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(54) **GUANYLATE CYCLASE RECEPTOR  
AGONISTS FOR THE TREATMENT OF  
TISSUE INFLAMMATION AND  
CARCINOGENESIS**

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**514/10; 514/13**

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**530/300, 326; 514/10, 13**  
See application file for complete search history.

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(57) **ABSTRACT**

A method of treatment of inflamed, pre-cancerous or can-  
cerous tissue or polyps in a mammalian subject is disclosed.  
The treatment involves administration of a composition of at  
least one peptide agonist of a guanylate cyclase receptor  
and/or other small molecules that enhance intracellular  
production of cGMP. The at least one peptide agonist of a  
guanylate cyclase receptor may be administered either alone  
or in combination with an inhibitor of cGMP-dependent  
phosphodiesterase. The inhibitor may be a small molecule,  
peptide, protein or other compound that inhibits the degra-  
dation of cGMP. Without requiring a particular mechanism  
of action, this treatment may restore a healthy balance  
between proliferation and apoptosis in the subject's popu-  
lation of epithelial cells, and also suppress carcinogenesis.  
Thus, the method may be used to treat, inter alia, inflam-  
mation, including gastrointestinal inflammatory disorders,  
general organ inflammation and asthma, and carcinogenesis  
of the lung, gastrointestinal tract, bladder, testis, prostate and  
pancreas, or polyps.

**6 Claims, No Drawings**

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**GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS**

**CROSS REFERENCE TO RELATED APPLICATIONS**

The present application claims the benefit of U.S. provisional application No. 60/348,646, filed on Jan. 17, 2002.

**FIELD OF THE INVENTION**

The present invention relates to the therapeutic use of guanylate cyclase receptor agonists as a means for enhancing the intracellular production of cGMP. The agonists may be used either alone or in combination with inhibitors of cGMP-specific phosphodiesterase to prevent or treat cancerous, pre-cancerous and metastatic growths, particularly in the gastrointestinal tract and lungs. In addition, the agonists may be used in the treatment of inflammatory disorders such as ulcerative colitis and asthma.

**BACKGROUND OF THE INVENTION**

Uroguanylin, guanylin and bacterial ST peptides are structurally related peptides that bind to a guanylate cyclase receptor and stimulate intracellular production of cyclic guanosine monophosphate (cGMP) (1-6). This results in the activation of the cystic fibrosis transmembrane conductance regulator (CFTR), an apical membrane channel for efflux of chloride from enterocytes lining the intestinal tract (1-6). Activation of CFTR and the subsequent enhancement of transepithelial secretion of chloride leads to stimulation of sodium and water secretion into the intestinal lumen. Therefore, by serving as paracrine regulators of CFTR activity, cGMP receptor agonists regulate fluid and electrolyte transport in the GI tract (1-6; U.S. Pat. No. 5,489,670).

The process of epithelial renewal involves the proliferation, migration, differentiation, senescence, and eventual loss of GI cells in the lumen (7,8 ). The GI mucosa can be divided into three distinct zones based on the proliferation index of epithelial cells. One of these zones, the proliferative zone, consists of undifferentiated stem cells responsible for providing a constant source of new cells. The stem cells migrate upward toward the lumen to which they are extruded. As they migrate, the cells lose their capacity to divide and become differentiated for carrying out specialized functions of the GI mucosa (9). Renewal of GI mucosa is very rapid with complete turnover occurring within a 24-48 hour period (9). During this process mutated and unwanted cells are replenished with new cells. Hence, homeostasis of the GI mucosa is regulated by continual maintenance of the balance between proliferation and apoptotic rates (8 ).

The rates of cell proliferation and apoptosis in the gut epithelium can be increased or decreased in a wide variety of different circumstances, e.g., in response to physiological stimuli such as aging, inflammatory signals, hormones, peptides, growth factors, chemicals and dietary habits. In addition, an enhanced proliferation rate is frequently associated with a reduction in turnover time and an expansion of the proliferative zone (10). The proliferation index has been observed to be much higher in pathological cases of ulcerative colitis and other GI disorders (11). Thus, intestinal

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In addition to a role for uroguanylin and guanylin as modulators of intestinal fluid and ion secretion, these peptides may also be involved in the continual renewal of GI mucosa. Previously published data in WO 01/25266 suggests a peptide with the active domain of uroguanylin may function as an inhibitor of polyp development in the colon and may constitute a treatment of colon cancer. However, the mechanism by which this is claimed to occur is questionable in that WO 01/25266 teaches uroguanylin agonist peptides that bind specifically to a guanylate cyclase receptor, termed GC-C, that was first described as the receptor for *E. coli* heat-stable enterotoxin (ST) (4). Knockout mice lacking this guanylate cyclase receptor show resistance to ST in intestine, but effects of uroguanylin and ST are not disturbed in the kidney in vivo (3). These results were further supported by the fact that membrane depolarization induced by guanylin was blocked by genistein, a tyrosine kinase inhibitor, whereas hyperpolarization induced by uroguanylin was not effected (12,13). Taken together these data suggest that uroguanylin also binds to a currently unknown receptor, which is distinct from GC-C.

