Gut-directed therapeutics in inflammatory bowel disease

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Purpose of review
Tissue-directed therapies (TDTs) provide potential advantages, including improved tolerance, safety, and efficacy. This review provides a conceptual framework for understanding intestinal TDT and summarizes the current landscape of TDT in inflammatory bowel disease (IBD).

Recent findings
Vedolizumab, a mAb targeting the gut homing α4β7 integrin, served as revolutionary proof-of-principle for the power of advanced TDT in IBD. The development of other monoclonal antibodies targeting cell adhesion molecules followed including abrilumab (α4β7), etrolizumab (β7), and ontamalimab (MAdCAM-1). MORF-057, an oral small molecule inhibitor of α4β7, is now in development for ulcerative colitis. Efforts have also been made toward gut specific JAK inhibitors. Microbiome-based therapies, including engineered probiotics, bacteriophages, and postbiotics, are gaining interest. There are also a number of innovative drug delivery methods, including engineered yeast, hydrogels, and nanoparticles, and viral-based gene therapy.

Summary
Gut-targeted therapies range from novel variations on traditional drugs (i.e., mAbs and small molecules) to microbiome-based therapeutics and engineered delivery systems. They can be used alone or in combination with currently available therapies. Future directions should focus on the development of tried-and-true modalities (mAbs, small molecules) as well as the microbiome and more innovative delivery systems.

Keywords
biologic, Crohn's disease, microbiome, small molecule, ulcerative colitis

INTRODUCTION

Tissue-directed therapy (TDT) is designed to deliver or concentrate therapies to specific tissues of interest. Another term in use is "tissue-targeted therapy (TTT)", which refers to therapies that target molecules or pathways specific to (or most relevant to) a particular tissue. In IBD, the first TDTs were mesalamine and corticosteroids, either given as rectal enemas or in controlled release formulas such as budesonide. Vedolizumab is a mAb that targets the α4β7 integrin to prevent the translocation of lymphocytes into the gastrointestinal tract [1]. Its introduction in 2014 marked the first gut-specific advanced therapy to be brought to market. Its high efficacy and excellent safety profile reinvigorated interest in gut-specific therapies for IBD.

TDTs and TTTs offer several advantages. They have fewer off-target effects, resulting in fewer systemic side effects, less immunogenicity, and a lower risk of immunosuppression. Over time, this is likely to result in better long-term tolerability and patient compliance. Whether by targeting specific receptors or by direct application, they accumulate in biologically relevant tissue, reaching high concentrations and reducing the required drug dosage. This results in a greater therapeutic index than systemically active treatments. Many are able to be taken orally, avoiding the discomfort and expense associated with intravenous and subcutaneous treatments. Their minimal systemic circulation reduces the chance of drug-drug interactions, potentially paving the way for their use as combination therapies.

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KEY POINTS

- Gut-directed therapies in IBD offer the potential of improved safety, efficacy, and tolerance by minimizing systemic exposure and targeting treatments directly to the intestinal tissue.
- Next-generation mAbs, oral integrin inhibitors, and gut-restricted small molecules – including JAK inhibitors and AHR agonists – are under development.
- Microbiome-based therapies, such as engineered probiotics, bacteriophages, and postbiotics, show promise in modulating gut inflammation and restoring microbial balance.
- Innovative delivery systems like hydrogels, nanoparticles, and viral gene therapies are being explored to localize treatment and overcome challenges in IBD drug delivery.
- Despite their promise, gut-directed therapies face challenges such as limited efficacy for extraintestinal symptoms, disease heterogeneity, and complexities in clinical trial design.

The armamentarium of gut specific therapies is diverse. Figure 1 addresses the concepts of intestinal TDT. It comprises the more traditional mAbs and small molecules which are typically gut specific by virtue of their receptor specificity. Like vedolizumab, which antagonizes the α4β7 integrin, their receptors are exclusively expressed in the cells of the gastrointestinal tract or on cells that home to the gastrointestinal tract. It also comprises drugs which are gut specific by virtue of their pharmacokinetics, for example, an antitumor necrosis factor alpha (TNFα) antibody derived from cow colostrum too large to be systemically absorbed [2]. Also included are microbial therapeutics, which include prebiotics and probiotics but also fecal microbiota transplants and bacteriophages. Lastly, it includes a number of engineered delivery systems like yeasts, nanoparticles, or hydrogels typically taken orally or administered endoscopically.

