerve, has received significant attention due to the potential to modulate inflammation and other GI pathologies, either through systemic action or through targeting of specific anatomical sites. Stimulation of the cervical vagus nerve has been most extensively studied in this regard. Vagal nerve stimulation (VNS) elicits the cholinergic anti-inflammatory reflex, an endogenous splenic circuit that modulates the immune response. SetPoint Medical developed a cervical vagal stimulator implant for chronic use that has been evaluated for safety and efficacy in treatment-refractory rheumatoid arthritis patients,[186] as well as in biologic-refractory CD patients, where VNS appeared to reduce disease activity and inflammatory markers.[187] While this is consistent with studies in other CD patient populations,[188–192] larger, sham-controlled trials will be needed to draw firm conclusions about the efficacy of VNS for IBD. Cervical VNS, and surgical implants in general, present safety issues and are relatively invasive in the context of other available therapeutic approaches in IBD. Modalities to enable more targeted and less invasive neuromodulation, including ultrasound, could expand the appeal of this approach, as proposed by GE Research and other groups.[188,193,194]

Behavioral therapy

It is well recognized that psychosocial factors are drivers of outcomes in IBD,[195] notably chronic pain,[51] and there is a consensus that provision of comprehensive and holistic care, including behavioral therapy, has the potential to improve outcomes in IBD.[12,196] Digital health products have the potential to increase access to behavioral therapy: for example, by enabling telehealth for patients in areas underserved by physical behavioral healthcare facilities. In particular, CBT has the potential to improve quality of life for IBD patients,[197] and clinically validated digital health products may serve to deliver that intervention. For example, Mahana Therapeutics recently received FDA authorization[198] to market a prescription-only digital therapeutic (PDT) intended to reduce the severity of IBS symptoms by delivering a telehealth CBT protocol shown to be effective in IBS.[199] Pear Therapeutics is also developing a PDT for IBS based on another published telehealth intervention.[200] Either or both of these PDTs could potentially be adapted for use in IBD.

Management of Complications

Stricturing complications

Biologics may have only a limited impact on strictures,[23] as illustrated by the fact that rates of surgery for CD have not dramatically decreased since their introduction.[5] To our knowledge, no medical anti-fibrotic therapy has yet been evaluated in a randomized trial in CD. Multiple challenges have limited progress in studying prevention or treatment of fibrosis, including limitations in mechanistic understanding,[15] preclinical models,[15] risk stratification,[11,13] and clinical trial endpoints.[11,13,201] Despite these challenges, this field is progressing rapidly.

Tumor necrosis factor-like cytokine 1A (TL1A) is a cytokine that regulates the immune, epithelial fibroblast function; genetic variants increase TL1A expression[202] and the risk of CD strictures.[202–205] Researchers from Cedars-Sinai demonstrated that TL1A expression drives stricture formation[206,207] and that a neutralizing antibody ameliorated fibrosis in preclinical models.[208,209] Two TL1A-neutralizing antibodies are in clinical development for IBD, 1 by Pfizer[210] and another by Prometheus Biosciences,[211] which is also developing a companion diagnostic for this program: a welcome innovation, as biomarkers will be particularly important for clinical trials in this area.[11] While TL1A neutralization in patients overexpressing this protein may have broader anti-inflammatory potential, the potential for prevention of strictures in patients at high risk is particularly exciting (Fig. 4). Bromodomain-containing protein 4 (Improved Anti-Inflammatories section) is also being studied given its role in pathogenic tissue remodeling in other tissues.[141]

Stimulation of myofibroblasts by mechanical stress and by secreted signals is considered to be an another important driver of stricture pathogenesis; thus, interrupting that process is a potential therapeutic mechanism.[212] Rho-associated coiled-coil-containing protein kinases (ROCKs) are a key mediator of these processes, but systemic inhibition of these kinases is toxic, leading several groups, including RedX Pharma,

to develop and evaluate gut-restricted ROCK inhibitors for the prevention and treatment of strictures (Fig. 4), with promising preclinical results reported.[212–214]

Penetrating Complications

Once fistulas are established, aggressive anti-inflammatory therapy is important but typically surgery is also necessary. Topical application of mesenchymal-derived stem-like cells (MSCs) has been extensively studied in specialized clinical settings to support perianal fistula healing,[215] likely due to multimodal immunomodulation as opposed to regenerative engraftment. Takeda's darvadstrocel, an MSC-based cell therapy for fistulizing CD, was recently approved in Europe, with Phase 3 trials in the United States ongoing.[216,217] Multiple companies, such as Ossium and Mesoblast, are developing additional cell therapies with potential for improved scalability, a reduced cost, and more precise biological activity[218,219] for fistulizing CD and other IBD indications.[220,221]

One key challenge in perianal fistulas is to enable rapid, durable closure of the fistula tract while supporting tissue ingrowth and healing and avoiding damage to the anal sphincter, as available sutures, plugs, and sealants are inadequate for this purpose.[14] The development of surgical glues that are nontoxic and bind durably to wet tissue has been a challenge, particularly for GI lesions. Tissium, a Paris-based startup, developed a versatile set of light-activated biopolymer and catheter technologies,[222–225] achieving a CE mark and Investigational Device Exemption for a sealant delivery device to repair heart defects in 2020. With support of IBD Ventures, Tissium is applying this platform to develop improved programmable biopolymer-based sealants that promote fistula healing (Fig. 4).

Targeted Drug Delivery

Many currently approved drugs or therapeutic candidates in development are efficacious in the GI tract but have side effects due to systemic exposure. Gut-targeting approaches could result in fewer untoward effects, due to limited systemic exposure, and allow an improved patient experience, perhaps by decreasing dose frequency, thus improving patient adherence. A variety of approaches to gut targeting have been developed and implemented over the years towards this goal.[226]

Targeted formulations

Oral formulations of an active pharmacological ingredient (API) coated in a pH-sensitive protective layer that limits degradation in the harsh conditions of the stomach have been employed for many years and continue to evolve,[227] including through incorporation of coatings that are specifically degraded by colonic bacteria,[228] with the goals of increasing lower GI exposure and minimizing systemic exposure.[229] Other novel formulation techniques include formulating API into emulsified microspheres or specialized nanoparticles that improve gut targeting.[230,231] Hydrogels are another class of formulation with the potential for physiologically triggered API delivery, such as an enema formulation under development by Intact Pharma that is liquid at room temperature but converts into a gel when warmed to body temperature, resulting in improved drug exposure and less leakage than a standard liquid enema.[232] Similarly, a hydrogel being developed by Alivio Therapeutics binds preferentially to sites of inflammation, releases the drug in the presence of inflammation-associated enzymes, and can be used to specifically target drug exposure to sites of inflammation, thus achieving sufficient local target engagement with lower systemic exposure.[233] While the capabilities of these formulation approaches vary, they generally offer some degree of "off-the-shelf" readiness for improving the gut targeting of small-molecule drugs (and, less commonly, large-molecule drugs).

