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Gut Restricted Therapeutic Approaches to Inflammatory Bowel Disease

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Received: 14 June 2021 Accepted: 1 July 2021 Published: 15 July 2021

Abstract

Inflammatory Bowel Disease (IBD), consisting of Crohn?s Disease (CD) and Ulcerative Colitis (UC), is a chronic intestinal disorder that arises due to the damaged intestinal epithelium tissue, which most often leads to relapsing. Major treatment options range from dietary intervention at an early stage of the disease, to the use of steroids or anti- inflammatory drugs for most severe conditions. However, the side effects and associated comorbidities which bring disease recurrences points towards the unmet needs of the existing treatment options, which are limited to their non-holistic mechanistic functionality. Among them, many drugs work specifically by acting locally on the gut tissue, in other words at the site of the disease, both to exert maximal efficacy as well as to avoid undesired side effects. Here we have reviewed the recent interests in the gut restricted therapeutic approaches for new IBD therapies.

Index terms— IBD, UC therapies, CD therapies, gut-restricted compounds, colon-specific compounds, non-systemic compounds

1 Introduction

BD is a chronic disorder of the gastrointestinal tract affecting severely the normal lifestyle of an individual. IBD comprises of CD and UC. While CD is characterized as epithelial damage throughout the intestinal tract from mouth to anus with multiple patches here and there in terms of their heterogeneous nature, morphology, and size; UC is more restricted to the damage of the colonic epithelia with a leaky gut localized mainly from cecum to rectum **??**1, **??**]. Today approximately 10 million people are living with IBD in different parts of the world in addition to many which are underreported or undiagnosed due to the nature of the complexity of the disease [3].

At present, there is no real ready-to-use noninvasive easy diagnostic tool available for a quick assessment of CD or UC. In recent times, the disease prevalence is growing at a faster rate due to the widespread use of modern food habits (western diet), environmental factors and genetic make us; which might soon take an epidemic form of the disease [4].

UC is the major component of IBD with clinical symptoms of chronic abdominal pain, diarrhea, bloody stool, fever, and weight loss. In general, people with a stomach infection has a higher risk of developing UC, but chronic life habits and conditions like smoking, high sugar or high-fat diet, and even anti-inflammatory or heavy antibiotic therapies are also the causes of developing UC [5]. Many patients develop colon cancer from UC. CD has a high prevalence from teenage group children to about 30 years old adults [6].

II.

2 IBD causes and factors

Image 1: Causal relationship between a healthy gut and IBD gut

Although the exact cause of the UC and CD is unknown, but epigenetic and environmental factors which affect the symbiotic ambience of gut microbiota and the overall immune status of the host body are the major causes thought to be the initiators of IBD. The disruption in the intestinal wall integrity, by virtue of breakage of the tight junction between intestinal epithelial cells, compromises the differentiation between good and bad bacteria on two sides of the intestinal wall. And this in turn provides an immunologically flaredup milieu of inflamed epithelial wall.

The human gut is the home for hundreds of trillion of bacteria and it is exposed to the constant flux of environmental bacteria that get ingested into our body through several pathways [7]. The pathogenic and commensal bacteria get distinguished by our innate immune system through the pattern recognition system. The pathogenic bacteria are eliminated by several mechanisms including the antimicrobial peptides secreted by intestinal epithelial cells in the gut epithelia. The commensal bacteria stays in symbiosis with the gut microbiota and protected from crossing the gut epithelia barrier by the integrity of epithelia cells through the protective mucous layer in the surface of the intestinal epithelial cells as well as by the tight junction protein which held epithelial cells tightly. The gut-associated lymphoid cells constantly sample the composition of the luminal environment and provide immunity to the gut barrier by pattern recognition and destroying pathogenic bacteria to maintain the integrity of the cellular lining [8]. But with the constant onslaught of different environmental factors on the intestinal epithelial cells by non-fibrous foods or dehydrations or low mucous production, the mucous barrier on the epithelial cells gets reduced, and for other reason the tight junction proteins also get lost. By these, the integrity of the intestinal epithelial lining gets compromised. This loss of strict seal of mucous barrier and tight cellular integrity creates a leaky gut wall, which in turn allows commensal bacteria to enter into the basal side of the intestine, lamina propia.

In a leaky-gut-environment, the innate immune system of the gut-associated lymphoid system sends out macrophages and dendritic cells to destroy those pathogenic bacteria and activates T cells to alert the immune system through inflammatory signals. The composition of the bacterial community changes during these instances. Although the interplay between leakygut, inflammation and dysbiosis of bacterial community is the real cause of the disruption or disease condition, but the true sequence of events or triggers are unknown. The gut-associated lymphoid system, consisting of innate immune cells, is activated and produces more inflammatory cytokines to keep the systemic immune balance. This balance goes out of hand with a constant influx of commensal bacteria in a leaky gut and slowly spreads all over part of the colon. A pan colitis kind of situation leads to the development of colon cancer [9].

The inflamed leaky gut lining is seen in the colonoscopies of both CD and UC patients. Intestinal epithelial cells show almost no mucous barrier and lost tight junction between cells. Major inflammatory cytokines like tumor necrosis factor alpha (TNF?), interleukin-8 (IL8), interleukin-6 (IL6), and interleukin-1beta (IL1?) are seen in very high level in the circulating plasma of those patients [10].