It is important to concede that few gut-targeted therapies are perfectly specific. Mesalamine has roughly 20% systemic absorption. Fluorescently labeled vedolizumab shows off target uptake into macrophages and eosinophils [3▪▪]. Regardless, gut-targeted therapies have a role as both mono and combination therapies in the treatment of IBD.

mABS AND PEPTIDES

Vedolizumab, a mAb that binds the α4β7 on T-cells, is the most familiar gut-directed therapy because of its success in safely and effectively treating both Crohn's disease and ulcerative colitis. Natalizumab, a precursor to vedolizumab, targeted the α4 subunit of both α4β7 and α4β1 (an integrin on brain homing T-cells). While effective for IBD and multiple sclerosis, it raised the risk of reactivating the human polyomavirus 2 (aka John Cunningham virus) and causing progressive multifocal leukoencephalopathy (PML), a rare but potentially lethal infection

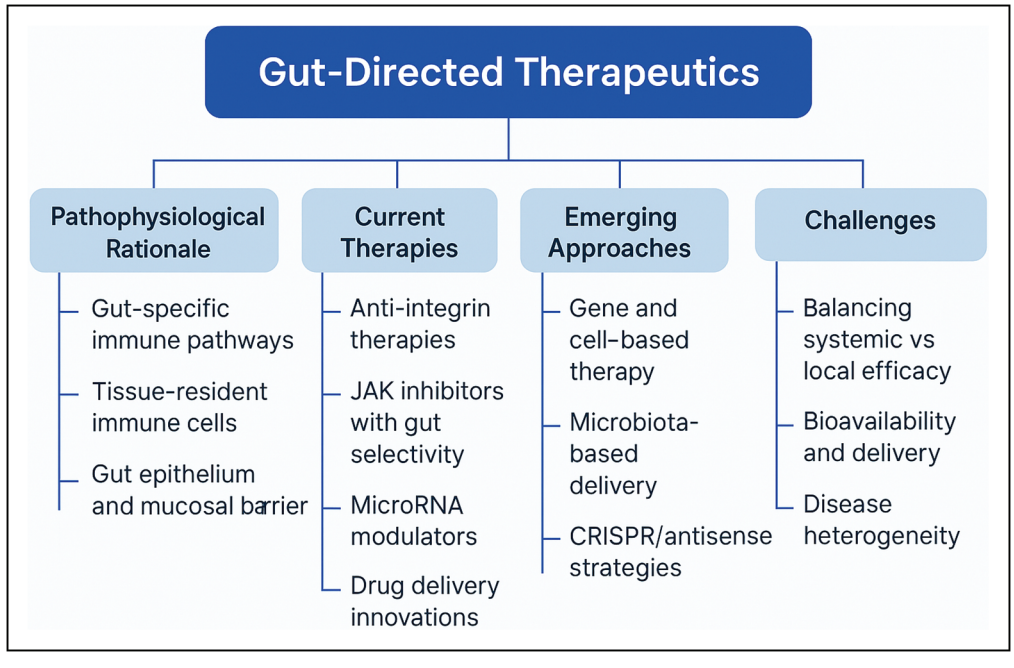

FIGURE 1. Summary of tissue-directed therapies in inflammatory bowel disease.

[4]. Fortunately, PML has not been linked to vedolizumab therapy, illustrating that specificity can improve safety.