Targeted molecules

Another approach to gut targeting is to chemically couple the API to a carrier molecule that will serve to direct the chimeric molecule to the location of choice. Naturally occurring molecular motifs that enable specialized trafficking are an interesting choice here. Applied Molecular Transport coupled a large molecule to a fragment of a bacterial protein, resulting in delivery of a large molecule across the gut epithelial cell barrier to the lamina propria.[132] Designer carrier molecules are also an option, such as bispecific antibodies or antibody-drug conjugates, which could in theory target epitopes associated with inflammation or specific tissues, such as cluster of differentiation 11a or mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1).[234,235] The approaches described above generally couple the carrier molecule to the API in such a way that the activity of the API is not altered by the carrier, but an alternative is to employ a prodrug approach. For example, delivery of a small molecule coupled to a carrier could allow enzymes found in the gut microbiome to bioactivate and release the API, as occurs when bacteria cleave sulfasalazine or olsalazine to release 5-aminosalicylic acid (5-ASA).[236] Additional options are to administer genetically engineered microbes that secrete API[237] or small molecules that undergo rapid clearance from the systemic, but not intestinal, compartment.[214]

Drug delivery devices

In addition to these technologies, there are a variety of devices in development that aim to deliver drugs specifically to the gut. Ingestible capsules have an intuitive appeal, but it has been technically challenging to automate accurate, targeted release and to deliver large enough doses while keeping capsules small enough for patient acceptance. Several techniques have been employed to localize capsule release sites, including changes in pH, calculations of transit time, and optical detection of anatomical landmarks, as reviewed in this issue and elsewhere.[43,238,239] The company Progenity and collaborators demonstrated that administration of tofacitinib directly into the cecum, bypassing upper GI absorption, can improve the therapeutic window in an animal model, and they have developed a robotic capsule that can recognize optical features of the cecum to trigger drug release; with the support of IBD Ventures, a first-in-human trial of this novel drug delivery device in UC will be performed.[240]

The best solution for localizing a given API to the gut depends on the characteristics of the API and the site of therapeutic action. What degree of gut restriction is necessary? Where in the gut tissue does the API need to be delivered (gut lumen, ulcer bed, lamina propria, etc.)? How does the chemistry of the API interact with various linker or localization moieties? What amount of API needs to be delivered over time? Also, it is important to note that most studies of gut targeting are conducted in healthy tissue, which may differ from inflamed tissue in ways that impact the degree of gut restriction observed. The proliferation of options for approaching gut restriction is a very promising development with the potential to add value broadly across the field of IBD drug development.

Conclusions

Blockbuster anti-inflammatory medications used across multiple chronic inflammatory indications have greatly improved patient care in IBD over the past decades. These medications arose out of basic research on the function of the immune system, and their use has contributed to a greater understanding of chronic inflammation and the risks and benefits of various approaches to treating it. Continued progress in the understanding of inflammation and immunity will likely continue to produce opportunities for medications with applicability across multiple chronic inflammatory conditions.

However, it has become apparent that anti-inflammatory medications may have reached a "ceiling" effect that leaves more than half of IBD patients in need of alternative or combination therapies to address their unmet needs. Therefore, there is a need to develop therapeutics that target disease-specific pathological mechanisms. In this review, we highlight the wealth of innovative investigational products addressing novel, disease-specific mechanisms relevant to CD and UC, as well as an array of novel treatment modalities, diagnostic tools, and devices with the potential to enable more precise treatment approaches. It is critical that researchers in academia, biotech, and pharma companies recognize the importance of these new approaches to advance novel, impactful products towards the clinic.

Taken together, these innovations, through precision medicine and combination therapy approaches, have significant potential to once again revolutionize patient care and greatly improve the lives of patients whose needs are not met by current treatment options.

Supplementary data

Supplementary data are available at *Inflammatory Bowel Diseases* online.

Acknowledgements

We thank the editors of this supplement issue, Sonia Friedman, Ben Blass, and Fabio Cominelli, for their editorial effort and for the invitation to submit this review. We thank Orna Ehrlich for her participation in planning the issue. The authors would also like to thank the members of the IBD Ventures review committee, who guided the selection of the Crohn's & Colitis Foundation portfolio projects described; the members of the IBD Ventures Council, who generously support the IBD Ventures program; authors who contributed manuscripts for this supplement issue; and the presenters who have participated in the IBD Innovate conference series, which has been generously supported by Celgene, Bristol-Myers Squibb, Takeda, PathAI, and Lilly.

Funding

None declared.

Supplement Sponsorship

This supplement was sponsored by the Crohn's & Colitis Foundation.

Conflicts of Interest

All authors declare that the Crohn's & Colitis Foundation has provided or is currently providing partial financial support to several companies and academic groups, highlighted in this manuscript, to advance their product opportunities. Companies include: PredictImmune, Glycominds, Vedanta, Artizan, Koutif Therapeutics, Tissium, Progenity. Academic institutions include: Cleveland Clinic, New York University, Johns Hopkins University and University of Texas Medical Branch.

References

1. Kobayashi T, Siegmund B, Le Berre C, et al. Ulcerative colitis. *Nat Rev Dis Primers*. 2020;6:74.
2. Roda G, Chien Ng S, Kotze PG, et al. Crohn's disease. *Nat Rev Dis Primers*. 2020;6(1):22.
3. Solberg IC, Vatn MH, Høie O, et al.; IBSEN Study Group. Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. *Clin Gastroenterol Hepatol*. 2007;5:1430–1438.
4. Lo B, Prosberg MV, Gluud LL, et al. Systematic review and meta-analysis: assessment of factors affecting disability in inflammatory bowel disease and the reliability of the inflammatory bowel disease disability index. *Aliment Pharmacol Ther*. 2018;47:6–15.
5. Candido FD, Fiorino G, Spadaccini M, et al. Are surgical rates decreasing in the biological era in IBD? *Curr Drug Targets*. 2019;20:1356–1362.
6. Mak JWY, Ng SC. Epidemiology of fibrostenosing inflammatory bowel disease. *J Dig Dis*. 2020;21(6):332–335.
7. Maconi G, Sampietro GM, Cristaldi M, et al. Preoperative characteristics and postoperative behavior of bowel wall on risk of recurrence after conservative surgery in Crohn's disease: a prospective study. *Ann Surg*. 2001;233:345–352.
8. Loftus EV Jr, Colombel JF, Feagan BG, et al. Long-term efficacy of vedolizumab for ulcerative colitis. *J Crohns Colitis*. 2017;11:400–411.
9. Hanauer SB, Feagan BG, Lichtenstein GR, et al.; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359:1541–1549.
10. Peyrin-Biroulet L, Danese S, Argollo M, et al. Loss of response to vedolizumab and ability of dose intensification to restore response in patients with Crohn's disease or ulcerative colitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2019;17:838–846.e2.
11. Honig G, Heller C, Hurtado-Lorenzo A. Defining the path forward for biomarkers to address unmet needs in inflammatory bowel diseases. *Inflamm Bowel Dis*. 2020;26:1451–1462.
12. Scott FI, Rubin DT, Kugathasan S, et al. Challenges in IBD research: pragmatic clinical research. *Inflamm Bowel Dis*. 2019;25(Suppl 2):S40–S47.
13. Denson LA, Curran M, McGovern DPB, et al. Challenges in IBD research: precision medicine. *Inflamm Bowel Dis*. 2019;25(Suppl 2):S31–S39.
14. Dhyani M, Joshi N, Bemelman WA, et al. Challenges in IBD research: novel technologies. *Inflamm Bowel Dis*. 2019;25(Suppl 2):S24–S30.
15. Pizarro TT, Stappenbeck TS, Rieder F, et al. Challenges in IBD research: preclinical human IBD mechanisms. *Inflamm Bowel Dis*. 2019;25(Suppl 2):S5–S12.
16. Institute of Medicine (US) Forum on Neuroscience and Nervous System Disorders. *Venture Philanthropy Strategies to Support Translational Research: Workshop Summary*. National Academies Press; 2009. doi:10.17226/12558
17. López JC, Suojanen C. Harnessing venture philanthropy to accelerate medical progress. *Nat Rev Drug Discov*. 2019;18:809–810.