3 a) Present treatment paradigm

The first-line therapy of IBD, at present, is mesala mine for a mild to the moderate condition of patients. Corticosteroids are used for severe conditions but with significantly high level of associated side effects. Immuno suppressants are also used for severe cases, but again with limitation as they have many a lot side effects. The biologics like Infliximab are not widely popular due to their high cost and low level of response rate [11,12].To a physician, the main goal of the treatment of IBD patient is to contain the remission. Reducing the inflammation to stop further damages and flare up the disease. Mucosal repair of the intestinal epithelial cells is another critical point of clinical significance to cure the disease and bring back the gut wall to its native form which are majorly investigated by colonoscopies during the treatment regimen [13]. Integrin inhibitors like Vedolizumab and Etrolizumab are used to limiting the infiltration of immune cells into lamina propia side of the gut wall. JAK inhibitors, IL23 antibody and IL22 antibody were used to contain the inflammatory signalling pathways [14,15]. Even the nonpathogenic good bacteria was used to limit the spread of inflammation and reverse the course of IBD in patients **??**16].

4 b) Gut-restricted function of present therapies

Several of the already approved IBD drugs exert their pharmacological action by modulating the components of factors present in the gut. The details of them are listed below in table 1. Mesalamine: The oldest among the drugs which act predominantly through the mechanism at the gut are Asacol and Lialda. They are the two different formulatory compositions of mesalamine. Both of them are prescribed as a first-line therapeutic option for mild to moderate UC and in a combination therapy for moderate to severe UC patients. Mesalamine, in its original form, is absorbed maximally in the small intestine leading to minimal exposure to the colon. The mechanism of action of mesalamine was through the modulation of multiple targets and was inconclusive as a major contributing pathway to the therapy. However few of the notables are, effect on mucosal cells, antiinflammatory effects on immune cells, as an antioxidant including COX2 inhibition, modulating nuclear hormone receptors like PPARg, etc. The exposure proportional side effect to nephrosis, pancreatitis, and cardiac effect was a major concern, besides the immune-related side effects. But many clinical trials and their meta-analysis were inconclusive due to the heterogeneous complexity of the patient population, non adherence, and their symptomatic improvement without having a distinct molecular biomarker. During the 1980s, several clinical trials were run on different formulations of mesalamine to evaluate the efficacy of the drug from its distributive properties in the intestine **??**17]. Time-dependent enterocoated mesalamine (Pentasa) was released in the duodenum, and matrix metallo enterocoated formulations (Lialda and Mezavant) were released in the terminal ileum and entire colon. Prodrugs like Salfasalazine, Osalazine, and Balsalazine which were primarily released in the colon, were also evaluated with comparable efficacy but with side effects. pHdependent mesalamine formulations (Asacol, Mesaal, etc) having

a pH>6 were largely released in the colon and showed maximal efficacy. Colonic delivery of mesalamine was also evaluated in the trial **??**18]. Presently several delayed-release and enterocoated mesalamine formulations are available in the market, a few of them are Asacol HD, Delzicol, Apriso, etc. Considering the safety, efficacy, and adherence profile, presently gut-restricted or gut-released mesalamine is the most prescribed IBD medicine globally.

Antibodies which are acting on intestinal epithelial cells: Vedolizumab and Etrolizumab were two approved antibodies against ?4?7 integrin for UC, which functions by blocking the interaction between ?4?7 integrin and MADCAM-1 and thereby stopping the leukocyte adhesion to the endothelium. MADCAM-1 is mostly expressed in the gut-associated lymph nodes. Although given through the systemic route, these antibodies work at the site of inflamed intestinal epithelial where UC or CD exists **??**19].

Rifaximine: Rifaximine was approved in 2015 for the irritable bowel syndrome with diarrhea. It's an antibacterial agent that works through the inhibition of the transcription process by binding to bacterial DNA. It has no absorption into the systemic circulation after oral administration and devoid of many side effects. Clinical studies have shown significant promise of remission in CD (69%) and UC (76%). Detailed studies are required to establish it for therapeutic use **??**20]. Image 2: Structure of known or disclosed small molecules drugs.

5 c) Upcoming gut restricted drugs for the treatment of IBD

i. TD1473 Theravance Biopharma initially tried to discover a unique formulation to make the pan JAK inhibitor tofacitinib to get restricted into the intestine and not to come into the systemic circulation to reduce the toxicity of systemic tofacitinib. Initial efficacy data in an oxazolone induced colitis model showed that the intracecal delivery of tofacitinib with 15 times lower dose had the similar efficacy and colon exposure even with 80 times lower plasma exposure to its oral delivery; providing the proof of concept about the local effect of JAK inhibitors in colonic gut epithelium Although initially, Theravance designed a gut restricted prodrug of tofacitinib, TD-3504; but discovered a chemically distinct new pan JAK, TYK inhibitor TD-1473 with gut restricted properties. In an oxazolone-induced colitis model, TD1473 showed a significant reduction of disease activity index at 1mpk oral dose, which is comparable to the 15mpk oral dose of tofacitinib in the same model. The oral exposures of those corresponding drugs were 4ng.hr/ml to 4.7ug.hr/ml which indicates that a gutrestricted compound with more than 1000 fold lesser plasma drug concentration can elicit the same efficacy, but only through the local gut effect. It also showed no immunosuppression, as generally observed with tofacitinib, by penetrating the intestinal wall to exert an anti-inflammatory effect locally on lamina propea and epithelial cells. It had slow absorption in the intestinal tract, but without any systemic plasma exposure **??**21].