Other papers have reported that production of uroguanylin and guanylin is dramatically decreased in pre-cancerous colon polyps and tumor tissues (14-17). In addition, genes for both uroguanylin and guanylin have been shown to be localized to regions of the genome frequently associated with loss of heterozygosity in human colon carcinoma (18-20). Taken together, these findings indicate that uroguanylin, guanylin and other peptides with similar activity may be used in the prevention or treatment of abnormal colon growths. This proposal is bolstered by a recent study demonstrating oral administration of uroguanylin inhibits polyp formation in mice (15,16).

Uroguanylin and guanylin peptides also appear to promote apoptosis by controlling cellular ion flux. Alterations in apoptosis have been associated with tumor progression to the metastatic phenotype. While a primary gastrointestinal (GI) cancer is limited to the small intestine, colon, and rectum, it may metastasize and spread to such localities as bone, lymph nodes, liver, lung, peritoneum, ovaries, brain. By enhancing the efflux of K<sup>+</sup> and influx of Ca<sup>++</sup>, uroguanylin and related peptides may promote the death of transformed cells and thereby inhibit metastasis.

One of the clinical manifestations of reduced CFTR activity is the inflammation of airway passages (21). This effect may be due to CFTR regulating the expression of NF-KB, chemokines and cytokines (22-25). Recent reports have also suggested that the CFTR channel is involved in the transport and maintenance of reduced glutathione, an antioxidant that plays an important role in protecting against inflammation caused by oxidative stress (39). Enhancement of intracellular levels of cGMP by way of guanylate cyclase activation or by way of inhibition of cGMP-specific phosphodiesterase would be expected to down-regulate these inflammatory stimuli. Thus, uroguanylin-type agonists should be useful in the prevention and treatment of inflammatory diseases of the lung (e.g., asthma), bowel (e.g., ulcerative colitis and Crohn's disease), pancreas and other organs.

Overall, it may be concluded that agonists of guanylate cyclase receptor such as uroguanylin have potential therapeutic value in the treatment of a wide variety of inflammatory conditions, cancer (particularly colon cancer) and

## SUMMARY OF THE INVENTION

The present invention is based upon the development of new agonists of guanylate cyclase receptor, and new uses of naturally occurring agonists. The agonists are analogs of uroguanylin, many of which have superior properties either in terms of improved receptor activation, stability, activity at low pH or reduced adverse effects. The peptides may be used to treat any condition that responds to enhanced intracellular levels of cGMP. Intracellular levels of cGMP can be increased by enhancing intracellular production of cGMP and/or by inhibition of its degradation by cGMP-specific phosphodiesterases. Among the specific conditions that can be treated or prevented are inflammatory conditions, cancer, polyps, and metastasis.

In its first aspect, the present invention is directed to a peptide consisting essentially of the amino acid sequence of any one of SEQ ID NOs:2-21 and to therapeutic compositions which contain these peptides. The term "consisting essentially of" includes peptides that are identical to a recited sequence identification number and other sequences that do not differ substantially in terms of either structure or function. For the purpose of the present application, a peptide differs substantially if its structure varies by more than three amino acids from a peptide of SEQ ID NOs:2-21 or if its activation of cellular cGMP production is reduced or enhanced by more than 50%. Preferably, substantially similar peptides should differ by no more than two amino acids and not differ by more than about 25% with respect to activating cGMP production. The most preferred peptide is a bicycle having the sequence of SEQ ID NO:20.

The peptides may be in a pharmaceutical composition in unit dose form, together with one or more pharmaceutically acceptable excipients. The term "unit dose form" refers to a single drug delivery entity, e.g., a tablet, capsule, solution or inhalation formulation. The amount of peptide present should be sufficient to have a positive therapeutic effect when administered to a patient (typically, between 100 µg and 3 g). What constitutes a "positive therapeutic effect" will depend upon the particular condition being treated and will include any significant improvement in a condition readily recognized by one of skill in the art. For example, it may constitute a reduction in inflammation, a shrinkage of polyps or tumors, a reduction in metastatic lesions, etc.