18. Crohn's & Colitis Foundation. *IBD plexus: partnering to accelerate science*. Accessed August 11, 2021. https://www.crohnscolitisfoundation.org/research/current-research-initiatives/ibd-plexus
19. Berinstein JA, Steiner CA, Higgins PDR. The IBD therapeutic pipeline is primed to produce. *Pract Gastroenterol*. 2019;XLIII(4):1.
20. D'Amico F, Peyrin-Biroulet L, Danese S, et al. New drugs in the pipeline for the treatment of inflammatory bowel diseases: what is coming? *Curr Opin Pharmacol*. 2020;55:141–150.
21. Sabino J, Verstockt B, Vermeire S, et al. New biologics and small molecules in inflammatory bowel disease: an update. *Ther Adv Gastroenterol*. 2019;12:1756284819853208.
22. Walters TD, Kim MO, Denson LA, et al.; PRO-KIIDS Research Group. Increased effectiveness of early therapy with anti-tumor necrosis factor-α vs an immunomodulator in children with Crohn's disease. *Gastroenterology*. 2014;146:383–391.
23. Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet*. 2017;389:1710–1718.
24. Siegel CA, Horton H, Siegel LS, et al. A validated web-based tool to display individualised Crohn's disease predicted outcomes based on clinical, serologic and genetic variables. *Aliment Pharmacol Ther*. 2016;43(2):262–271.
25. Rieder F, Schleder S, Wolf A, et al. Serum anti-glycan antibodies predict complicated Crohn's disease behavior: a cohort study. *Inflamm Bowel Dis*. 2010;16(8):1367–1375.
26. National Institute for Health and Care Excellence. *PredictSURE IBD and IBDX to guide treatment of Crohn's disease*. Accessed August 11, 2021. https://www.nice.org.uk/guidance/gid-dg10029/documents/html-content
27. Biasci D, Lee JC, Noor NM, et al. A blood-based prognostic biomarker in IBD. *Gut*. 2019;68:1386–1395.
28. U.S. National Library of Medicine. Clinicaltrials.gov website. Accessed August 11, 2021. https://clinicaltrials.gov/ct2/show/NCT03952364
29. Parkes M, Noor NM, Dowling F, et al. Predicting Outcomes for Crohn's Disease Using a Molecular Biomarker (PROFILE): protocol for a multicentre, randomised, biomarker-stratified trial. *BMJ Open*. 2018;8:e026767.
30. American Association for the Advancement of Science. EurekAlert! website. Accessed August 11, 2021. https://www.eurekalert.org/news-releases/666427
31. Ananthakrishnan AN, Luo C, Yajnik V, et al. Gut microbiome function predicts response to anti-integrin biologic therapy in inflammatory bowel diseases. *Cell Host Microbe*. 2017;21:603–610.e3.
32. Ananthakrishnan AN. Microbiome-based biomarkers for IBD. *Inflamm Bowel Dis*. 2020;26:1463–1469.
33. National Institute for Health Research. *Development of RxSelex: A microbiome-based predictive diagnostic of IBD biologics treatment outcome*. Accessed August 11, 2021. https://fundingawards.nihr.ac.uk/award/NIHR200983
34. Busquets D, Oliver L, Amoedo J, et al. RAID-Prediction: a faecal microbial signature with capacity to predict the response to an anti-TNFα treatment: A pilot study. Submitted for publication.
35. Ungaro RC, Yzet C, Bossuyt P, et al. Deep remission at 1 year prevents progression of early Crohn's disease. *Gastroenterology*. 2020;159:139–147.
36. Ungaro R, Colombel JF, Lissoos T, et al. A Treat-to-target update in ulcerative colitis: a systematic review. *Am J Gastroenterol*. 2019;114:874–883.
37. Allocca M, Furfaro F, Fiorino G, et al. Point-of-care ultrasound in inflammatory bowel disease. *J Crohns Colitis*. 2021;15(1):143–151.
38. Porter AC, Aubrecht J, Birch C, et al. Biomarkers of Crohn's disease to support the development of new therapeutic interventions. *Inflamm Bowel Dis*. 2020;26:1498–1508.
39. D'Haens G, Kelly O, Battat R, et al. Development and validation of a test to monitor endoscopic activity in patients with Crohn's disease based on serum levels of proteins. *Gastroenterology*. 2020;158:515–526.e10.
40. de Bruyn M, Ringold R, Martens E, et al. The ulcerative colitis response index for detection of mucosal healing in patients treated with anti-tumour necrosis factor. *J Crohns Colitis*. 2020;14:176–184.
41. Jagannath B, Lin KC, Pali M, et al. A Sweat-based wearable enabling technology for real-time monitoring of IL-1β and CRP as potential markers for inflammatory bowel disease. *Inflamm Bowel Dis*. 2020;26:1533–1542.
42. Papalia I, Quah S, Tan C, et al. Colon capsule endoscopy in the assessment of mucosal healing in Crohn's Disease. *Inflamm Bowel Dis*. 2021;27:S9–S16.
43. Yau YY, Wasinger VC, Hirten RP, et al. Current trends in inflammatory bowel disease–development of mucosal based biomarkers and a novel minimally invasive recoverable sampling system. *Inflamm Bowel Dis*. 2021;27:S1–S8.
44. Thomas S, Izard J, Walsh E, et al. The host microbiome regulates and maintains human health: a primer and perspective for non-microbiologists. *Cancer Res*. 2017;77:1783–1812.
45. Mishima Y, Sartor RB. Manipulating resident microbiota to enhance regulatory immune function to treat inflammatory bowel diseases. *J Gastroenterol*. 2020;55:4–14.
46. Oka A, Sartor RB. Microbial-based and microbial-targeted therapies for inflammatory bowel diseases. *Dig Dis Sci*. 2020;65:757–788.
47. Imdad A, Nicholson MR, Tanner-Smith EE, et al. Fecal transplantation for treatment of inflammatory bowel disease. *Cochrane Database Syst Rev*. 2018;11:CD012774.
48. Costello SP, Hughes PA, Waters O, et al. Effect of fecal microbiota transplantation on 8-week remission in patients with ulcerative colitis: a randomized clinical trial. *JAMA*. 2019;321(2):156–164.
49. Dubinsky V, Reshef L, Bar N, et al. Predominantly antibiotic-resistant intestinal microbiome persists in patients with pouchitis who respond to antibiotic therapy. *Gastroenterology*. 2020;158:610–624.e13.
50. Machiels K, Pozuelo Del Río M, Martinez-De la Torre A, et al. Early postoperative endoscopic recurrence in Crohn's disease is characterised by distinct microbiota recolonisation. *J Crohns Colitis*. 2020;14:1535–1546.
51. Hurtado-Lorenzo A, Honig G, Weaver SA, et al. Chronic abdominal pain in IBD research initiative: unraveling biological mechanisms and patient heterogeneity to personalize treatment and improve clinical outcomes. *Crohns Colitis 360*. 2021;3(3):otab034.
52. Henn MR, O'Brien EJ, Diao L, et al. A phase 1b safety study of SER-287, a spore-based microbiome therapeutic, for active mild to moderate ulcerative colitis. *Gastroenterology*. 2021;160(1):115–127.e30.
53. U.S. National Library of Medicine. Clinicaltrials.gov website. Accessed August 11, 2021. https://clinicaltrials.gov/ct2/show/NCT03759041
54. Seres Therapeutics. *Seres Therapeutics announces topline results for SER0287 Phase 2b study in mild-to-moderate ulcerative colitis*. Accessed August 11, 2021. https://ir.serestherapeutics.com/news-releases/news-release-details/seres-therapeutics-announces-topline-results-ser-287-phase-2b
55. Atarashi K, Tanoue T, Oshima K, et al. Treg induction by a rationally selected mixture of *Clostridia* strains from the human microbiota. *Nature*. 2013;500:232–236.
56. Atarashi K, Tanoue T, Shima T, et al. Induction of colonic regulatory T cells by indigenous *Clostridium* species. *Science*. 2011;331:337–341.
57. Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature*. 2013;504:446–450.
58. Nadalian B, Yadegar A, Houri H, et al. Prevalence of the pathobiont adherent-invasive *Escherichia coli* and inflammatory bowel disease: a