Phase I clinical trial of TD-1473 with healthy volunteers for SAD (n=40) and MAD (n=32) showed tolerability upto 1000mg (SAD) and 300mg (MAD) for 14 days without any serious side effects. To extrapolate the similar observation from the preclinical pharmacokinetic pattern, in human also there was a low systemic exposure of the molecule and excreted largely through feces. A placebo-controlled exploratory phase Ib in 40 UC patients with 20 mg, 80 mg, and 270 mg doses showed >30% clinical response along with endoscopic mucosal healing (>20% patients) when treated for four weeks. Also, they had an improved histologic and rectal bleeding score. **??**22]. A significant percent of patients (>30%) showed the reduction of CRP and calprotectin without any immunosuppression (reduction of lymphocytes, leukocytes, and neutrophils) **??**23]. In collaboration with Jansen pharma, TD-1473 is now undergoing a phase 2 clinical trial in CD and phase 2b/3 UC patients **??**24].

ii. PTG-100 and PTG-943

The clinical proof of principal of ?4?7 integrin inhibition for the treatment of UC and AD was established with the approval of monoclonal antibodies Natalizumab, Vedolizumab, and Etrolizumab. ?4?7 integrin, majorly expressed in monocytes and macrophages, binds to the MAdCAM1 and VCAM1 in gut epithelial cells and Piears patches for T cell homing and thereby bacterial infiltration. Protagonist therapeutics discovered an oral small molecule cyclic peptide, PTG-100, as an ?4?7 integrin antagonist whose exposure was restricted to gut. The molecule had a subnanomolar potency in inhibiting the ?4?7 integrin and MAdCAM1 interaction while selective for VCAM and ICAM and in cellular adhesion assay as well **??**25]. This cyclic peptide showed great proteolytic and chemical stability in gastric fluid, intestinal fluid, plasma, and liver. PTG-100 showed almost no plasma concentration in rodents and mostly found in Peyer's Patches and colon (about 4uM). A similar effect was observed in a monkey PK study with an even higher colonic exposure of 15uM compared to any in plasma. **??**26]. PTG-110 showed efficacy in the rodent model on the prevention of T cell homing and mucus injury, most probably by a local effect on lymphoid cells of the intestine. In a placebocontrolled phase I clinical trial PTG-100 showed safety and tolerability till 100 mg dose with a high faecal concentration and extremely low plasma concentration **??**27]. The initial phase II data showed a dose-dependent target engagement saturating at about 60-70% level and receptor occupancy saturation at 300 mg dose. The histological remission was about 44% at 900mg dose. Further clinical testing was halted after an independent internal assessment of data predicted to be moderate efficacy of the molecule.

Instead, Protagonist placed a second-generation molecule PTG-493, which is superior to PTG-100 in every aspect in preclinical studies and early clinical studies. PTG-943 is about five times more potent and stays on target for about three times longer than PTG-100 in invitro assays. In monkey studies, it showed a higher level of target occupancy than PTG-100, although having similar low plasma exposure. In rat, it had about 400-500 times higher intestinal concentration than plasma. In healthy mice, PTG-943 was more effective in donor T-cell

homing in illeal Lamina Propia as well as preserving colon integrity. In a phase I clinical studies, PTG-943 showed better target engagement of about 100% with a saturable receptor occupancy at 1000 mg dose **??**28]. A phase II clinical trial of PTG-943 is currently ongoing **??**29].

6 iii. JNJ-67864238 (PTG200)

JnJ-67864238 (PTG200) is an IL23 antibody developed by Protagonist Therapeutics in collaboration with Jansen Biotech. The recent FDA approval of Ustekinuzumab confirmed the proof of concept of the IL23 inhibition for the treatment of IBD. In addition to that, few more IL23 antibodies (Brazikumab, MEDI2070, BI655066, Mirikizumab, Guselkumab, and Risankizumab) are in advanced stages of clinical trials for their potential entry into the market. While all those antibodies were injectables, Protagonist Therapeutics with their special peptide technology discovered and developed a gut restricted antibody, PTG200, to inhibit IL23 locally in the intestine for IBD treatment. A TNBS induced rat colitis model showed dose-dependent improvement of the colitis parameters of body weight, colon length along with MPO, LCN2, and IL17 concentration in feces collected from distal colon and blood cytokines to validate the hypothesis of local IL23 inhibition with an oral gut restricted antibody **??**30, **??**1].

A randomised, double-blinded placebocontrolled phase I clinical trial of PTG200 demonstrated tolerability and safety of the molecule. Also, this study showed the consistent pharmacokinetics and pharmacodynamics of the gut-restricted properties. A phase IIb clinical trial is underway with 90 patients in Australia **??**32].