The invention also encompasses combination therapy utilizing a guanylate cyclase receptor agonist administered either alone or together with an inhibitor of cGMP-dependent phosphodiesterase, an anti-inflammatory agent or an anticancer agent. These agents should be present in amounts known in the art to be therapeutically effective when administered to a patient. Anti-neoplastic agents may include alkylating agents, epipodophyllotoxins, nitrosoureas, anti-metabolites, vinca alkaloids, anthracycline antibiotics, nitrogen mustard agents, and the like. Particular anti-neoplastic agents may include tamoxifen, TAXOL™, etoposide and 5-fluorouracil. Antiviral and monoclonal antibody therapies may be combined with chemotherapeutic compositions comprising at least one guanylate cyclase receptor agonist in devising a treatment regimen tailored to a patient's specific needs.

In another aspect, the invention is directed to a method for preventing, treating or retarding the onset of cancer, particularly cancer of epithelial cells, or polyps in a subject by administering a composition comprising an effective amount of a guanylate cyclase receptor agonist, preferably a synthetic agonist, such as uroguanylin. The term "synthetic"

increase intracellular levels of cGMP. The term "synthetic" refers to a peptide created to bind a guanylate cyclase receptor, but containing certain amino acid sequence substitutions not present in known endogenous guanylate cyclase agonists, such as uroguanylin. The agonist should be a peptide selected from those defined by SEQ ID NOs:2-21 and which are listed in Tables 2 and 3. Also included in the invention are methods of treating primary cancers, other than primary colon cancer, by administering an effective dosage of a peptide selected from the group consisting of: uroguanylin; guanylin; and *E. coli* ST peptide. Any known form of uroguanylin or guanylin can be used for this purpose, although the human peptides are preferred.

The invention also includes methods of preventing or treating tumor metastasis from a primary tumor mass. Metastatic tumor cells having guanylate cyclase receptors may be targeted by peptides generated according to the invention. In a preferred embodiment, the targeted receptor is found on cells of gastrointestinal (GI) cancers and on metastasized cells derived from those cancers. Such receptors are typically transmembrane proteins with an extracellular ligand-binding domain, a membrane-spanning domain, and an intracellular domain with guanylate cyclase activity. Although the invention is not bound by any particular mechanism of action, it is believed that the peptides will act by binding to these cellular receptors and inducing apoptosis. Metastatic tumors may also be treated by administering any known form of uroguanylin or guanylin (preferably human) or by administering *E. coli* ST peptide.

Peptides may be administered either alone or together with one or more inhibitors of cGMP dependent phosphodiesterase. Examples of cGMP dependent phosphodiesterase inhibitors include suldinac sulfone, zaprinast, and motapizone. Treatable forms of cancer include breast cancer, colorectal cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, and testicular cancer. Colon carcinogenesis may be prevented by inhibiting precancerous colorectal polyp development via administration of a composition according to the invention. It is believed that the peptides should be especially effective with respect to the treatment of colon cancer and in preventing the metastasis of colon tumors.

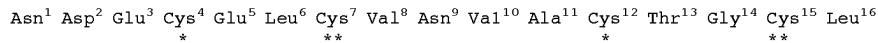
In another aspect, the invention is directed to a method for treating, preventing, or retarding the onset of organ inflammation (e.g., inflammation associated with the GI tract, asthma, nephritis, hepatitis, pancreatitis, bronchitis, or cystic fibrosis) of a subject by administering a composition comprising an agonist of a guanylate cyclase receptor that enhances intracellular production of cGMP. Preferred peptide agonists are selected from the group defined by SEQ ID NOs:2-21 shown in Tables 2 and 3, or uroguanylin, or guanylin, or *E. coli* ST peptide. These peptides may optionally be administered with one or more inhibitors of cGMP dependent phosphodiesterase, e.g., suldinac sulfone, zaprinast, or motapizone. In a preferred embodiment, the invention is directed to a method of treating an inflammatory disorder in a mammalian gastrointestinal tract. The inflammatory disorder may be classified as an inflammatory bowel disease, and more particularly may be Crohn's disease or ulcerative colitis. Administration may be enteric, and employ formulations tailored to target enterocytes.

In a broader sense, the invention includes methods of inducing apoptosis in a patient by administering an effective amount of a peptide having the sequence of any one of SEQ ID NO:2-SEQ ID NO:21, or uroguanylin, or guanylin or *E. coli* ST peptide. An "effective amount" is sufficient to

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a target tissue. For example, sufficient peptide may be given to induce an increased rate of cell death in a neoplastic growth.

The most preferred peptide for use in the methods described above is the peptide defined by SEQ ID NO:20. The sequence is as follows (see also Table 3):



and wherein there is one disulfide linkage between the cysteine at position 4 and the cysteine at position 12; and a second disulfide linkage between the cysteine at position 7 and the cysteine at position 15 (SEQ ID NO:20). This peptide has been found to have enhanced biological activity as an agonist of cGMP production due to its enhanced binding constant for the guanylate cyclase receptor, and is superior to uroguanylin with regard to temperature and protease stability and with regard to its biological activity at the physiologically favorable pH range (pH 6 to 7) in the large intestine.