systematic review and meta-analysis. *J Gastroenterol Hepatol*. 2021;36:852–863.
59. Bushman FD, Conrad M, Ren Y, et al. Multi-omic analysis of the interaction between *Clostridioides difficile* infection and pediatric inflammatory bowel disease. *Cell Host Microbe*. 2020;28:422–433.e7.
60. Palmela C, Chevarin C, Xu Z, et al. Adherent-invasive *Escherichia coli* in inflammatory bowel disease. *Gut*. 2018;67:574–587.
61. Tavoukjian V. Faecal microbiota transplantation for the decolonization of antibiotic-resistant bacteria in the gut: a systematic review and meta-analysis. *J Hosp Infect*. 2019;102:174–188.
62. Vedanta Biosciences. *Vedanta Biosciences receives award from the Crohn's & Colitis Foundation to advance a microbiome-derived therapeutic program for interception and treatment of inflammatory bowel disease*. Accessed August 11, 2021. https://www.vedantabio.com/news-media/press-releases/detail/2367/vedanta-biosciences-receives-award-from-the-crohns
63. Czaplewski L, Bax R, Clokie M, et al. Alternatives to antibiotics-a pipeline portfolio review. *Lancet Infect Dis*. 2016;16:239–251.
64. Atarashi K, Suda W, Luo C, et al. Ectopic colonization of oral bacteria in the intestine drives TH1 cell induction and inflammation. *Science*. 2017;358:359–365.
65. BiomX. *BiomX announces positive results of a Phase 1a pharmacokinetic study for inflammatory bowel disease/primary sclerosing cholangitis (IBD/PSC) evaluating delivery of oral BX002 phage therapy*. Accessed August 11, 2021. https://ir.biomx.com/news-events/press-releases/detail/42/biomx-announces-positive-results-of-a-phase-1a
66. Mydock-McGrane LK, Hannan TJ, Janetka JW. Rational design strategies for FimH antagonists: new drugs on the horizon for urinary tract infection and Crohn's disease. *Expert Opin Drug Discov*. 2017;12:711–731.
67. Sivignon A, Bouckaert J, Bernard J, et al. The potential of FimH as a novel therapeutic target for the treatment of Crohn's disease. *Expert Opin Ther Targets*. 2017;21:837–847.
68. Poole NM, Green SI, Rajan A, et al. Role for FimH in extraintestinal pathogenic *Escherichia coli* invasion and translocation through the intestinal epithelium. *Infect Immun*. 2017;85(11):e00581–00517.
69. U.S. National Library of Medicine. Clinicaltrials.gov website. Accessed August 11, 2021. https://clinicaltrials.gov/ct2/show/NCT03943446
70. Wilcox MH, Gerding DN, Poxton IR, et al.; MODIFY I and MODIFY II Investigators. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. *N Engl J Med*. 2017;376:305–317.
71. Kelly CP, Wilcox MH, Glerup H, et al. Bezlotoxumab for *Clostridium difficile* infection complicating inflammatory bowel disease. *Gastroenterology*. 2018;155:1270–1271.
72. U.S. National Library of Medicine. Clinicaltrials.gov website. Accessed August 11, 2021. https://ClinicalTrials.gov/show/NCT04626947.
73. Shapiro JM, de Zoete MR, Palm NW, et al. Immunoglobulin A targets a unique subset of the microbiota in inflammatory bowel disease. *Cell Host Microbe*. 2021;29:83–93.e3.
74. Palm NW, de Zoete MR, Cullen TW, et al. Immunoglobulin A coating identifies colitogenic bacteria in inflammatory bowel disease. *Cell*. 2014;158:1000–1010.
75. Schoultz I, Keita ÅV. Cellular and molecular therapeutic targets in inflammatory bowel disease-focusing on intestinal barrier function. *Cells*. 2019;8(2):193.
76. Chiodini RJ, Dowd SE, Galandiuk S, et al. The predominant site of bacterial translocation across the intestinal mucosal barrier occurs at the advancing disease margin in Crohn's disease. *Microbiology (Reading)*. 2016;162:1608–1619.
77. Campbell HK, Maiers JL, DeMali KA. Interplay between tight junctions and adherens junctions. *Exp Cell Res*. 2017;358:39–44.
78. Buckley A, Turner JR. Cell biology of tight junction barrier regulation and mucosal disease. *Cold Spring Harb Perspect Biol*. 2018;10(1):a029314.
79. Cornick S, Tawiah A, Chadee K. Roles and regulation of the mucus barrier in the gut. *Tissue Barriers*. 2015;3:e982426.
80. Wehkamp J, Stange EF. An update review on the paneth cell as key to ileal Crohn's disease. *Front Immunol*. 2020;11:646.
81. Turpin W, Lee SH, Raygoza Garay JA, et al. Increased intestinal permeability is associated with later development of Crohn's disease. *Gastroenterology*. 2020;159(6):2092–2100.e5.
82. Kiesslich R, Duckworth CA, Moussata D, et al. Local barrier dysfunction identified by confocal laser endomicroscopy predicts relapse in inflammatory bowel disease. *Gut*. 2012;61:1146–1153.
83. Lim LG, Neumann J, Hansen T, et al. Confocal endomicroscopy identifies loss of local barrier function in the duodenum of patients with Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis*. 2014;20:892–900.
84. Chang J, Leong RW, Wasinger VC, et al. Impaired intestinal permeability contributes to ongoing bowel symptoms in patients with inflammatory bowel disease and mucosal healing. *Gastroenterology*. 2017;153:723–731.e1.
85. Landén NX, Li D, Ståhle M. Transition from inflammation to proliferation: a critical step during wound healing. *Cell Mol Life Sci*. 2016;73:3861–3885.
86. Martini E, Krug SM, Siegmund B, et al. Mend your fences: the epithelial barrier and its relationship with mucosal immunity in inflammatory bowel disease. *Cell Mol Gastroenterol Hepatol*. 2017;4:33–46.
87. Subramanian S, Geng H, Tan XD. Cell death of intestinal epithelial cells in intestinal diseases. *Sheng Li Xue Bao*. 2020;72(3):308–324.
88. Cholapranee A, Hazlewood GS, Kaplan GG, et al. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. *Aliment Pharmacol Ther*. 2017;45:1291–1302.
89. Christensen B, Rubin DT. Understanding endoscopic disease activity in IBD: how to incorporate it into practice. *Curr Gastroenterol Rep*. 2016;18:5.
90. Walsh A, Palmer R, Travis S. Mucosal healing as a target of therapy for colonic inflammatory bowel disease and methods to score disease activity. *Gastrointest Endosc Clin N Am*. 2014;24:367–378.
91. Colombel JF, D'haens G, Lee WJ, et al. Outcomes and strategies to support a treat-to-target approach in inflammatory bowel disease: a systematic review. *J Crohns Colitis*. 2020;14:254–266.
92. Yzet C, Diouf M, Le Mouel JP, et al. Complete endoscopic healing associated with better outcomes than partial endoscopic healing in patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2020;18:2256–2261.
93. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature*. 2014;510(7503):92–101.
94. Ungaro F, Rubbino F, Danese S, et al. Actors and factors in the resolution of intestinal inflammation: lipid mediators as a new approach to therapy in inflammatory bowel diseases. *Front Immunol*. 2017;8:1331.
95. Quiros M, Feier D, Birkl D, et al. Resolvin E1 is a pro-repair molecule that promotes intestinal epithelial wound healing. *Proc Natl Acad Sci USA*. 2020;117:9477–9482.
96. Takeuchi K, Amagase K. Roles of cyclooxygenase, prostaglandin E2 and EP receptors in mucosal protection and ulcer healing in the gastrointestinal tract. *Curr Pharm Des*. 2018;24:2002–2011.
97. Zhang Y, Desai A, Yang SY, et al. Tissue regeneration. Inhibition of the prostaglandin-degrading enzyme 15-PGDH potentiates tissue regeneration. *Science*. 2015;348(6240):aaa2340.
98. Brubaker PL. Glucagon-like peptide-2 and the regulation of intestinal growth and function. *Compr Physiol*. 2018;8:1185–1210.
99. Fesler Z, Mitova E, Brubaker PL. GLP-2, EGF, and the intestinal epithelial IGF-1 receptor interactions in the regulation of crypt cell proliferation. *Endocrinology*. 2020;161(4):bqaa040.
100. Buchman AL, Katz S, Fang JC, et al.; Teduglutide Study Group. Teduglutide, a novel mucosally active analog of glucagon-like peptide-2 (GLP-2) for the treatment of moderate to severe Crohn's disease. *Inflamm Bowel Dis*. 2010;16:962–973.