7 iv. BT-11

BT-11 is a first-in-class LANCL2 activator that is being developed by Landos Pharma **??**33]. CD4+ Treg cells control the production of inflammatory cytokines IFN?, IL17, and TNF? to contain the flares of inflammation on the intestinal wall and gut mucosa. Lanthionine Synthetase Cyclase-like Receptor 2 (LANCL2) is majorly expressed in hematopoietic cells and gut-specific Treg and colon epithelial cells. Although, abscisic acid is the natural lig and for LANCL2, a computational approach by an academic lab produced a hit, which later optimized to give BT-11 [34]. BT-11 is a gut-restricted and locally acting (intestinal epithelium) molecule that is well tolerated until 1000mpk tested in rats and dogs. A 500mpk rat exploratory PK suggested a small but rapid absorption of the molecule with rapid clearance. The plasma concentration was very low, about 20 ng/ml at 500mpk dose [35]. A high volume of distribution (3.3L/kg) initially suggested a drug localization or non-systemic fractionation. BT-11 has been shown to be efficacious in various genetically and chemically induced rodent models of IBD, and along with the reduction of cytokines in the blood samples taken from CD patients, compared to the tofacitinib [36]. It showed the reduction of expression of TNF? in intestinal cells to promise a better or similar effect to a standard of care with TNF? inhibition with this new mechanism of action. A randomized, double-blind, placebo-control phase I SAD and MAD study of BT-11 with CD and UC patients (n=70) showed that 100mg of once-daily oral dose of BT-11 is safe. Drug concentration analysis showed a significantly low level (1:6000) of the drug in plasma compared to the feces and colon [37]. The faecal concentration increased dose proportionally. BT-11 showed a significant decrease of TNF?+, IFN ?+ CD4+ T cells, and an increase of FOXP3+ CD4+ T cells in colonic mononuclear cells from patients with CD and UC. A phase II clinical of BT-11 is undergoing **??**38].

BBT-401: BBT-401 is a potent first-in-class, gut restricted pellino-1 inhibitor discovered by researchers at Sungkyunkwan University and Korea Research Institute of Chemical Technology and later licensed and developed by Bridge Biotherapeutics. Pellino-1 is a ligase that plays a key role in multiple immune receptor signalling pathways, including Toll-like receptors, interleukin-1 receptor, and T-cell receptors [39]. BBT-401 is a lipidated tetra-peptide that binds to Pellin-1 and thereby dissociates the multiprotein signalling complex comprising of MYD88, RIP1, and others. In preclinical cellular and animal models, the compound showed the inhibition of TLR-NF?B signalling and pro-inflammatory cytokine expression. In an animal model, it was shown to be safe in GLP tox studies. In animal models of colitis, compound showed significant efficacy with an improvement of colitis symptoms at a dose of 3mpk along with the mucosal healing. It was not systemically absorbed, and hence the efficacy was mainly attributed to the local effect of the molecule [40]. In a phase 1 clinical trial with 80 healthy volunteers, BBT-401 was found to be safe and well-tolerated till 1600 mg of daily doses for seven days. It was also shown that the molecule has no systemic exposure. A randomised, placebo-controlled, dose-dependent phase 2 study is undergoing right now [41].

8 v. EB8018

Enterome Biosciences developed a first-in-class non-biological, non-steroidal and non-anti-inflammatory small molecule drug for CD by inhibiting the FimH binding of the gut bacteria. Bacteria like AIEC (Adherent and invasive E. Coli) and Klebsiella bind to proteins like CEACAM6 that are overly expressed in chronically inflamed epithelial cells of the gut wall of CD and UC patients through the interaction of their FimH protein adhesion and thereby adhere to the gut cells and increases the bacterial concentration in gut mucosa [42]. FimH inhibition is also implicated in the urinary tract infection and other infections through the mechanism of biofilm formation [43]. Based on the available crystal structure of FimH and its natural ligand d-mannose, many efforts have been put to discover FimH inhibitors for therapeutics [44]. But most of the molecules suffered from metabolic and

chemical instability in the GI tract. Disaccharides as well as monosaccharides with and without heterocycles were tried most. Many molecules showed unique physicochemical properties with high solubility but a very low systemic absorption, and stayed mostly in the intestinal tract. In a rodent model of CD, they showed a reduction of pathogenic AIEC in feces; and in the colonic and ileal mucosa showing early promise of the antiadhesive therapy [45]. Enterome developed EB8018 into phase I clinical trial and reported that the molecule is highly soluble and rapidly absorbed but only in a small amount (123ng/ml at 1500 mg dose) and mostly (97%) excreted through feces. The molecule was well-tolerated till 1500 mg dose with no clinically significant adverse effects that led to the progression of the molecule into phase II clinical trial. Takeda Pharmaceutical has collaborated on this ??46].

9 vi. AVX-470

Avaxia Biologics [47] discovered AVX-470 (Avaximab), an oral gut restricted anti-TNF antibody for IBD. Although the systemic anti-TNF therapy for IBD was already approved (Adalizimab and Tofacitinib), but AVX-470 was designed to act only locally at the inflammation site of the gut wall of CD and UC patients to reduce the immunogenic and immunosuppressive toxicity associated with systemic anti-TNF drugs. AVX-470 was a lactose-free formulation of polyclonal immunoglobin (Ig) obtained from the early milk of cows immunized with recombinant human TNF and later enterically coated to pH 6.0. It was stable in GI track, resistant to the cleavage and digestion by peptidases. It was localized into the colon and had minimal systemic circulation. The molecule had a comparable in vitro potency to Infliximab. In a chemically induced (DSS or TNBS) mice colitis model, AVX-470 showed a significant reduction in disease activity score and inflammatory cytokines comparable to the standard of care like Prednisolone and a matched murine antibody (AVX-470m). Also, it was found to be penetrated into colonic mucosa to inhibit TNF driven mucosal inflammation [48].

