SP-333, an agonist of GC-C and an analog of uroguanylin, for treatment of inflammatory bowel diseases

GC-C agonists are rapidly emerging as novel drug candidates for treatment of chronic idiopathic constipation (CC) and constipation-predominant irritable bowel syndrome (IBS-C). Our flagship drug candidate plecanatide is already in advanced stages of clinical development for treatments of CC and IBS-C (1-3). Another physiological role for GC-C agonists involves activation of a cyclic GMP signal transduction pathway that regulates homeostasis in epithelial cells lining the gastrointestinal (GI) mucosa (4).

Inflammatory bowel disease (IBD) is a group of gastrointestinal inflammatory diseases consisting of Crohn's disease and ulcerative colitis. Incidence of IBD is increasing worldwide (5). The diseases generally begin in young adulthood and last throughout life (5). Although the etiology of IBD is still not clearly understood, generally it is considered a hyper-proliferative disease, involving morphological and cellular transformation, due largely to deregulation of apoptosis, resulting in uncontrolled cellular proliferation in the GI mucosa (6).

The intestinal epithelium is constantly undergoing a dynamic renewal process within the GI mucosa, removing damaged cells, and replacing them with new epithelial cells (7). Any imbalance in this homeostasis process, due to reduced expression of uroguanylin, can lead to higher proliferative rates in the intestinal mucosa, resulting in inflammation, cancer and other diseases in the GI tract (4, 8). Indeed, expression of
mRNAs encoding uroguanylin and a sister peptide guanylin are markedly suppressed in colon polyps and tumors (9). Similarly, reduced expression of uroguanylin is also observed in inflamed tissue from patients with Crohn’s disease and ulcerative colitis (10). Moreover, treatment of T84 cells with uroguanylin induces apoptosis and inhibits T84 proliferation via a cGMP-dependent mechanism (9).

Functional integrity of the intestinal mucosa and its barrier function depend on a number of factors, including: coordinated replenishment of the mucus layer, maintenance of intercellular tight junctions, and continual renewal of epithelial cells lining the GI mucosa (4). The GI mucus layer overlying the epithelium provides the first line of defense against physical and chemical injury caused by ingested food, microbes and microbial products. Depletion of this mucus layer, known to closely associate with disruption in intestinal barrier function, has been implicated as one of the primary factors in the pathogenesis of IBD as well as irritable bowel syndrome (11). Recently, it was shown that loss of GC-C signaling in transgenic knock-out mice (GC-C -/- and uroguanylin -/-) resulted in increased permeability and in disruption of intestinal barrier function (12).

Taken together, these findings suggest that GC-C agonists mediate not only intestinal electrolyte and water transport but also intestinal epithelial cell growth and differentiation. Normal functioning of GC-C signaling might also be critical for regulation of the renewal process in the GI mucosa, and for maintenance of the intestinal barrier function (4). A therapeutic approach utilizing an oral GC-C agonist to augment intestinal
GC-C activation represents a novel approach for restoring mucosal barrier function and suppressing inflammation.

SP-333, an analog of UG, is designed to be a more proteolytically stable version of uroguanylin, exhibiting considerably higher resistance to proteolysis in simulated gastric fluid, and in simulated intestinal fluid (13). SP-333 is a synthetic hexa-decapeptide designed to mimic the actions of the natriuretic peptide uroguanylin, a member of the guanylin family of enteric peptides.

A formulation of SP-333 is presently being developed for use in patients with ulcerative colitis.

The anti-inflammatory mechanism-of-action of SP-333 has been elucidated through a number of cell culture, colon explant culture and animal studies (8-10).
In experimental models of colitis in mice, oral treatment with SP-333 ameliorates GI inflammation, possibly through inhibition of NF-κB signaling to suppress production of pro-inflammatory cytokines (12, 13). In addition, oral treatment with GC-C agonists also delays formation of colonic tumors in mice (14, 15, 16). A Phase I clinical trial of SP-333 in healthy volunteers is currently underway.
Cited References:
inflammatory bowel diseases. Annual meeting of Neurogastroenterology (NGM) held in Luzern, Switzerland.