101. Yang PY, Zou H, Lee C, et al. Stapled, long-acting glucagon-like peptide 2 analog with efficacy in dextran sodium sulfate induced mouse colitis models. *J Med Chem*. 2018;61:3218–3223.
102. Smith EB. Haemostatic factors and atherogenesis. *Atherosclerosis*. 1996;124:137–143.
103. Kaiko GE, Chen F, Lai CW, et al. PAI-1 augments mucosal damage in colitis. *Sci Transl Med*. 2019;11(482):eaat0852.
104. Anderson CA, Boucher G, Lees CW, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nat Genet*. 2011;43:246–252.
105. Rivas MA, Beaudoin M, Gardet A, et al. Deep resequencing of GWAS loci identifies independent rare variants associated with inflammatory bowel disease. *Nat Genet*. 2011;43(11):1066–1073.
106. Mohanan V, Nakata T, Desch AN, et al. C1orf106 is a colitis risk gene that regulates stability of epithelial adherens junctions. *Science*. 2018;359:1161–1166.
107. Hurtado-Lorenzo A, Skinner M, El Annan J, et al. V-ATPase interacts with ARNO and Arf6 in early endosomes and regulates the protein degradative pathway. *Nat Cell Biol*. 2006;8:124–136.
108. Donaldson JG, Jackson CL. ARF family G proteins and their regulators: roles in membrane transport, development and disease. *Nat Rev Mol Cell Biol*. 2011;12:362–375.
109. Cunningham KE, Turner JR. Myosin light chain kinase: pulling the strings of epithelial tight junction function. *Ann NY Acad Sci*. 2012;1258:34–42.
110. Graham WV, He W, Marchiando AM, et al. Intracellular MLCK1 diversion reverses barrier loss to restore mucosal homeostasis. *Nat Med*. 2019;25:690–700.
111. Motta J, Deraison C, Le Grand S, et al. PAR1 antagonism to promote gut mucosa healing in Crohn's disease patients: A new avenue for CVT120165. *Inflamm Bowel Dis*. 2021;27:S17–S21.
112. Linsalata M, Riezzo G, Clemente C, et al. Noninvasive biomarkers of gut barrier function in patients suffering from diarrhea predominant-IBS: an update. *Dis Markers*. 2020;2020:2886268.
113. Colombel JF. When should combination therapy for patients with Crohn's disease be discontinued? *Gastroenterol Hepatol (N Y)*. 2012;8:259–262.
114. Hanauer SB. Combination therapy for inflammatory bowel disease. *Gastroenterol Hepatol (N Y)*. 2017;13:296–298.
115. Hu A, Kotze PG, Burgevin A, et al. Combination therapy does not improve rate of clinical or endoscopic remission in patients with inflammatory bowel diseases treated with vedolizumab or ustekinumab. *Clin Gastroenterol Hepatol*. 2021;19:1366–1376.e2.
116. Li Y, Chen J, Bolinger AA, et al. Target-based small molecule drug discovery towards novel therapeutics for inflammatory bowel diseases. *Inflamm Bowel Dis*. 2021;27:S38–S62.
117. Jefremow A, Neurath MF. All are equal, some are more equal: targeting IL 12 and 23 in IBD–a clinical perspective. *Immunotargets Ther*. 2020;9:289–297.
118. Coskun M, Vermeire S, Nielsen OH. Novel targeted therapies for inflammatory bowel disease. *Trends Pharmacol Sci*. 2017;38:127–142.
119. Katsanos KH, Papadakis KA. Inflammatory bowel disease: updates on molecular targets for biologics. *Gut Liver*. 2017;11:455–463.
120. Friedrich M, Pohin M, Powrie F. Cytokine networks in the pathophysiology of inflammatory bowel disease. *Immunity*. 2019;50:992–1006.
121. Leppkes M, Neurath MF. Cytokines in inflammatory bowel diseases–update 2020. *Pharmacol Res*. 2020;158:104835.
122. Hueber W, Sands BE, Lewitzky S, et al.; Secukinumab in Crohn's Disease Study Group. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut*. 2012;61:1693–1700.
123. Fauny M, Moulin D, D'Amico F, et al. Paradoxical gastrointestinal effects of interleukin-17 blockers. *Ann Rheum Dis*. 2020;79:1132–1138.
124. Omidian Z, Ahmed R, Giwa A, Donner T, Hamad ARA. IL-17 and limits of success. *Cell Immunol*. 2019;339:33–40.
125. West NR, Hegazy AN, Owens BMJ, et al. Oncostatin M drives intestinal inflammation and predicts response to tumor necrosis factor-neutralizing therapy in patients with inflammatory bowel disease. *Nat Med*. 2017;23(5):579–589.
126. Minar P, Lehn C, Tsai YT, Jackson K, Rosen MJ, Denson LA. Elevated pretreatment plasma oncostatin M is associated with poor biochemical response to infliximab. *Crohns Colitis 360*. 2019;1:otz026.
127. Reid J, Zamuner S, Edwards K, et al. In vivo affinity and target engagement in skin and blood in a first-time-in-human study of an anti-oncostatin M monoclonal antibody. *Br J Clin Pharmacol*. 2018;84:2280–2291.
128. U.S. National Library of Medicine. Clinicaltrials.gov website. Accessed August 11, 2021. https://clinicaltrials.gov/ct2/show/NCT04151225
129. Saxton RA, Tsutsumi N, Su LL, et al. Structure-based decoupling of the pro- and anti-inflammatory functions of interleukin-10. *Science*. 2021;371(6535):eabc8433.
130. Wei HX, Wang B, Li B. IL-10 and IL-22 in mucosal immunity: driving protection and pathology. *Front Immunol*. 2020;11:1315.
131. U.S. National Library of Medicine. Clinicaltrials.gov website. Accessed August 11, 2021. https://clinicaltrials.gov/ct2/show/NCT04583358
132. Fay NC, Muthusamy BP, Nyugen LP, et al. A novel fusion of IL-10 engineered to traffic across intestinal epithelium to treat colitis. *J Immunol*. 2020;205:3191–3204.
133. Ihara S, Hirata Y, Koike K. TGF-β in inflammatory bowel disease: a key regulator of immune cells, epithelium, and the intestinal microbiota. *J Gastroenterol*. 2017;52:777–787.
134. Marafini I, Troncone E, Salvatori S, Monteleone G. TGF-β activity restoration and phosphodiesterase 4 inhibition as therapeutic options for inflammatory bowel diseases. *Pharmacol Res*. 2020;155:104757.
135. Rothenberg ME, Wang Y, Lekkerkerker A, et al. Randomized Phase I healthy volunteer study of UTTR1147A (IL-22Fc): a potential therapy for epithelial injury. *Clin Pharmacol Ther*. 2019;105:177–189.
136. Beattie DT, Pulido-Rios MT, Shen F, et al. Intestinally-restricted Janus kinase inhibition: a potential approach to maximize the therapeutic index in inflammatory bowel disease therapy. *J Inflamm (Lond)*. 2017;14:28.
137. Panés J, Vermeire S, Dubinsky MC, et al. Efficacy and safety of tofacitinib retreatment for ulcerative colitis after treatment interruption: results from the OCTAVE clinical trials [published online ahead of print April 21, 2021]. *J Crohns Colitis*. doi:10.1093/ecco-jcc/jjab065
138. Sandborn WJ, Su C, Sands BE, et al.; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376:1723–1736.
139. Chen BB, Coon TA, Glasser JR, et al. A combinatorial F box protein directed pathway controls TRAF adaptor stability to regulate inflammation. *Nat Immunol*. 2013;14:470–479.
140. Mallampalli RK, Coon TA, Glasser JR, et al. Targeting F box protein Fbxo3 to control cytokine-driven inflammation. *J Immunol*. 2013;191:5247–5255.
141. Brasier AR, Zhou J. Validation of the epigenetic reader bromodomain-containing protein 4 (BRD4) as a therapeutic target for treatment of airway remodeling. *Drug Discov Today*. 2020;25:126–132.
142. Liu Z, Wang P, Chen H, et al. Drug discovery targeting bromodomain-containing protein 4. *J Med Chem*. 2017;60:4533–4558.

