Colonic Drug Targeting Approaches for Treatment of Inflammatory Bowel Disease

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ABSTRACT

Occurrence of inflammatory bowel diseases has increased at an alarming rate. The predominant inflammatory bowel diseases are Ulcerative colitis and Crohn’s disease. The treatment and extent of therapy is decided by the severity of the conditions. The most common drugs prescribed in the treatment include anti-inflammatory agents like 5 amino salicylates, corticosteroids and immunosuppressants. Conventional therapies are inadequate and are associated with several systemic side effects due to lack to localization of active moiety at the inflamed site. Colonic drug targeting is a novel potentially active area of research intended and focused on drug delivery for treating localized disease. Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects. The present chapter discusses the novel and the latest proposed approaches of colonic drug targeting specifically concentrating the drug at inflamed site and thereby achieving successful treatment regimen.
Keywords: Inflammatory Bowel Disease; Colon, Crohn’s Disease; Ulcerative Colitis; Targeting; Azopolymers; CODES; Lectin; Timed Release; PCDS

INTRODUCTION

Inflammatory bowel disease (IBD) is an idiopathic, relapsing disease involving chronic inflammation of the digestive tract, either in part or entire. IBD primarily includes Crohn’s disease (CD) and ulcerative colitis (UC) with a high prevalence rate in the industrialized world, with North America noting the highest frequency of people suffering with CD [1]. Incidence of IBD is from 31 to 71 per 100,000 people for CD and 18-31 per 100,000 for UC and is increasing at an alarming rate. Although, adults are the most frequently diagnosed ones, reports show a significant population of paediatric is also being diagnosed with IBD [2].

CD results in inflammation throughout the digestive tract lining and this inflammation often spreads deeper into tissues. Moreover, UC results in chronic inflammation, ulcers and sores in the innermost lining of large intestine especially in colon and rectum [3]. The situation could increase the complications with diarrhoea, fatigue, pain, and weight loss and at times usher to life-threatening conditions.

The exact etiology of IBD remains unknown [4]. Nevertheless, genetic predisposition, immune malfunction, and environmental factors increase the risk of inflammation [5,6]. There is no cure for IBD. Therapeutic goals are aimed in improving the patient’s quality of life by maintaining remission, predicting, preventing and treating complications, restoring nutritional deficits, providing appropriate psychosocial support, and modifying the course in those individuals with aggressive disease [7]. Treatment of IBD majorly includes anti-inflammatory drugs, antibiotics, biologic agents, immunosuppressants or those for symptomatic relief only [7]. Commonly, two different paradigms for IBD treatment are followed. The “step-up” paradigm starts initially with milder drugs i.e. aminosalicylates, immunomodulators (corticosteroids) followed by surgery or biologics while “step-down,” follows the vice versa [8].

The current chapter deals with the different approaches for the therapeutic management of IBD encompassing conventional and novel targeting strategies.

DRUG DELIVERY STRATEGIES FOR MANAGEMENT OF IBD

An ideal drug delivery system for IBD should release the drug at the affected site of gastrointestinal tract (GIT) preferably colon with localization and reduced dosing frequency. Moreover, it should delay the release of drug in order to achieve effective concentration required for local action

Conventional Targeting Strategies

Conventional strategies studied in the management of IBD rely on the controlled and sustained delivery systems. They basically take the advantage of the GIT physiology, particularly
the colon [9]. The mechanisms used in these delivery systems can be either based on chemical modification using the prodrug approach or those based on formulation i.e. i) coating with pH sensitive polymers, ii) Time Released systems, iii) Embedding in polysaccharide matrices and iv) Azopolymeric hydrogels. The approaches are depicted in Figure 1.

Figure 1: Conventional delivery approaches in IBD via oral route [23].

Prodrug approaches

Prodrug undergoes *in vivo* biotransformation and releases the drug at the desired site. The covalent linkage between the drug and carrier is acted upon by the colonic enzymes and drug is bioavailable (Figure 2). Various colonic enzymes are azoreductase [10], glycosidase [11], xylosidase and nitroreductase [12], etc.