Perhaps unsurprisingly, the next generation of gut-directed mAbs also targeted interactions between T-cells and the gut endothelium. The α4β7 integrin, also known as lymphocyte Peyer's patch adhesion molecule (LPAM), is expressed on the surface of lymphocytes. It binds to mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) which is expressed on intestinal lamina propria postcapillary venules and Peyer's patches. Thus, it functions as a homing receptor to direct lymphocytes to gut-associated lymphoid tissue [5,6]. Other mAbs which target the α4β7 integrin include Abrilumab, Etrolizumab, and PN-943. Abrilumab met varying success in phase II trials [7,8], but development was discontinued. Etrolizumab (which also targets αEβ7) and PN-943 (an oral peptide therapeutic mimicking vedolizumab activity) unfortunately met with similar results [9]. By characterizing the β7+ T cell compartment in patients with Crohn's disease, it was shown that Etrolizumab fails to block a specific subset of $\alpha4\beta7\beta1^{hi}$ T cells which is thought to explain its failure to meet the defined endpoint in phase III trials [10▪].

There have also been efforts to develop an anti-MAdCAM-1 antibody, the most successful of which has been ontamalimab. It was studied for both Crohn's disease (OPERA [11], TOSCA [12], OPERA II [13]), and ulcerative colitis (TURNADOT [14]) with good tolerability, safety, and efficacy in phase II trials. Multiple phase III studies, undertaken by Takeda, were terminated early for business and regulatory reasons [15]. However, induction and maintenance data showed significant differences in achieving clinical remission at week 12 and week 52 [16].

Other approaches to gut specific antibodies have been tried. The development of AVX-470 applied the approach of immunizing cows with recombinant human TNFα, resulting in an anti-TNFα antibody purified from cows' colostrum. The antibody, on the order of hundreds of kiloDaltons, is too large to be absorbed systemically. A first in-human, double-blinded, placebo-controlled study compared 0.1 g twice daily, 0.78 g twice daily, and 1.17 g three times daily in 37 patients with ulcerative colitis. About 25.9% of patients achieved clinical response compared with 11.1% on placebo [2]. Overall, AVX-470 was found to be well tolerated even among patients with prior exposure to TNFα therapies. A follow-up study showed reductions of greater than 10-fold in TNFα in proximal and distal colon biopsies after 4 weeks of treatment in the highest dose group [17]. There has also been interest in developing bispecific antibody combinations, that is antibodies which recognize two different epitopes. The integrin-adhesion molecules targeted currently by mAbs may be good candidates for developing novel bispecific antibody combinations such as MAdCAM-1 plus TNFα [18].

SMALL MOLECULES

The success of the JAK1 selective inhibitor upadacitinib has highlighted the role that small molecules can play in the rapid and sustained treatment of moderate to severe IBD. Unlike the commercially available monoclonal antibodies, small molecules are administered orally which is more convenient for patients and less burdensome for the healthcare system. Though there are no commercially available gut specific small molecules, there have been efforts to develop both gut specific α4β7 integrin inhibitors and JAK inhibitors.

MORF-057 is an oral small molecule inhibitor of the α4β7 integrin. Phase I studies in healthy volunteers showed a favorable safety profile and good tolerability [19]. Phase II studies are active in both Crohn's disease (NCT06226883) and ulcerative colitis (NCT05291689, EMERALD-2: NCT05611671). Promising results and the potential for use as a combination therapy led Eli Lilly to acquire Morphic Therapeutic, the developer of MORF-057 for $3.2 billion [20].

AJM300 (carotegrast methyl), an oral antagonist of α4-integrin, was shown to induce remission in bio-naive patients with moderately active ulcerative colitis and is available as a TID medication in Japan [21]. AJM347, a next-generation orally active prodrug of CAN2281, blocks binding of the α4β7 integrin to MAdCAM-1, thereby preventing trafficking of lymphocytes to the gut endothelium [22]. It has high specificity for α4β7/MAdCAM-1 binding and was shown to prevent the development of colitis in an in-vivo mouse model. A Phase I trial established that it is well absorbed orally and well tolerated (NCT03133468), though no further trials have been registered. EA1080 is another oral α4β7 integrin antagonist which was shown in Phase I studies to nearly completely block binding of MAdCAM-1 [23].