143. Tang P, Zhang J, Liu J, Chiang CM, Ouyang L. Targeting bromodomain and extraterminal proteins for drug discovery: from current progress to technological development. *J Med Chem*. 2021;64:2419–2435.
144. Xu Q, Zhou X, Strober W, Mao L. Inflammasome regulation: therapeutic potential for inflammatory bowel disease. *Molecules*. 2021;26(6):1725.
145. Khatri V, Kalyanasundaram R. Therapeutic implications of inflammasome in inflammatory bowel disease. *FASEB J*. 2021;35(5):e21439.
146. Veny M, Fernández-Clotet A, Panés J. Controlling leukocyte trafficking in IBD. *Pharmacol Res*. 2020;159:105050.
147. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al.; VARSITY Study Group. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med*. 2019;381:1215–1226.
148. Argollo M, Furfaro F, Gilardi D, et al. Modulation of sphingosine-1-phosphate in ulcerative colitis. *Expert Opin Biol Ther*. 2020;20:413–420.
149. Genentech. *Genentech provides update on Phase III studies of etrolizumab in people with moderately to severely active ulcerative colitis*. Accessed August 11, 2021. https://www.gene.com/media/press-releases/14870/2020-08-09/genentech-provides-update-on-phase-iii-s
150. Wang Y, Marier JF, Lavigne J, Kassir N, Martin P. Population pharmacokinetics and pharmacodynamics of ontamalimab (SHP647), a fully human monoclonal antibody against mucosal addressin cell adhesion molecule-1 (MAdCAM-1), in patients with ulcerative colitis or Crohn's disease. *J Clin Pharmacol*. 2020;60:903–914.
151. Reinisch W, Sandborn WJ, Danese S, et al. Long-term safety and efficacy of the Anti-MAdCAM-1 monoclonal antibody ontamalimab [SHP647] for the treatment of ulcerative colitis: the open-label study TURANDOT II. *J Crohns Colitis*. 2021;15:938–949.
152. *Efficacy and safety study of ontamalimab as maintenance treatment in participants with moderate to severe Crohn's disease (CARMEN CD 307) (CARMEN CD 307)*. Accessed August 11, 2021. https://clinicaltrials.gov/ct2/show/NCT03627091
153. U.S. National Library of Medicine. Clinicaltrials.gov website. Accessed August 11, 2021. https://clinicaltrials.gov/ct2/show/NCT03290781
154. Adams B. *Takeda culls Shire pipeline med after no one wants it*. *Fierce Biotech*. Accessed August 11, 2021. https://www.fiercebiotech.com/biotech/takeda-doesn-t-have-to-divest-shire-pipeline-med-as-no-one-wants-it-so-it-tosses-it-out
155. Business Wire. *European Commission releases Takeda from commitment to divest Shire's pipeline compound SHP647*. Accessed 11 August 2021. https://www.businesswire.com/news/home/20200528005415/en/
156. Cully M. Integrin-targeted therapies branch out. *Nat Rev Drug Discov* 2020;19(11):739–741.
157. Dixit D, Okuniewska M, Schwab SR. Secrets and lyase: control of sphingosine 1-phosphate distribution. *Immunol Rev*. 2019;289:173–185.
158. Mendoza A, Bréart B, Ramos-Perez WD, et al. The transporter Spns2 is required for secretion of lymph but not plasma sphingosine-1-phosphate. *Cell Rep*. 2012;2:1104–1110.
159. Clough JN, Omer OS, Tasker S, Lord GM, Irving PM. Regulatory T-cell therapy in Crohn's disease: challenges and advances. *Gut*. 2020;69:942–952.
160. Lord JD. Promises and paradoxes of regulatory T cells in inflammatory bowel disease. *World J Gastroenterol*. 2015;21:11236–11245.
161. Canavan JB, Scottà C, Vossenkämper A, et al. Developing in vitro expanded CD45RA+ regulatory T cells as an adoptive cell therapy for Crohn's disease. *Gut*. 2016;65:584–594.
162. Goldberg R, Scotta C, Cooper D, et al. Correction of defective t-regulatory cells from patients with Crohn's disease by ex vivo ligation of retinoic acid receptor-α. *Gastroenterology*. 2019;156:1775–1787.
163. U.S. National Library of Medicine. Clinicaltrials.gov website. Accessed August 11, 2021. https://clinicaltrials.gov/ct2/show/NCT03185000
164. Shanafelt AB, Lin Y, Shanafelt MC, et al. A T-cell-selective interleukin 2 mutein exhibits potent antitumor activity and is well tolerated in vivo. *Nat Biotechnol*. 2000;18:1197–1202.
165. Goettel JA, Kotlarz D, Emani R, et al. Low-dose interleukin-2 ameliorates colitis in a preclinical humanized mouse model. *Cell Mol Gastroenterol Hepatol*. 2019;8:193–195.
166. Allegretti J, Canavan J, Mitsialis V, et al. Low dose IL-2 for the treatment of moderate to severe ulcerative colitis. *Inflamm Bowel Dis*. 2021;27(Suppl 1):S6–S7.
167. Chen X, Ai X, Wu C, et al. A novel human IL-2 mutein with minimal systemic toxicity exerts greater antitumor efficacy than wild-type IL-2. *Cell Death Dis*. 2018;9:989.
168. Khoryati L, Pham MN, Sherve M, et al. An IL-2 mutein engineered to promote expansion of regulatory T cells arrests ongoing autoimmunity in mice. *Sci Immunol*. 2020;5(50):eaba5264.
169. Peterson LB, Bell CJM, Howlett SK, et al. A long-lived IL-2 mutein that selectively activates and expands regulatory T cells as a therapy for autoimmune disease. *J Autoimmun*. 2018;95:1–14.
170. GlobeNewswire. *Pandion Therapeutics announces positive top-line Phase 1a clinical data showing PT101 was well-tolerated and selectively expanded regulatory T cells*. Accessed August 11, 2021. https://www.globenewswire.com/news-release/2021/01/04/2152594/0/en/Pandion-Therapeutics-Announces-Positive-Top-Line-Phase-1a-Clinical-Data-Showing-PT101-was-Well-Tolerated-and-Selectively-Expanded-Regulatory-T-cells.html
171. Ness S, Lin S, Gordon JR. Regulatory dendritic cells, T cell tolerance, and dendritic cell therapy for immunologic disease. *Front Immunol*. 2021;12:633436.
172. Eggenhuizen PJ, Ng BH, Ooi JD. Treg enhancing therapies to treat autoimmune diseases. *Int J Mol Sci*. 2020;21(19):7015.
173. Mikami N, Kawakami R, Sakaguchi S. New Treg cell-based therapies of autoimmune diseases: towards antigen-specific immune suppression. *Curr Opin Immunol*. 2020;67:36–41.
174. Moorman CD, Sohn SJ, Phee H. Emerging therapeutics for immune tolerance: tolerogenic vaccines, T cell therapy, and IL-2 therapy. *Front Immunol*. 2021;12:657768.
175. Hebbandi Nanjundappa R, Ronchi F, Wang J, et al. A gut microbial mimic that hijacks diabetogenic autoreactivity to suppress colitis. *Cell*. 2017;171:655–667.e17.
176. Zhao Q, Duck LW, Huang F, et al. CD4(+) T cell activation and concomitant mTOR metabolic inhibition can ablate microbiota-specific memory cells and prevent colitis. *Sci Immunol*. 2020;5(54):eabc6373.
177. Thapar N, Benninga MA, Crowell MD, et al. Paediatric functional abdominal pain disorders. *Nat Rev Dis Primers*. 2020;6:89.
178. Spear ET, Mawe GM. Enteric neuroplasticity and dysmotility in inflammatory disease: key players and possible therapeutic targets. *Am J Physiol Gastrointest Liver Physiol*. 2019;317:G853–G861.
179. Eberhardson M, Tarnawski L, Centa M, Olofsson PS. Neural control of inflammation: bioelectronic medicine in treatment of chronic inflammatory Disease. *Cold Spring Harb Perspect Med*. 2020;10(3):a034181.
180. Vornov JJ, Peters D, Nedelcovych M, Hollinger K, Rais R, Slusher BS. Looking for drugs in all the wrong places: use of GCPII inhibitors outside the brain. *Neurochem Res*. 2020;45:1256–1267.
181. Zhang T, Song B, Zhu W, et al. An ileal Crohn's disease gene signature based on whole human genome expression profiles of disease unaffected ileal mucosal biopsies. *PLoS One*. 2012;7(5):e37139.
182. Rais R, Jiang W, Zhai H, et al. FOLH1/GCPII is elevated in IBD patients, and its inhibition ameliorates murine IBD abnormalities. *JCI Insight*. 2016;1(12):e88634.
183. Date AA, Rais R, Babu T, et al. Local enema treatment to inhibit FOLH1/GCPII as a novel therapy for inflammatory bowel disease. *J Control Release*. 2017;263:132–138.