Figure 2: Prodrug sulphasalazine a conjugate of 5-amino salicylic acid (5-ASA) and sulphapyridine.
Robust and stable series of colon targeting compounds can be generated by conjugation of drugs with cyclodextrins, aminoacids, glucuronides etc. Covalent azo linkages between 5-aminoSalicylates (5-ASA) and carrier molecules are most common prodrugs used in IBD [13]. Similar more prodrugs used in management of IBD are cited in Table 1.

**Table 1:** Prodrug Design Strategies used in management of IBD.

<table>
<thead>
<tr>
<th>Type of conjugation</th>
<th>Drug (Trade Name)</th>
<th>Drug</th>
<th>Carriers</th>
<th>Active Bacterial Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azo-linkage</td>
<td>Sulphasalazine (Azulfidine®)</td>
<td>5-ASA</td>
<td>Sulfapyridine</td>
<td>Azoreductase</td>
</tr>
<tr>
<td></td>
<td>Balsalazide (Colazal®)</td>
<td>5-ASA</td>
<td>4-aminobenzoyl-ß-alanine</td>
<td>Azoreductase</td>
</tr>
<tr>
<td></td>
<td>Olsalazine (Dipentum®)</td>
<td>5-ASA</td>
<td>5-ASA</td>
<td>Azoreductase</td>
</tr>
<tr>
<td>Amino acid</td>
<td>5-ASA-Gly</td>
<td>5-ASA</td>
<td>Glycine</td>
<td>Pptidase</td>
</tr>
<tr>
<td>Glycoside</td>
<td>Galac-5-ASA</td>
<td>5-ASA</td>
<td>ß-D-galactose</td>
<td>Galactosidase</td>
</tr>
<tr>
<td></td>
<td>Gluco-Dex</td>
<td>Dexamethasone</td>
<td>ß-D-glucose</td>
<td>Glycosidase</td>
</tr>
<tr>
<td>Glucuronide</td>
<td>Glucu-Dex</td>
<td>Dexamethasone</td>
<td>ß-D-glucuronide</td>
<td>Glucuronidase</td>
</tr>
<tr>
<td>Cyclo- Dextrins</td>
<td>CyD-5-ASA</td>
<td>5-ASA</td>
<td>Cyclodextrin</td>
<td>Hydrolysis / Reduction</td>
</tr>
<tr>
<td>(CyD)</td>
<td>CyD-Pred</td>
<td>Prednisolone</td>
<td>Cyclodextrin</td>
<td>Hydrolysis / Reduction</td>
</tr>
<tr>
<td>Dextrans</td>
<td>Dextran-5- ASA</td>
<td>5-ASA</td>
<td>Dextran</td>
<td>Azoreductase</td>
</tr>
</tbody>
</table>

**Coating with pH-sensitive polymers**

The ileum and colon exhibit higher pH in the GIT [14]. Dosage form that can disintegrate at this high pH ranges can be easily targeted to colon and latter part of ileum. Pharmaceutical industry has been using this technique to modify dosage forms by film coating capsules and tablets with pH - sensitive biocompatible polymers. Enteric coating films dissolve at intestinal pH and thus preserve the drug from the harsh acidic pH in stomach, acidic bile and microbial degradation. In the process, an extended and delayed release profile for the drug is observed such that it is released only in the intestinal area and increase therapeutic efficacy (Figure 3).

![Figure 3: Release in pH sensitive polymer coated systems.](image-url)
Commonly used enteric polymers include derivatives of acrylic acids, co-polymers of methylacrylate (Eudragit®) and cellulose polymers such as cellulose acetate trimellate and phthalate exhibiting a threshold pH in the range 4.5 -7.0 [13]. The system has also been extended for preparing nanoparticles, microparticles and pellets. Subsequently these particles are filled in capsules. Such delivery systems (Table 2) thus improve the efficacy with site-specific drug release [15].

