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

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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 pathological 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, neuremodulation, 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. 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. 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. 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. 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, 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. 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, 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...
Plexus®, an exceptional biorepository of IBD patient samples and provides opportunities for companies to access IBD novel therapies, diagnostics, devices, and 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.

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 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. 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 activities currently advancing at the preclinical and early clinical development stages, and compare it to the late-stage clinical trial pipeline, reviewed in detail elsewhere. 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-inflammatory therapies; (5) development of neuromodulatory and behavioral therapies; (6) management of disease complications; and (7) targeted drug delivery. 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. 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.

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.
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-effectiveness26 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 Conformité Européenne (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 study28 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).14

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.11,13,34–38 Blood-based protein panel tests to monitor inflammation and healing have been developed for CD39 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.41 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 sensor42 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.47 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 pouchitis49 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.32 SER-287 is intended to recapitate 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 endpoint.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.37

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.39 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), certain Enterobacteriaceae species, such as adherent-invasive Escherichia coli (AIEC) and Klebsiella pneumoniae
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(BP) species, are expanded in many IBD patients and can drive colitis in preclinical models due to exacerbation of proinflammatary 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 lytic bacteriophages against AIEC in a Phase 1/2a trial of AIEC-positive and food antigens into the submucosa.\(^{75,76}\) Epithelial cells are 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.\(^{75,78}\) 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.\(^{80}\)

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 entercocyte 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 proinflammatary mediators, and an inhibitor of GCP II may abrogate local neuroinflammatary 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; GCP II, glutamate carboxypeptidase I I; 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.

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,\(^{65,74}\) 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.\(^{73,75}\) 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.\(^{75,78}\) 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.110,111 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 pursued as mediator of mucosal repair is prostaglandin E2, which regulates epithelial growth and repair.96 Prostaglandin E2 is rapidly activated 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 cascade102 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.109 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 healing112 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 paracelllular 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-inflammatory drugs 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-inflammatory drugs 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-inflammatory drugs 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 doses136 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 3150–153 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.116,116

The other prominent pathway where approved drugs target leukocyte trafficking is the sphingosine 1-phosphate (SIP) signaling pathway, with several drugs approved for other indications and ozanimod, recently FDA-approved for the treatment of moderate-to-severe UC.156 Next-generation strategies targeting SIP signaling include efforts by researchers at New York University, supported via IBD Ventures, to target sphingolipid transporter 2 (SPNS2), an SIP transporter that contributes to SIP 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,164,167,168 including PT101, which was reported to upregulate Tregs in a recent study of healthy subjects.160 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 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.180 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.181–183 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 vagal nerve has been most extensively studied in this regard. Vagal nerve stimulation (VNS) elicits the cholinergic anti-inflammatory reflex, an endogenous spinal 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, notably chronic pain, 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 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
Stricture management
Biologics may have only a limited impact on strictures, as illustrated by the fact that rates of surgery for CD have not dramatically decreased since their introduction. 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, preclinical models, risk stratification, and clinical trial endpoints. 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 and the risk of CD strictures. Researchers from Cedars-Sinai demonstrated that TL1A expression drives stricture formation and that a neutralizing antibody ameliorated fibrosis in preclinical models. Two TL1A-neutralizing antibodies are in clinical development for IBD, one by Pfizer and another by Prometheus Biosciences, 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. 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.

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. 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.218,219

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 polymer 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.234 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 API237 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.51,238,239 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.

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