A double-blind, placebo-controlled, phase I study (n=37) with three different doses of oral administration of AVX470 showed high intestinal localization of the drug and no traces in the blood circulation. The colonoscopic samples showed the presence in both luminal and basal side as it penetrated through the inflamed leaky gut epithelia. Twice daily dosing (till 3.5mg/day) showed no black box warning, which were generally present in systemic anti-TNF antibodies due to their immunosuppressive side effects In moderate to severe IBD patients, it showed similar efficacy in initiating the remission but better efficacy in maintaining the remission; comparable to systemic anti-TNF antibodies. It showed a significant reduction of CRP and IL6 [49].

10 vii. TD-5202

Recently Theravance has disclosed another gut selective irreversible JAK3 inhibitor (TD-5202) by taking advantage of the differentiated structural feature of an active site cysteine of JAK3. The exact structure and the preclinical data of this molecule are not available in the public domain. Again partnering with Jansen pharma, TD5202 is undergoing a phase I clinical trial indicating the inflammatory intestinal disease [50].

11 viii. GB004 (AKB-4924)

Aerpio Pharmaceuticals discovered AKB-4926, which later got licensed by Gossamer Bio to develop and commercialize for IBD as GB004. This is an oral gut restricted prolyl hydroxylase (PHD) inhibitor which selectively stabilizes Hypoxia-inducible factor 1-alpha (HIF1?). In a hypoxic condition, when oxygen demand from stressed cells are far more than the supply, master regulators like HIF1? gets over expressed to kick start induction of inflammatory genes to produce inflammatory cytokines and erythropoiesis [51]. In a disease condition like IBD, where gut epithelial cells suffer from stress and the high flux of inflammatory cytokines in a hypoxic condition, AKB-4924 plays a vital role in exerting an antiinflammatory effect and mucosal healing effect by stabilizing HIF1?. They later proposed the detailed mechanistic pathway of HIF-IL-12p40 involvement in the Th1/Th17 pathway for HIF1? mediated mucosal healing [52] Importantly, this molecule is gut-restricted when given orally and hence doesn't inhibit the systemic HIF1? which protects the renal and cardiac tissues, which are of general concern for this target to inhibit [53]. Also, AKB-4924 selective against HIF2?, which is otherwise known to cause inflammation. These were shown in a preclinical model of TNBS induced colitis in rats. Also, molecule showed the improvement of parameters of colitis and inflammation along with the mucosal healing of the protective effect of inflamed gut epithelial lining in this colitis model [54].

Gossamer Bio presently is running a placebocontrolled phase 1 clinical trial on GB004 to evaluate the safety, tolerability, and pharmacokinetics of the molecule on IBD patients ??38].

12 ix. Tenapanor

Tenapanor is an inhibitor of sodium/hydrogen exchanger 3 (NHE3), located in the apical surface of the small intestine and colon and responsible for the intestinal absorption of dietary sodium. Ardelyx Inc ??55] developed this compound for Irritable Bowel Syndrome with constipation (IBS-C) and got FDA approval in Nov 2019. By inhibiting the NHE3, Tenapanor decreases the sodium absorption and increases the moisture content of the mucosal surface. This effect results in the softening of the stool in patients. The molecule worked locally on the epithelial tissues of the colon and intestine [56].

In a phase I clinical trial, Tenapanor showed minimal absorption to the systemic circulation to below the detectable limit of 0.5ng/ml. The major excretion of about 70-80% was through feces. In phase III clinical trial, it showed significant efficacy in patients with IBS-C [57].

13 x. ST-0529

Sublimility Therapeutics developed a proprietary SmPill technology, unlike IV or oral, for specific delivery of cyclosporine directly into the colon for moderate to severe UC patients. In a 100 patients phase 2a study, it showed good tolerability and safety to progress into 280 patient phase 2b study **??**58]. Earlier, it was reported that the cyclosporine (through IV route) had about 80% disease response in acute severe UC patients, who are refractory to steroid treatment, and that effect was similar to TNF therapy [59]. ST-0529 is now undergoing a clinical trial with the hope to provide safe and more efficacious cyclosporine for UC patients without major side effects.

14 xi. Safalcone

A recent publication from University of Korea showed that the anticolitic agent Safalcone when conjugated with natural amino acids to make it a gutrestricted compound, the inflammatory components, and the disease index were improved significantly in a TNBS rat model of ulcerative colitis. The molecule showed almost no systemic exposure and was excreted through feces. It was already known that the anti-colitis properties of Safalcone are achieved through the inhibition of NRF2 and HO-1 [60].

15 xii. Inflazome

Recently Inflazome disclosed their pipeline with a molecule in the pipeline in the discovery phase with a gut-restricted NLRP3 inhibitor for the treatment of UC and CD [61].