### Table 2: Marketed tablets using pH-sensitive polymers.

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Drug</th>
<th>Polymer</th>
<th>pH threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asacol®</td>
<td>Mesalamine</td>
<td>Eudragit-S</td>
<td>7.0</td>
</tr>
<tr>
<td>Salofac®</td>
<td>Mesalamine</td>
<td>Eudragit-L</td>
<td>6.0</td>
</tr>
<tr>
<td>Claversal®</td>
<td>Mesalamine</td>
<td>Eudragit-L</td>
<td>6.0</td>
</tr>
<tr>
<td>Calitoflak®</td>
<td>Mesalamine</td>
<td>Eudragit-L</td>
<td>6.0</td>
</tr>
</tbody>
</table>

**Time dependent release systems**

Time dependent release systems release drugs at predefined time at the desired site of GIT [15]. This approach relies on the GI transit time from mouth to colon. Usually a lag time of 5 hours (h) is considered sufficient for colon delivery as the transit time for small intestine is about 34 h. The lag time is dependent upon the gastric motility and size of dosage form. The dosage forms selectively releases the drug either by osmosis, swelling, or their combination and is unaffected by pH or microbial flora in the intestine. Pulsincap® device is based on this approach (Figure 4). The device essentially has a non-disintegrating half capsule body. The open end of the capsule is locked with a hydrogel plug and then covered with the water-soluble capsule cap. The entire capsule is then coated with any enteric polymer. Enteric coating avoids premature release in case of variable gastric emptying. On reaching the intestine, the enteric coat dissolves and the hydrogel plug starts to swell. The quantity of hydrogel is adjusted in such a way that it pops out only after the stipulated period of time and the contents are released at specific site [16].
In another similar approach, a hydrophobic material is coated upon the tablet with the surfactant. The hydrophobic admixture retains the capacity to rehydrate and re-disperse in aqueous environment in a time directly proportional to the film thickness (Figure 5). TIME CLOCK containing diltiazem hydrochloride though not available commercially is a time dependent release mechanism with site specific delivery in inflamed ileum or colon [17].
Embedding in polysaccharide matrices

Most of the polysaccharides are stable in presence of the GI enzymes. However, they are degraded in colon due to bacterial flora [13]. Amylose, chitosan, chondroitin sulphate, cyclodextrins, dextran, inulin, guar gum, pectin and locust bean gum, are among those polysaccharides known to be stable in proximal GIT, however degrades in distal GIT by colonic bacterial flora. The drug is thus released exclusively in the colon. Derivatives of polysaccharides with improved properties, stability and bioadhesion are being used lately [18,19].

Azopolymeric hydrogels

These pH- sensitive hydrogels contain acid side chains and azo aromatic cross-linker that are enzymatically degradable. At acidic pH, the hydrogels do not swell and hence exhibit minimum drug release. However, in intestinal pH the hydrogel swells with slow release of drug (Figure 6). Swelling of the hydrogels exposes the azo linkages to the enzymes. Cleavage of the azo bonds releases the drug in colon [20].
Figure 6: Azo hydrogels and its mechanism [21].

Polyanionic hydrogels made of polyacrylic acids and linked with azo aromatic cross linkers have been studied for colon targeting. These hydrogels yield minimum release of drug in the stomach. However in alkaline pH ionization of the carboxylic groups occurs and the hydrogel swells exposing the azo cross-links to azoreductase present in colon [21].

CODESTM

CODESTM utilizes the combination of all approaches used in conventional targeting strategies i.e. pH, time and bacterial flora. The system essentially consists of a trilayered coated tablet with core drug and biodegradable polysaccharides (Figure 7). The drug containing tablet core is coated with an acid soluble polymer, viz. Eudragit E. This is further coated with polysaccharide such as lactulose and subsequently coated with an enteric polymer Eudragit L. Eudragit L protects the tablet from stomach and immediately dissolves after gastric emptying. In colon region, the bacteria flora enzymatically degrade the polysaccharide (lactulose) into organic acid. This further lowers the pH and solubilizes acid soluble coating [22].
Novel strategies

Conventional targeting approaches discussed above though are designed specific to target the colon, but the variations in their specificity and release profile is not yet guaranteed. Some of the delivery systems continuously release the drug throughout the GIT. Thus these systems show reduced drug availability in the colon and chances of systemic adverse effects increases. Development of novel drug delivery systems with precise targeting and release of drug in colon is thus very crucial. Localization of drug would thus increase in inflamed intestinal tissues with increased therapeutic efficacy and reduced adverse effects [23]. The other shortcomings of the conventional strategies are summarized in Table 3.
**Table 3:** Limitations of conventional drug delivery strategies.