Currently available JAK inhibitors used for the treatment of IBD, upadacitinib and tofacitinib, carry a "black box warning" for risk of cardiac events, cancer, blood clots, and death. To increase the therapeutic index of JAK inhibitors, gut specific molecules have been developed. Izencitinib, also known as TD-1473, is a gut specific oral pan JAK inhibitor. It was designed to optimize cellular penetration in gastrointestinal tissue while minimizing systemic absorption [24,25]. Mice administered TD-1473 had decreased oxazolone induced colitis compared

to placebo. As predicted, the concentration of the drug was high in colonic tissue and low systemically. Phase I studies in patients with moderate to severe ulcerative colitis showed good tolerability with a trend toward clinical response and improvement in endoscopic disease activity [25]. However, phase II trials were terminated early, as they failed to achieve both primary and secondary endpoints of change in total Mayo score at week 8 and clinical remission at week 8, respectively [26]. Development of OST-122, another gut selective oral JAK inhibitor specific for JAK3, TYK2, and ARK5 is ongoing. Results of a phase Ib/IIa trial were recently published [27]. A double-blind, placebo-controlled study randomized administration of OST-122 to 37 adult patients with moderate to severe ulcerative colitis in a 3 : 1 ratio of OST-122 400 mg or placebo for 28 days. Sixty-three percent versus 33% of patients showed improvement in rectal bleeding and 44 versus 11% achieved clinical response. There were no significant differences between the two groups in the number of adverse events.

Indigo naturalis, known as QingDai in traditional Chinese medicine, is an herbal extract used for ulcerative colitis [28]. It targets the Aryl hydrocarbon receptor (AHR), a transcription factor which acts as a xenosensor for a diverse range of metabolic, environmental, and dietary stimuli. AHR plays a role in regulation of T cell differentiation, intestinal barrier function, and the intestinal microbiome [29,30]. Decreased levels have been found in patients with IBD [31]. A number of small molecules which target AHR in a gut specific manner are under development including AT-177 [32] and AQ-312 [33]. Both are in the preclinical stages of development. Recent work by Ben-Horin *et al.* [34▪] combined curcumin with QingDai and found that patients receiving the combination were significantly more likely to achieve clinical response, clinical remission, endoscopic improvement, and a 50% reduction in fecal calprotectin through up regulation of Cytochrome P450 1A1 expression.

MICROBIOME THERAPIES

Perturbation in the microbiome plays a significant role in the development, progression, and complications of IBD. Unsurprisingly, there has been an increased interest in targeting the microbiome to influence the pathogenesis of IBD. Beyond antibiotics, therapies can focus on the modulation of prebiotics, substrates used by probiotics; probiotics, microorganisms with beneficial health effects; and postbiotics, both beneficial and harmful molecules produced by probiotics [35].

Gut-restricted antibiotics have been trialed in IBD. In a study of 402 patients with moderately active Crohn's disease, an extended-release form of rifaximin was more effective than placebo at inducing remission (62 versus 43%) [36]. While promising, this was not further pursued and is not part of the current IBD treatment algorithms. This is likely due to the significant limitations and caveats including a very high placebo effect, exclusion of severe disease, and lack of objective markers of inflammation in inclusion criteria. Unlike current trials which included objective markers of inflammation, this trial only used the Crohn's Disease Activity Index (CDAI), a measurement tool that produces false-positive results as it can be influenced by irritable bowel syndrome. Rifaximin provided no benefit to patients with primary sclerosing cholangitis (PSC), a liver disease closely associated with IBD [37]. Finally, vancomycin, a nonabsorbable antibiotic with activity against Gram-positive bacteria, is highly effective at treating *Clostridium difficile* infection. Interestingly, vancomycin may provide benefit for a subset of patients with PSC and IBD [38▪▪].

Prebiotics are nondigestible food ingredients that feed beneficial host microorganisms [39]. They include substances such as inulin, lactulose, and various oligosaccharides. Though numerous, the small clinical trials exploring the role of prebiotics in the treatment of IBD to date have not shown substantial, significant positive effects in IBD [40,41]. Flatulence and bloating are also common side effects that may limit usage of specific prebiotic supplements.