16 III.

17 Conclusion

As the prevalence of the irritable bowel disease (IBD) cases is growing rapidly worldwide due to rapid industrialization, which causes major environmental changes and also the food habits of people especially those living in the urban setting changes, the for a real disease-modifying therapy of IBD is of prime importance. Although presently, there exist numerous therapies, the response rate is not significant, and coupled with the low adherence to the therapy, creates a huge unmet need for patients suffering from this chronic disease. The remission of the disease is the most common factor in both UC and CD. Most of the present therapies come with a lot of side effects and comorbidities. When the disease gets severe, ultimately, almost ~30% of the patients go through the surgery for removal of the intestine after the 15-20 years of the diagnosis of the disease. Also, in very severe cases, IBD leads to colon cancer.

To avoid side effects arising out of systemic exposure to the drug and also to limit the mechanism of action localized to the site of the disease, there are number of efforts underway to make those drugs delivered in a gut-restricted manner so that the efficacy can be achieved maximally as well as the side effects arising out of systemic circulation of the drug can be contained. Considering the historical functioning of the existing drugs, mesalamine, and antibodies, pharma companies' effort on this unique mode of therapy could lead to a transformation to the therapy with more effective disease modification.

18 Conflict of interest:

[1]

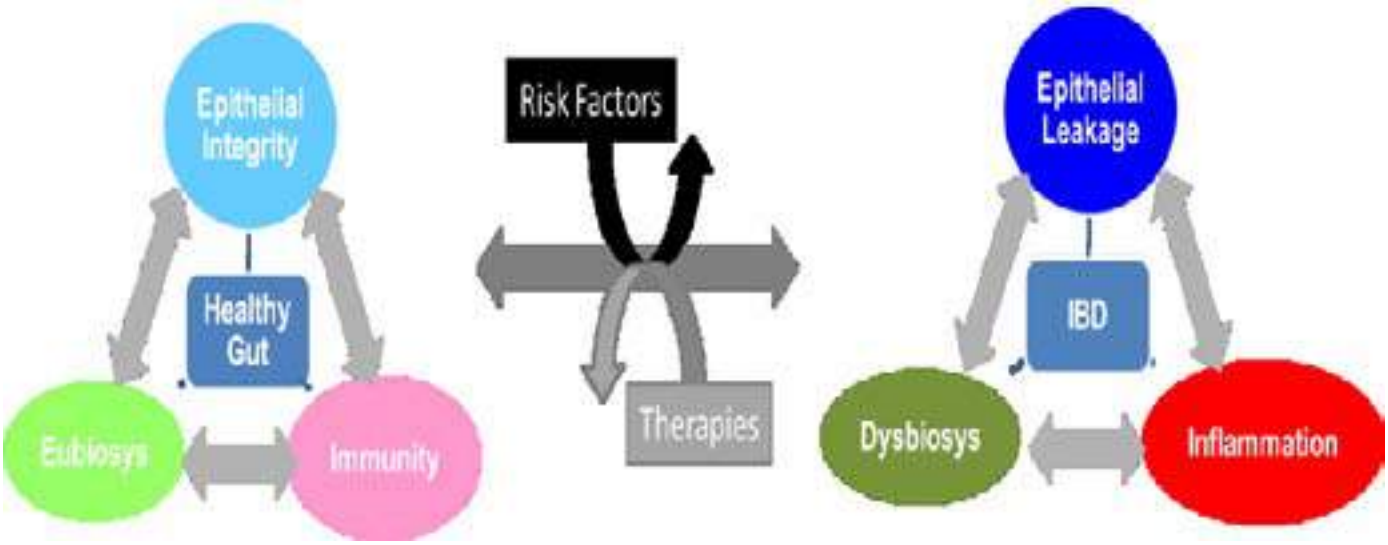

Figure 1:

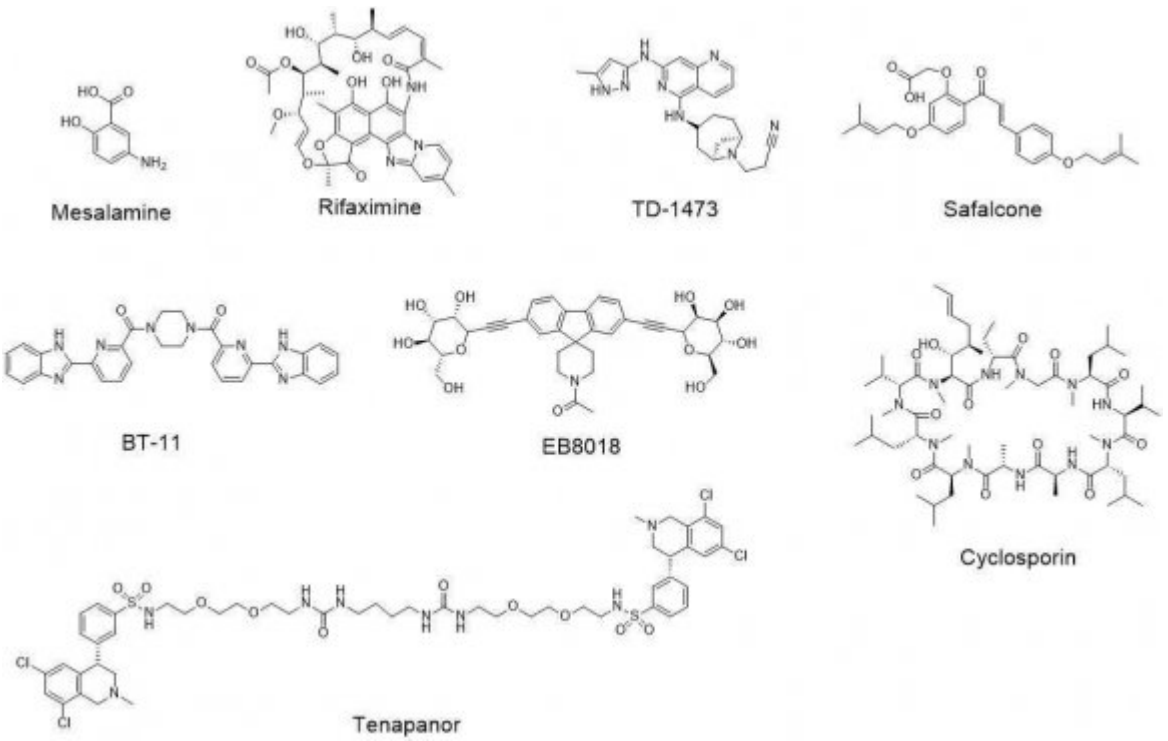

Figure 2:

1

Drug	Route	Type	Mechanism of Action	Approved for
Mesalamine (Asakol & Lialda)	Oral	Small Molecule	Anti-inflammatory	CD/UC
Vedolizumab	IV	Monoclonal antibody	?4?7 integrin inhibition	CD/UC
Etrolizumab	IV	Monoclonal antibody	?4?7 integrin inhibition	CD/UC
Rifaximine	Oral	Small molecule	Anti-bacterial	CD/UC

Figure 3: Table 1 :

2

Drug	Company	Type	Mechanism of Action	Status
TD-1473	Theravance Biopharma	Small Molecule	Pan-JAK and TYK inhibition	Phase 2/3
PTG-100 PTG-943	Protagonist Therapeutics	Peptide	a4b7 integrin inhibition	Phase 2
JNJ67864238 (PTG 200)	JnJ (Protagonist Therapeutics)	Monoclonal Antibody	IL23 inhibition	Phase 2
BT-11	Landos Pharma	Small Molecule	LANCL2 activation	Phase 2
BBT-401	Bridge Therapeutics	Peptide	Pellino-1 inhibition	Phase 2

Figure 4: Table 2 :

Multidonor intensive fecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. Lancet. 2017; 389:1218-28.

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[Note: 17]

Figure 5:

[Murphy et al.] , M Murphy , Y Xiong , G Pattabiraman .

[Totsika et al. ()] 'A FimH inhibitor prevents acute bladder infection and treats chronic cystitis caused by multidrug-resistant uropathogenic Escherichia coli ST131'. M Totsika , M Kostakioti , T J Hannan . *J Infec Dis* 2013. 208 p. .

[Leber et al. ()] 'Activation of LANCL2 by BT-11 ameliorates IBD by supporting regulatory T Cell stability through immunometabolic mechanisms'. A Leber , R Hontecillas , V Zoccoli-Rodriguez . *Inflam Bowel Dis* 2018. 24 p. .

[Palmela et al. ()] 'Adherentinvasive Escherichia Coli in inflammatory bowel disease'. C Palmela , C Chevarin , Z Xu . *Gut* 2018. 67 p. .

[Thurgate et al. ()] 'An overview of inflammatory bowel disease unclassified in children'. L E Thurgate , D A Lemberg , A S Day . *Inflamm Intest Dis* 2019. 4 p. .

[Harris et al. ()] 'AVX-470, an orally delivered anti-tumour necrosis factor antibody for treatment for acute ulcerative colitis: results of a first-in-human trial'. M S Harris , D Hartman , B R Lemos . *J Crohns Colitis* 2016. 10 p. .

[Bhol et al. ()] 'AVX470 -a novel oral anti TNF antibody with therapeutic potential in inflammatory bowel disease'. K C Bhol , D E Tracey , B R Lemos . *Inflam Bowel Dis* 2013. 19 p. .

[Lee et al. ()] 'BBT-401 is a selective Pellino-1 protein-protein interaction inhibitor in clinical development targeting a first-in-class drug for UC treatment'. G Lee , Y Lee , M Chang . *Inflam Bowel Dis* 2019. 25 p. S58.

[Hendrickson et al. ()] 'Clinical aspects and pathophysiology of inflammatory bowel syndrome'. B A Hendrickson , R Gokhale , J H Cho . *Clin Microbiol Rev* 2002. p. .

[Loftus ()] 'Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences'. E V LoftusJr . *Gastroenterology* 2004. 126 p. .

[Lu et al. ()] 'Computational modeling-based discovery of novel classes of antiinflammatory drugs that target lanthionine synthetase C-like protein 2'. P Lu , R Hontecillas , W T Horne . *PLOS one* 2012. 7 p. e34643.

[Keely et al. ()] 'Contribution of epithelial innate immunity to systemic protection afforded by prolyl hydroxylase inhibition in murine colitis'. S Keely , E L Campbell , A W Baird . *Mucosal Immunol* 2014. 22 p. .

[Markus ()] 'Cytokines in inflammatory bowel disease'. F N Markus . *Nat Rev Immun* 2014. p. .