<table>
<thead>
<tr>
<th>Design strategy</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrugs</td>
<td>Activation of prodrugs could be affected by altered enzyme activity in case of diseased conditions.</td>
</tr>
</tbody>
</table>
| pH-dependent systems| 1) Unpredictable site-specificity of drug release because of inter-/intra subject variation  
                          2) Similarity of pH solubility of polymers in small intestine/colon |
| Time dependent systems | Transit times in small intestine though consistent, high variation in gastric retention time increases complication |
| Micro flora activated system | Altered microbial flora may influence the degradation rate of polysaccharides |

**Pressure controlled drug delivery system (PCDS)**

PCDS is based on the fact that the luminal pressure in colon is higher than that found in small intestine. PCDS bears the luminal pressure found in small intestine but collapses in high colonic pressure. This results in drug release after 3-7 h of oral administration [15]. PCDS are capsule shaped suppositories coated with water insoluble polymer ethyl cellulose. Upon oral administration, the suppository base liquefies and ethyl cellulose forms balloon. PCDS are not subjected to higher luminal pressure as sufficient fluid content is available in proximal GIT. However, re-absorption of water in colon increases the viscosity of luminal contents resulting in increased intestinal pressure. The increased pressure and high-amplitude colonic peristalsis ruptures the PCDS and releases the drug in colon [9]. Some of the products based on this mechanism are available commercially [15].

**Osmotic controlled systems**

This is a well studied mechanism used for delayed or pulsed delivery. Osmotic gradient arises due to increased water diffusion into osmotic layer. Drug and osmogen is directly compressed to form a core and this core is coated with a semipermeable membrane bearing a hole to permit the entry of intestinal fluid. This driving force results in release of drug through laser drilled holes. This system is essentially controlled by the water diffusion rate into the system and hence shows a constant zero order release. However the entire system (OROS-CT) is further coated with enteric coating so that drug is not released in upper GIT (Figure 8).
Multiparticulate drug delivery system

Single-unit delivery systems face with varied challenges viz., unpredicted disintegration during GI transit with systemic side effects and reduced bioavailability at site of action [22]. Systemic side effects of drugs used in IBD is of major concern. Multiparticulate systems are known for controlled, sustained oral drug release with better chances of local targeting and increased stability in GI conditions due to encapsulation [24]. Particulate delivery systems show higher adhesion at the site of inflammation due to increased mucus production, enhanced permeability due to disease state and particle uptake due to a number of immune cells (Figure 9). This phenomenon is found to be size dependent.

Generally particles in the range of 5–15 µm have enhanced drug residence time in the colon with increased adhesion. While some reports state that microparticles in the size range of 10–300 µm target the inflamed tissue in IBD better [22]. Encapsulation of drug also prevents drug exposure to the P-glycoprotein efflux receptors and to mucosal metabolism usually Cytochrome P450 3A. These systems can also be combined with multiple approaches like pH and time. Local bioavailability of the drug thus increases. Multiparticulate systems thus perform better than single unit systems in vivo as they can easily spread along the length of the intestine. Thus multiparticulates result in less irritation and prolonged transit in the colon with reproducible release profile [25]. Some examples on different pre-clinical studies with microparticles is given in Table 4.
Table 4: Literature reports on microparticles for IBD management.

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Polymer used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA (500-400 µm)</td>
<td>Ethyl cellulose, gelatin</td>
<td>[25]</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Enteric polymer, gelatin, guar gum</td>
<td>[26]</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Eudragit S and Ethyl cellulose(1:1)</td>
<td>[27]</td>
</tr>
<tr>
<td>5-Fluorouracil(15-35µm)</td>
<td>Eudragit S100, Chitosan</td>
<td>[28]</td>
</tr>
<tr>
<td>-</td>
<td>Ethyl cellulose, pectin alginate</td>
<td>[29]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Eudragit S 100, chitosan</td>
<td>[30]</td>
</tr>
</tbody>
</table>
Highest efficiency is found with nanoparticulates than microparticulates because of enhanced bioavailability and targeting. The small size and increased surface area of nanoparticles facilitate easy uptake by immune cells like macrophages and neutrophils in the inflamed areas. It also enhances retention at the desired site of action i.e. the mucosal layer which is thicker in inflamed areas [22]. A 3-fold uptake is observed with nanoparticles in inflamed tissues compared to healthy tissues. Particle size lower than 100nm can easily diffuse through the pores [15]. Some preclinical literature reports have been discussed in Table 5.

