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## SP-304 Science

### SP-304 – A Platform to Treat Gastrointestinal Disease

SP-304 is an analog of a natural hormone peptide called uroguanylin - a key regulator of intestinal function. Details of the biology of the guanylate cyclase C receptor and the therapeutic potential of SP-304 in GI diseases are discussed below.

### Uroguanylin and the Guanylate Cyclase C Receptor

Uroguanylin was discovered in the early 1990's by Drs. Leonard Forte and Mark Currie and their research teams (1, 2). It is secreted among other places in the intestinal tract and there functions by binding to a unique receptor found on epithelial cells of the intestine. This receptor, the guanylate cyclase C receptor or GC-C, mediates the synthesis of intracellular cyclic GMP (cGMP), a key regulator of cellular functions. Uroguanylin works as an "agonist" of this receptor – binding of uroguanylin activates the receptor and promotes the intracellular synthesis of cGMP. cGMP in turn regulates a number of biochemical and physiological responses that have important implications in the treatment of several gastrointestinal disorders as well as colon cancer.

Certain bacteria, including *E. coli*, produce an enterotoxin called ST-peptide that is structurally related to uroguanylin. This peptide over-activates the GC-C receptor and promotes an unregulated fluid transport into the intestine, producing what is commonly called travelers diarrhea.

### The Development of SP-304

Uroguanylin is a linear peptide comprised of 16 amino acids that is folded into a three-dimensional structure (or conformation) containing two intra-molecular disulfide linkages. This spatial structure and rigidity gives the hormone considerable stability in the intestinal tract. In addition, uroguanylin is quite temperature and protease resistant, but not sufficient enough to permit its use as a direct pharmacological agent. The native uroguanylin peptide also assumes active and inactive conformers in aqueous solution, reducing the overall potency of the natural hormone.

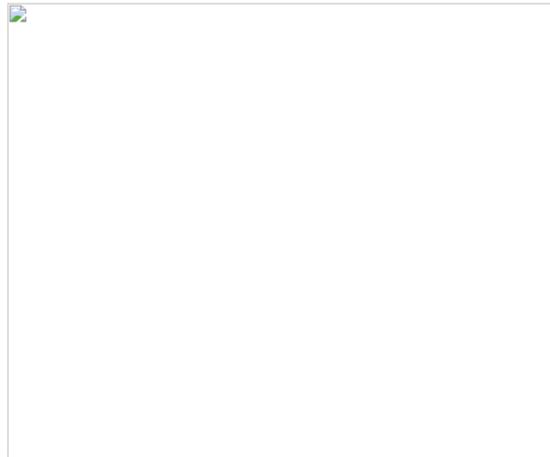
In 2000, Callisto scientists headed by Dr. Kunwar Shailubhai used structure-function studies to develop a series of analogs of uroguanylin that were tested for biological activity and stability. This research effort led to the creation of SP-304. By changing just one key amino acid in uroguanylin the Callisto team created a compound that has superior pharmacological properties compared to uroguanylin (3). Unlike uroguanylin, SP-304 primarily exists in a single bioactive conformation. The compound is stable, protease resistant and more potent than uroguanylin. It can be given orally, and is not systemically absorbed (i.e. taken up in the blood and distributed throughout the body) which means that the compound is likely to be very safe in clinical use. Since the GC-C receptors are found on the inside of the gastrointestinal lining, systemic absorption is not needed for SP-304 to function as intended. The compound exerts its action locally in the intestines.

### GC-C agonists for treatment of chronic constipation and IBS-C

Water plays a vital physiological role in the intestine. Proper water content of the intestinal lumen ensures normal transport of the content through the bowel. Water also facilitates maintenance of the intestinal mucus layer, which protects the GI mucosa from mechanical damage and the harmful effects of stomach acid and bacterial or viral pathogens. Too low water content can cause constipation, whereas too high water content, as occurs in diseases like cholera and toxic *E. coli* infections, typically leads to diarrhea. One of the major functions of uroguanylin is to regulate fluid and ion transport into the lumen of the intestine.

In the GI tract uroguanylin is produced by goblet cells and excreted into the lumen of the intestine. Uroguanylin then diffuses within the intestine to GC-C receptors on epithelial cells.