[Ray et al. ()] 'Ecological and evolutionary forces shaping microbial diversity in the human intestine'. L E Ray , Peterson Da , J I Gordon . *Cell* 2006. 124 p. .

[Sandborn et al. ()] 'Efficacy and Safety of Anti-Interleukin-23 Therapy with Mirikizumab (LY3074828) in Patients with Moderate-To-Severe Ulcerative Colitis in a Phase 2 Study'. W J Sandborn , M Ferrante , B R Bhandari . *Gastroenterology* 2018. 154 p. .

[Chey et al. ()] 'Efficacy of Tenapanor in Treating Patients With Irritable Bowel Syndrome With Constipation: A 12-Week, Placebo-Controlled Phase 3 Trial (T3MPO-1)'. W D Chey , A J Lembo , D P Rosenbaum . *Am J Gastro* 2020. 115 p. .

[Artis ()] 'Epithelial cell recognition of commensal bacteria and maintenance of immune homeostasis in the gut'. D Artis . *Nat Rev Immun* 2008. 8 p. .

[Bissell et al. ()] 'Exploratory studies with BT-11: a proposed orally active therapeutic for Crohn's Disease'. P Bissell , K Boes , J Hinkley . *Int J Tox* 2016. 35 p. .

[Moschen et al. ()] 'IL-12, IL-23 and IL-17 in IBD: immunobiology and therapeutic targeting'. A Moschen , H Tilg , T Raine . *Nat. Rev. Gastro. Hep* 2019. 16 p. .

[Fakhoury et al. ()] 'Inflammatory bowel disease: clinical aspects and treatments'. M Fakhoury , R Negrulj , A Mooranian . *J Inflamm Res* 2014. 7 p. .

[King et al. ()] 'Inhibition of sodium/hydrogen exchanger 3 in the gastrointestinal tract by tenapanor reduces paracellular phosphate permeability'. A J King , M Siegel , Y He . *Sci Transl Med* 2018. 10 p. 456.

[Schreiner et al. ()] 'Mechanism-Based Treatment Strategies for IBD: Cytokines'. P Schreiner , M F Neurath , S C Ng . *JAK Inhibitors, Gut Flora, and More. Inflam Intest Dis* 2019. 4 p. . (Cell Adhesion Molecules)

[News from the Crohn's and Colitis Congress (2019)] *News from the Crohn's and Colitis Congress*, Feb 2019. Las Vegas.

[Duijvestein et al. ()] 'Novel therapies and treatment strategies for patients with inflammatory bowel disease'. M Duijvestein , R Battat , C N Cande . *Current Treatment Options in Gastroenterology* 2018. 16 p. .

[Marks et al. ()] 'Oral delivery of prolyl hydroxylase inhibitor: AKB-4924 promotes localized mucosal healing in a mouse model of colitis'. E Marks , B J Goggins , J Cordona . *Inflam Bowel Dis* 2015. 21 p. .

18 CONFLICT OF INTEREST:

[Positively Regulates Toll-like Receptor (TLR) 2 and TLR4 Signaling and Is Suppressed upon Induction of Endotoxin Tolerance ‘Positively Regulates Toll-like Receptor (TLR) 2 and TLR4 Signaling and Is Suppressed upon Induction of Endotoxin Tolerance’. *J Biol Chem* 2015. 290 p. .

[Mydock-Mcgrane et al. ()] *Rational design strategies for FimH antagonists: new drugs on the horizon for urimary tract infection and Crohn's Disease. Exp Opin Drug Disc*, L Mydock-Mcgrane , T J Hannan , J W Jenetka . 2017. 12 p. .

[Marks et al. ()] ‘Regulation of IL-12p40 by HIF Controls Th1/Th17 Responses to Prevent Mucosal Inflammation’. E Marks , C Naudin , G Nolan . *Mucosal Immunol* 2017. 10 p. .

[Alvarez et al. ()] ‘The Antiadhesive strategy in Crohn?s Disease: orally active mannosides to decolonize pathogenic escherichia coli from the gut’. D D Alvarez , A Sivignon , T Chalopini . *ChemBioChem* 2016. 17 p. .

[Kaplan ()] ‘The global burden of IBD: from 2015 to 2025’. G G Kaplan . *Nat Rev Gastro Hepatol* 2015. 12 p. .

[Bowser et al. ()] ‘The hypoxiaadenosine link during intestinal inflammation’. J L Bowser , L H Phan , H K Eltzschig . *J Immun* 2018. 200 p. .

[Leber et al. ()] ‘The Safety, tolerability, and pharmacokinetics profile of BT-11, an oral, gut-restricted Lanthionine Synthetase C-Like 2 agonist investigational new drug for inflammatory boweldisease: a randomized, double-blind, placebo-controlled phase I clinical trial’. A Leber , R Hontecillas , V Zoccoli-Rodriguez . *Inflam Bowel Dis* 2020. 26 p. .

[Colombel et al. ()] ‘Tu1744 -Targeted release oral cyclosporine (ST-0529) as a potential new therapy for ulcerative colitis: Phase I study results’. J F Colombel , J Hall , M Rosa . *Gastro* 2019. 156 p. S1108.

[Ekbom et al. ()] ‘Ulcerative colitis and colorectal cancer: a population-based study’. A Ekbom , C Helmick , M Zack . *New Eng J Med* 1990. 323 p. .