Table 5: Literature reports on nanoparticles for IBD management.

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Polymer used</th>
<th>Key findings</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curcumin</td>
<td>Eudragit S100, PLGA</td>
<td>Enhanced permeation and reduced TNF-α secretion</td>
<td>[31]</td>
</tr>
<tr>
<td>Budesonide (200nm)</td>
<td>EudragitFS30D, Eudragit RS 100</td>
<td>Initial burst release at acidic pH was prevented because of this approach. Sustain release at alkaline colonic pH achieved</td>
<td>[32]</td>
</tr>
<tr>
<td>Prednisolone (≈570 nm)</td>
<td>Eudragit S 100</td>
<td>Releases the drug after 4.5-hrs lag time (corresponding time to reach colon)</td>
<td>[33]</td>
</tr>
<tr>
<td>Coumarin-6(244nm)</td>
<td>Azopolyurethane, Eudragit S100</td>
<td>Sustained release because of Azopolyurethane</td>
<td>[34]</td>
</tr>
<tr>
<td>Budesonide (240nm)</td>
<td>PLGA, methyl acrylate</td>
<td>Premature release was overcome and efficacy was improved.</td>
<td>[35]</td>
</tr>
</tbody>
</table>

In one study, intravenously administered radiolabelled nano sized liposomes showed high uptake in the inflamed colonic tissue. The endothelium fenestration in the inflamed area allowed scintigraphic visualizations of the lesions in colitis model [25]. The negatively charged liposomes encapsulating drug can be aimed at IBD therapy. In UC and inflamed bowel conditions, low pH is observed in colon lumen and transferrin is found to be upregulated. Transferrin helps in accumulation of anionic liposomes in inflamed area [22]. Cellular uptake by immune cells is also observed with liposomes. However, stability of liposomes in the GI conditions and stability against lipase needs to be addressed. Non-phospholipid liposomes exhibit better stability compared to those of phospholipids. pH sensitive and mucoadhesive polymers coated upon liposomes can ensure delivery to colon following oral administration.

Active targeting approaches couple ligands to the surface of nanoparticles or liposomes permitting more specific targeting to inflamed regions within the colon. Change in cellular compositions, surface receptors and proteins due to disease can be exploited for active targeting. Monoclonal antibodies – immunoliposomes can be affixed to liposomal surface. Majority of the immuneliposome-based formulations have however been studied via the parenteral route Oral administration of immuneliposomes again possess challenges, as the antibodies can be degraded in stomach and by GIT enzymes [4].
Liposomes sized 200 - 300 nm enclosed in enteric coated capsules delivered the liposome specifically in initial segment of colon in case of UC. The lipoidal nature permitted better membrane transfer [36]. Nanostructured lipid carriers sized ~ 200 nm and with negative zeta potential incorporating budesonide reduced secretion of TNF-α by J774 cells - activated macrophages. The drug containing lipoidal carriers were much effective than blank carriers and budesonide plain suspension when tested in murine model of dextran sulfate-induced colitis. It decreased neutrophil infiltration and pro-inflammatory cytokines IL-1β [37].

Redox sensitive polymer coating

Inflamed tissues in case of IBD have higher levels of reactive oxygen species (ROS). Thus polymers containing thioketals sensitive to ROS can be used for coating dosage forms so that they get dissolved only in inflamed tissues. Upon oral administration the abnormal high levels of ROS will dissolve the polymer and provide site specific delivery [22]. Increased uptake of redox nanoparticles was also observed in ROS treated epithelial colonic cells than those with reactive oxygen species untreated cells. Similar observation was seen in vivo inflamed colon in colitis induced mice model. Indirectly the ROS decreased and inflammation also subsided. The dose response efficacy ousted the positive control 5-ASA [38]. In another example, redox nanoparticles with nitrooxide radicals in the core revealed high accumulation in colonic mucosa and cancer tissues. Hence no toxicity was observed on long term oral administration in mice. Nitrooxide radicals effectively scavenged ROS and suppressed tumor growth. Combination of redox nanoparticles with irinotecan further improved the therapeutic efficacy and suppressed the side effect [39].