Probiotics and fecal microbiota transplants (FMT) for IBD have been extensively reviewed [42,43]. Positive signals are noted for multistrain probiotics for some patients with pouchitis receiving FMT of certain donor stools in ulcerative colitis [44]. There are particular *Lactobacillus*, Lachnospiraceae, *Bifidobacterium*, and *Bacteroides* that have been shown to beneficially alter the immune response in IBD. They are understood to do so by producing short chain fatty acids and secondary bile acids, enhancing regulatory T cells, reducing pro-inflammatory IL-1β, and enhancing intestinal barrier function [45]. Research on novel probiotic combinations is ongoing, with Di Martino *et al.* [46] recently reporting that administering a combination of *Saccharomyces boulardii, Lactobacillus rhamnosus, Lactobacillus acidophilus,* and *Bifidobacterium breve* to mice ameliorates Crohn's disease like ileitis. However, there are no FDA-approved probiotic therapies for IBD.

Postbiotics are the beneficial and harmful molecules produced by bacteria, in IBD the most significant of which are organic acids (e.g. butyric acid,

propionic acid), short chain fatty acids, tryptophan, and bacteriocins [41,47]. These metabolites have anti-inflammatory and antioxidant properties and often work by fortifying the intestinal barrier. There have been multiple randomized controlled trials on postbiotics in the past few years with promising results [48–50]. The secondary bile acid, tauroursodeoxycholic acid (TUDCA) has been shown to alleviate ulcerative colitis disease activity and endosplasmic reticulum stress [51▪▪].

Bacteriophages are viruses that infect and kill bacteria and have potential for decreasing the population of harmful bacteria in the gut of patients with IBD. Adherent invasive *Escherichia coli* (AIEC) are known to be abnormally abundant in the ileal mucosa of patients with Crohn's disease where they bind to the CEACAM6 receptor. Galtier *et al.* [52] showed that administering a cocktail of three bacteriophages to transgenic mice expressing the human CEACAM6 receptor and colonized with AIEC decreased the number of *E. coli* in feces and in the flora of the intestines. Furthermore, the cocktail reduced dextran sulphate sodium induced-colitis symptoms in mice colonized with AIEC [52]. Federici *et al.* [53] identified a clade of Klebsiella pneumoniae strains that was strongly associated with IBD exacerbation and severity across four geographically distinct cohorts. They then generated a lytic five-phage combination which targets Klebsiella clade members through distinct mechanisms and showed that it suppresses intestinal inflammation in a mouse model of IBD [53].

ENGINEERED DELIVERY SYSTEMS

Engineered probiotics have also been developed for the treatment of IBD. Scott *et al.* [54] engineered *Saccharomyces cerevisiae,* a yeast probiotic, to express a human P2Y2 purinergic receptor with high sensitivity for extracellular adenosine triphosphate (ATP), a proinflammatory molecule produced by commensal microbiota. Activation of the P2Y2 receptor induces *Saccharomyces* to secrete the ATP-degrading enzyme apyrase, thus neutralizing pro-inflammatory signals. It has shown activity in a mouse model of IBD [54]. Efforts have also been undertaken to engineer *Saccharomyces* to produce butyrate and acetate, postbiotics with a variety of beneficial effects, including promoting mucosal repair, regulating intestinal flora, and reducing inflammation. One study cultivated *Saccharomyces* engineered to produce butyrate with gut microbiota derived from patients with mild to moderate ulcerative colitis. The result was an increase in the beneficial probiotics *Bifidobacterium* and *Lactobacillus* and a decrease in harmful bacteria. Furthermore, administration of the engineered yeast to mice improved trinitrobenzene sulfonic acid-induced colitis [55▪▪]. Another study engineered *Saccharomyces* to produce supraphysiologic levels of acetate. Administering the engineered yeast attenuated disease activity in a dextran sulfate sodium model of colitis [56].