184. Haberman Y, Tickle TL, Dexheimer PJ, et al. Pediatric Crohn disease patients exhibit specific ileal transcriptome and microbiome signature. *J Clin Invest*. 2014;124:3617–3633.
185. Ben-Shachar S, Yanai H, Baram L, et al. Gene expression profiles of ileal inflammatory bowel disease correlate with disease phenotype and advance understanding of its immunopathogenesis. *Inflamm Bowel Dis*. 2013;19:2509–2521.
186. Koopman FA, Chavan SS, Miljko S, et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *Proc Natl Acad Sci USA*. 2016;113:8284–8289.
187. D'Haens G, Cabrijan Z, Eberhardson M, et al. P574 The effects of vagus nerve stimulation in biologic-refractory Crohn's disease: a prospective clinical trial. *J Crohn's Colitis*. 2018;12(Suppl 1):S397–S398.
188. Mogilevski T, Burgell R, Aziz Q, Gibson PR. Review article: the role of the autonomic nervous system in the pathogenesis and therapy of IBD. *Aliment Pharmacol Ther*. 2019;50:720–737.
189. Bonaz B, Sinniger V, Pellissier S. Therapeutic potential of vagus nerve stimulation for inflammatory bowel diseases. *Front Neurosci*. 2021;15:650971.
190. Sinniger V, Pellissier S, Fauvelle F, et al. A 12-month pilot study outcomes of vagus nerve stimulation in Crohn's disease. *Neurogastroenterol Motil*. 2020;32(10):e13911.
191. Bhatti S, Jaafar I, Hassan H, et al. Effects of gastric neuromodulation on Crohn's disease in patients with coexisting symptoms of gastroparesis. *Neuromodulation*. 2020;23:1196–1200.
192. Bonaz B, Sinniger V, Hoffmann D, et al. Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study. *Neurogastroenterol Motil*. 2016;28(6):948–953.
193. Cotero V, Fan Y, Tsaava T, et al. Noninvasive sub-organ ultrasound stimulation for targeted neuromodulation. *Nat Commun*. 2019;10:952.
194. Akhtar K, Hirschstein Z, Stefanelli A, et al. Non-invasive peripheral focused ultrasound neuromodulation of the celiac plexus ameliorates symptoms in a rat model of inflammatory bowel disease. *Exp Physiol*. 2021;106(4):1038–1060.
195. Bitton A, Dobkin PL, Edwardes MD, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut*. 2008;57:1386–1392.
196. Mikocka-Walus A, Andrews JM, Rampton D, Goodhand J, van der Woude J, Bernstein CN. How can we improve models of care in inflammatory bowel disease? An international survey of IBD health professionals. *J Crohns Colitis*. 2014;8:1668–1674.
197. Paulides E, Boukema I, van der Woude CJ, de Boer NKH. The effect of psychotherapy on quality of life in IBD patients: a systematic review. *Inflamm Bowel Dis*. 2021;27:711–724.
198. Mahana Therapeutics. *Mahana Therapeutics obtains FDA marketing authorization for the first prescription digital therapeutic to treat irritable bowel syndrome*. Accessed August 11, 2021. https://www.mahanatx.com/press/parallel-fda-authorization
199. Everitt HA, Landau S, O'Reilly G, et al.; ACTIB trial group. Assessing telephone-delivered cognitive-behavioural therapy (CBT) and web-delivered CBT versus treatment as usual in irritable bowel syndrome (ACTIB): a multicentre randomised trial. *Gut*. 2019;68:1613–1623.
200. Ljótsson B, Andersson G, Andersson E, et al. Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial. *BMC Gastroenterol*. 2011;11:110.
201. Rieder F, Bettenworth D, Ma C, et al. An expert consensus to standardise definitions, diagnosis and treatment targets for antifibrotic stricture therapies in Crohn's disease. *Aliment Pharmacol Ther*. 2018;48(3):347–357.
202. Michelsen KS, Thomas LS, Taylor KD, et al. IBD-associated TL1A gene (TNFSF15) haplotypes determine increased expression of TL1A protein. *PLoS One*. 2009;4:e4719.
203. Yang DH, Yang SK, Song K, et al. TNFSF15 is an independent predictor for the development of Crohn's disease-related complications in Koreans. *J Crohns Colitis*. 2014;8:1315–1326.
204. Tung CC, Wong JM, Lee WC, et al. Combining TNFSF15 and ASCA IgA can be used as a predictor for the stenosis/perforating phenotype of Crohn's disease. *J Gastroenterol Hepatol*. 2014;29:723–729.
205. Hirano A, Yamazaki K, Umeno J, et al. Association study of 71 European Crohn's disease susceptibility loci in a Japanese population. *Inflamm Bowel Dis*. 2013;19:526–533.
206. Barrett R, Zhang X, Koon HW, et al. Constitutive TL1A expression under colitogenic conditions modulates the severity and location of gut mucosal inflammation and induces fibrostenosis. *Am J Pathol*. 2012;180:636–649.
207. Jacob N, Jacobs JP, Kumagai K, et al. Inflammation-independent TL1A-mediated intestinal fibrosis is dependent on the gut microbiome. *Mucosal Immunol*. 2018;11:1466–1476.
208. Shih DQ, Zheng L, Zhang X, et al. Inhibition of a novel fibrogenic factor Tl1a reverses established colonic fibrosis. *Mucosal Immunol*. 2014;7:1492–1503.
209. Li H, Song J, Niu G, et al. TL1A blocking ameliorates intestinal fibrosis in the T cell transfer model of chronic colitis in mice. *Pathol Res Pract*. 2018;214(2):217–227.
210. U.S. National Library of Medicine. Clinicaltrials.gov website. Accessed August 11, 2021. https://ClinicalTrials.gov/show/NCT04090411
211. Prometheus Biosciences. *Prometheus Biosciences commences dosing in multiple ascending dose (MAD) portion of ongoing Phase 1a clinical study of PRA023*. Accessed August 11, 2021. https://prometheusbiosciences.investorroom.com/2021-03-03-Prometheus-Biosciences-Commences-Dosing-in-Multiple-Ascending-Dose-MAD-Portion-of-Ongoing-Phase-1a-Clinical-Study-of-PRA023
212. Rieder F. ROCKing the field of intestinal fibrosis or between a ROCK and a hard place? *Gastroenterology*. 2017;153:895–897.
213. Holvoet T, Devriese S, Castermans K, et al. Treatment of intestinal fibrosis in experimental inflammatory bowel disease by the pleiotropic actions of a local Rho kinase inhibitor. *Gastroenterology*. 2017;153:1054–1067.
214. Jones C, Bunyard P, Eckersley K, et al. P016 GI restricted ROCK inhibitors show potential to treat fibrosis and stenosis associated with inflammatory bowel disease. *J Crohns Colitis*. 2018;12(Suppl 1):S100–S101.
215. Ko JZ, Johnson S, Dave M. Efficacy and safety of mesenchymal stem/stromal cell therapy for inflammatory bowel diseases: an up-to-date systematic review. *Biomolecules*. 2021;11(1):82.
216. Bislenghi G, Wolthuis A, Van Assche G, Vermeire S, Ferrante M, D'Hoore A. Cx601 (darvadstrocel) for the treatment of perianal fistulizing Crohn's disease. *Expert Opin Biol Ther*. 2019;19:607–616.
217. Meng ZW, Baumgart DC. Darvadstrocel for the treatment of perianal fistulas in Crohn's disease. *Expert Rev Gastroenterol Hepatol*. 2020;14:405–410.
218. Levy O, Kuai R, Siren EMJ, et al. Shattering barriers toward clinically meaningful MSC therapies. *Sci Adv*. 2020;6:eaba6884.
219. Johnstone BH, Miller HM, Beck MR, et al. Identification and characterization of a large source of primary mesenchymal stem cells tightly adhered to bone surfaces of human vertebral body marrow cavities. *Cytotherapy*. 2020;22:617–628.
220. Mannon PJ. Remestemcel-L: human mesenchymal stem cells as an emerging therapy for Crohn's disease. *Expert Opin Biol Ther*. 2011;11:1249–1256.
221. Patel AN, Genovese J. Potential clinical applications of adult human mesenchymal stem cell (Prochymal®) therapy. *Stem Cells Cloning*. 2011;4:61–72.
222. Pereira MJ, Sundback CA, Lang N, et al. Combined surface micropatterning and reactive chemistry maximizes tissue adhesion with minimal inflammation. *Adv Healthc Mater*. 2014;3:565–571.
223. Lang N, Pereira MJ, Lee Y, et al. A blood-resistant surgical glue for minimally invasive repair of vessels and heart defects. *Sci Transl Med*. 2014;6:218ra6.
224. Roche ET, Fabozzo A, Lee Y, et al. A light-reflecting balloon catheter for atraumatic tissue defect repair. *Sci Transl Med*. 2015;7:306ra149.