Uroguanylin Function as Fluid Regulator in Intestine



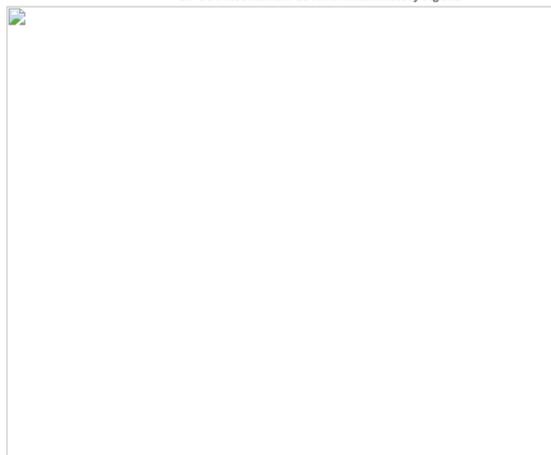
Upon activation, the GC-C receptor promotes the intracellular synthesis of cGMP, which in turn eventually activates the cystic fibrosis transmembrane receptor (CFTR) on these cells (CFTR is not related to cystic fibrosis in this location). The CFTR next secretes chloride and bicarbonate ions to regulate the salt content of the intestinal lumen. Water is also carried with the salt ions. The end effect is a secretion of salts and water into the intestine, resulting in a looser intestine content that is more easily transported through the bowel.

Agonists of GC-C receptor provide a novel approach to the treatment of chronic idiopathic constipation and constipation predominant irritable bowel syndrome (IBS-C). By using a GC-C receptor agonist to promote fluid and ion transport into the intestine, it is possible to counteract the reduced motility and intestinal blockage common in constipation and IBS-C. GC-C receptor agonists have been clinically validated. Recent clinical data

#### SP-304 for treatment of Ulcerative Colitis

The GC-C pathway also regulates the anti-inflammatory effects of mediators such as nitric oxide and hemoxygenase-1. Therapies that induce cGMP (phosphodiesterase-4 inhibitors) demonstrate efficacy in murine models of inflammatory bowel disease (IBD). SP-304 was recently shown to produce anti-inflammatory effects in animal models of ulcerative colitis, including TNBS- and DSS-induced colitis in mice (6). Importantly, the reduced inflammation was associated with down-regulation of key pro-inflammatory cytokines including IL-4, IL-5, IL-23, and TNF (7). SP-304 treatment also down-regulates production of cyclooxygenase-2 (COX-2) mediated production of prostaglandin E2 (PGE<sub>2</sub>), which is an important inflammatory second messenger.

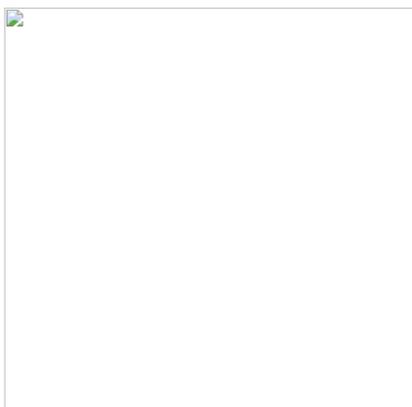
#### SP-304 Mechanism as Anti-Inflammatory Agent



#### SP-304 for prevention and control of colon cancer

Recent studies demonstrate that uroguanylin as well as a similar human intestinal hormone guanylin are key regulators of growth and apoptosis in the epithelial layer of the intestinal mucosa (8). Disruption and/or irregularities in the turnover of cells, as is the case with individuals displaying reduced levels of endogenous uroguanylin, can lead to the development of polyps, colon cancer and inflammatory bowel diseases. Treatment of colon carcinoma cells with uroguanylin or with ST peptide was shown to inhibit cell proliferation and to induce apoptosis in a dose-dependent manner (9, 10).

#### Induction of Cell Apoptosis Through Uroguanylin



A deficiency of uroguanylin is thought to be one of the primary reasons for the development of polyps in the colon, considerably increasing the risk of colon cancer. Oral treatment with uroguanylin in an animal model of colon cancer, the Apc +/min mouse, showed that uroguanylin inhibits polyp formation and also retards the progression of polyps to adenocarcinomas (10). These mice are genetically engineered such that they mimic the etiology of colon carcinogenesis in humans. Thus, SP-304 has potential as an agent both to treat and prevent colon and other GI cancers.

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