Hydrogels are another novel engineered delivery system that can be applied directly to the gastrointestinal tract to locally deliver therapy. They can be made from various polymers including hyaluronic acid, alginate, or engineered protein sequences and are generally designed to solidify at physiologic temperature. By carefully tuning degradation parameters, hydrogels slowly and longitudinally release the drug of interest to the gastrointestinal epithelium [57]. There have even been efforts to develop sprayable hydrogels that could be applied endoscopically to areas with significant inflammation [58].

Nanoparticles are nanoscale, engineered materials assembled from substrates as varied as synthetic polymers, lipids, or carbon or gold nanotubes. By tuning various parameters, they can target delivery to a particular location along the gastrointestinal tract [59,60]. Given the success of the TNFα inhibitors, many have been focused on targeted delivery of these biologic therapies. For example, Mohan *et al.* [61] adsorbed infliximab to the surface of poly(lactic-co-glycolic acid) polyethylene gycol nanoparticles and observed differential accumulation of nanoparticles based on size at an inflamed cell barrier model.

Gene therapy uses viral or other vectors to deliver nucleic acids to target cells. This approach has led to several recent breakthroughs in previously untreatable or difficult to treat diseases including spinal muscular atrophy, hemophilia, and severe combined immunodeficiency. Although gene therapy for IBD has been an area of interest for decades, progress in the field is still nascent. Areas of potential interest include correction of monogenic IBD such as mutations in IL-10 or the IL-10 receptor, gene delivery of anti-inflammatory cytokines such as IL-10 and IL-22, engineering of autologous T-regulator cells, and correction of gene expression such as XBP1, NOD2, or MUC2 in epithelial cells. Current challenges include the complexity of IBD pathophysiology, the need to develop well tolerated and effective tools for delivering the payload to the gut mucosa, and establishing long-term expression if needed. These considerations notwithstanding, the achievement of effective gene delivery remains the paramount challenge for application of gene therapy to gastrointestinal disease. In this regard, recent technologic advances in adenovirus-based gene therapy such as antibody tagged molecular glue conjugates hold significant promise in addressing some of these limitations and provide a

foundation for discovery of novel IBD treatment approaches [62].

LIMITATIONS AND CHALLENGES

There are some considerations for the future of gut directed therapies in IBD. First, IBD presents as a systemic disease with up to 40% of patients experiencing extraintestinal manifestations including inflammatory conditions of the joints, skin, liver, and eyes. Systemic therapies like inhibitors of TNFα, JAK kinases, and IL-12/23 treat some or all of these, while the prototypical TDT vedolizumab does not. Second, IBD is a heterogenous disease; Crohn's disease can affect any part of the digestive system from mouth to anus and can cause penetrating disease, including perianal fistula, while ulcerative colitis may involve the whole colon or only the rectum. Thus, depending on where the disease is most active, there may be issues with bioavailability, tissue penetration, and spatial distribution of drug delivery. Third, some gut restricted agents such as PN-943 and TD-1473 produced bell-shaped efficacy curves in humans and mice respectively, where efficacy rose as the dose increased up to a point and then fell at higher doses. Whether this is a veritable physiologic phenomenon or happenstance is not known. Finally, clinical trial design with consideration of eventual therapeutic positioning is crucial for new IBD therapeutics. The availability of effective medications poses a high bar for new therapeutics to enter the market, consequently slowing trial enrollment. A potential solution is to trial these gut-directed therapies as adjuncts to enhance the efficacy of existing treatments safely.

CONCLUSION

Despite the introduction of multiple new IBD therapies over the last decade, numerous unmet therapeutic needs remain, including refractory disease, stricturing disease, and complications such as fistula. Moreover, the most effective anti-inflammatory medications (infliximab and upadacitinib) carry risks of infection, malignancy, and potentially death. Gut-targeted therapeutics such as next-generation biologics, small molecules, microbial therapies, and engineered delivery vehicles that deliver therapeutic payloads directly to the gastrointestinal tract endothelium have the potential to address these gaps in treatment.

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Conflicts of interest

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