225. Pellenc Q, Touma J, Coscas R, et al. Preclinical and clinical evaluation of a novel synthetic bioresorbable, on-demand, light-activated sealant in vascular reconstruction. *J Cardiovasc Surg (Torino)*. 2019;60:599–611.
226. Hua S. Advances in oral drug delivery for regional targeting in the gastrointestinal tract–influence of physiological, pathophysiological and pharmaceutical factors. *Front Pharmacol*. 2020;11:524.
227. Thakral S, Thakral NK, Majumdar DK. Eudragit: a technology evaluation. *Expert Opin Drug Deliv*. 2013;10:131–149.
228. Ibekwe VC, Khela MK, Evans DF, Basit AW. A new concept in colonic drug targeting: a combined pH-responsive and bacterially-triggered drug delivery technology. *Aliment Pharmacol Ther*. 2008;28(7):911–916.
229. Goyanes A, Hatton GB, Merchant HA, Basit AW. Gastrointestinal release behaviour of modified-release drug products: dynamic dissolution testing of mesalazine formulations. *Int J Pharm*. 2015;484(1–2):103–108.
230. Shah M, Li Y, Pingyuan W, et al. Nanoparticle-encapsulated bromodomain-containing protein 4 inhibitors for therapeutics of inflammatory bowel disease. *Inflamm Bowel Dis*. 2021;27(Suppl 1):S3–S4.
231. Yang C, Merlin D. Nanoparticle-mediated drug delivery systems for the treatment of IBD: current perspectives. *Int J Nanomedicine*. 2019;14:8875–8889.
232. Sinha SR, Nguyen LP, Inayathullah M, et al. A thermo-sensitive delivery platform for topical administration of inflammatory bowel disease therapies. *Gastroenterology*. 2015;149:52–55.e2.
233. Zhang S, Ermann J, Succi MD, et al. An inflammation-targeting hydrogel for local drug delivery in inflammatory bowel disease. *Sci Transl Med*. 2015;7:300ra128.
234. Yu S, Pearson AD, Lim RK, et al. Targeted delivery of an anti-inflammatory PDE4 inhibitor to immune cells via an antibody-drug conjugate. *Mol Ther*. 2016;24:2078–2089.
235. Truffi M, Sevieri M, Morelli L, et al. Anti-MAdCAM-1-conjugated nanocarriers delivering quantum dots enable specific imaging of inflammatory bowel disease. *Int J Nanomedicine*. 2020;15:8537–8552.
236. Oz HS, Ebersole JL. Application of prodrugs to inflammatory diseases of the gut. *Molecules*. 2008;13:452–474.
237. Chen K, Zhu Y, Zhang Y, et al. A probiotic yeast-based immunotherapy against *Clostridioides difficile* infection. *Sci Transl Med*. 2020;12(567):eaax4905.
238. Mandsberg NK, Christfort JF, Kamguyan K, Boisen A, Srivastava SK. Orally ingestible medical devices for gut engineering. *Adv Drug Deliv Rev*. 2020;165–166:142–154.
239. Alsunaydih FN, Yuce MR. Next-generation ingestible devices: sensing, locomotion and navigation. *Physiol Meas*. 2021;42(4):04TR01.
240. Huntsman M, Lee SN, Stylli J, et al. Development of a novel drug delivery system to deliver drugs directly to the colonic mucosa, resulting in improved efficacy and reduced systemic exposure for the treatment of ulcerative colitis [published online ahead of print July 7, 2021]. *Crohns Colitis 360*. doi:10.1093/crocol/otab045