FUTURE PROSPECTS

Lectin – Carbohydrate Targeting

Lectins are known for epithelial adhesion due to their sugar binding proteins [15]. Lectins get specifically bound to glycolipids or glycoproteins expressed on cell surface membranes of the intestinal mucosa [40]. They also cause cell invasion via receptor-associated endocytosis, resulting into accumulation of drugs in specific M-cells and sub-cellular organelles like lysosomes. Inflammation of colon changes the glycoconjugate expression pattern [41]. Specific binding of lectins thus holds promise in binding to the inflamed colon tissues. The immunogenicity of lectin however limits the use of lectin in drug delivery.

Nutraceuticals

IBD patients have imbalanced biodiversity with poor gut microflora and increased fungal proportion especially those with CD. Consumption of probiotics such as non-pathogenic *E. coli nissle*, *bifidobacteria*, *Lactobacilli* provide beneficial effects like anti-inflammatory, anti-diarrhoea / constipation, anti-microbial and immunomodulation. Inflammatory mediators and proinflammatoy cytokines are down regulated. *E.coli* strain nis- Sle1917 has been proved to be as
effective as mesalazine (5-ASA) in remission of UC during controlled trials [22]. *Saccharomyces boulardii* yeast maintained the remission of inactive CD in combination with mesalazine compared to mesalazine alone. Some probiotics (VSL#3) however have shown disappointing results in clinical trials [31]. More studies are needed in this direction to support the theory of admixture of drugs and probiotics or novel drug delivery systems of probiotics.

*Andrographis paniculata* exhibited potent anti-inflammatory effect with inhibition of NF-kB activity. It has been studied in experimental colitis model affecting T cell proliferation and immune response. Currently it is under phase II clinical trials.

**Bacteria Attached Nanoparticles**

Immune response increases due to proliferation of lymphocytes and macrophages in IBD. Bacteria containing nanoparticles would be easily phagocytosed by these cells. Nanoparticles loaded with anti-inflammatory agents or immune suppressants and attached to bacteria would reduce the immunological activity upon phagocytosis of bacteria attached nanoparticle. Bacteria attached to nanoparticles allows specific targeting to immune cells specifically over-expressed in inflamed colon tissues. However the studies are in primitive stage [15].

**Macrophages**

In contrast to the above mentioned approach macrophages loaded with nanoparticles *ex vivo* via phagocytosis can be re-injected into systemic circulation. These macrophages would then be used to deliver anti-inflammatory agents or immunosuppressive agents. Macrophages by default would be attracted to the site of inflammation [15].

**NEW THERAPEUTIC TARGETS IN TARGETING IBD**

Recently, anti-adhesion agent like natalizumab, vedolizumab, etc., have been reported to prevent the recruitment and adhesion of T lymphocytes to the gut mucosa and are under clinical trials. Likewise, Janus kinase inhibitors of tyrosine kinases family and chemokines such as interferon γ-inducible protein-10 and CD98 could be used as specific targets in IBD especially UC and are under clinical trials [42,43]. Inflammation is associated with upregulation of endothelial cells adhesion molecules. This could be specifically used for targeting the endothelial cells of GIT. Poly(lactic acid) and poly(ethylene glycol) particles conjugated to adhesion molecules exhibited enhanced adhesion to inflamed endothelium cells [23].

**CONCLUSION**

The ever-increasing alarming rate of IBD needs development of new and sustained efforts in design of delivery approaches in IBD. Numerous issues such as stability in GIT, bio-distribution and reduced side-effects need to be addressed to prove their superiority over existing conventional therapies.
References


6. Sartor RB. Genetics and Environmental Interactions Shape the Intestinal Microbiome to Promote Inflammatory Bowel Disease Versus Mucosal Homeostasis. Gastroenterology. 2010; 139: 1816-1819.