The guanylate cyclase receptor agonists used in the methods described above may be administered either orally, systemically or locally. Dosage forms include preparations for inhalation or injection, solutions, suspensions, emulsions, tablets, capsules, topical salves and lotions, transdermal compositions, other known peptide formulations and pegylated peptide analogs. An effective dosage of the composition will typically be between about 1 µg and about 10 mg per kilogram body weight, preferably between about 10 µg to 5 mg of the compound per kilogram body weight. Adjustments in dosage will be made using methods that are routine in the art and will be based upon the particular composition being used and clinical considerations. Agonists may be administered as either the sole active agent or in combination with other drugs, e.g., an inhibitor of cGMP-dependent phosphodiesterase. In all cases, additional drugs should be administered at a dosage that is therapeutically effective using the existing art as a guide. Drugs may be administered in a single composition or sequentially.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based upon several concepts. The first is that there is a cGMP-dependent mechanism which regulates the balance between cellular proliferation and apoptosis and that a reduction in cGMP levels, due to a deficiency of uroguanylin/guanylin and/or due to the activation of cGMP-specific phosphodiesterases, is an early and critical step in neoplastic transformation. A second concept is that the release of arachidonic acid from membrane phospholipids, which leads to the activation of cPLA<sub>2</sub>, COX-2 and possibly 5-lipoxygenase during the process of inflammation, is down-regulated by a cGMP-dependent mechanism, leading to reduced levels of prostaglandins and leukotrienes, and that increasing intracellular levels of cGMP may therefore produce an anti-inflammatory response. In addition, a cGMP-dependent mechanism, is thought to be involved in the control of proinflammatory processes. Therefore, elevating intracellular levels of cGMP

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disease and other organ inflammation (e.g., associated with asthma, nephritis, hepatitis, pancreatitis, bronchitis, cystic fibrosis).

Without intending to be bound by any theory, it is envisioned that ion transport across the plasma membrane may prove to be an important regulator of the balance

between cell proliferation and apoptosis that will be affected by compositions altering cGMP concentrations. Uroguanylin has been shown to stimulate K<sup>+</sup> efflux, Ca<sup>++</sup> influx and water transport in the gastrointestinal tract (3). Moreover, atrial natriuretic peptide (ANP), a peptide that also binds to a specific guanylate cyclase receptor, has also been shown to induce apoptosis in rat mesangial cells, and to induce apoptosis in cardiac myocytes by a cGMP mechanism (26–29). It is believed that binding of the present agonists to a guanylate cyclase receptor stimulates production of cGMP. This ligand-receptor interaction, via activation of a cascade of cGMP-dependent protein kinases and CFTR, is then expected to induce apoptosis in target cells. Therefore, administration of the novel peptides defined by SEQ ID NOs:2–21, as shown in Tables 2 and 3, or uroguanylin, or guanylin or *E. coli* ST peptide is expected to eliminate or, at least retard, the onset of inflammatory diseases of the GI tract and general organ inflammation (e.g., asthma, nephritis, hepatitis, pancreatitis, bronchitis, cystic fibrosis).

In another aspect, the invention is directed to a method for preventing, treating or retarding the onset of cancer, particularly cancer of epithelial cells, in a subject by administering a composition comprising an effective amount of a guanylate cyclase receptor agonist, preferably a synthetic guanylate cyclase receptor agonist. The term “effective amount” refers to sufficient agonist to measurably increase intracellular levels of cGMP. The term “synthetic” refers to a peptide created to bind a guanylate cyclase receptor, but containing certain amino acid sequence substitutions not present in known endogenous guanylate cyclase agonists, such as uroguanylin. The agonist should be a peptide selected from those defined by SEQ ID NOs:2–21 and which are listed in Tables 2 and 3. Also included in the invention are methods of treating primary and metastatic cancers, other than primary colon cancer, by administering an effective dosage of a peptide selected from the group consisting of: uroguanylin; guanylin; and *E. coli* ST peptide. Any known form of uroguanylin or guanylin can be used for this purpose, although the human peptides are preferred.

The cGMP-dependent mechanism that regulates the balance between cellular proliferation and apoptosis in metastatic tumor cells may serve as a mechanism for targeting and treating metastatic tumors. The liver is the most common site of metastasis from a primary colorectal cancer. Toward later stages of disease, colorectal metastatic cells may also invade other parts of the body. It is important to note that metastatic cells originating from the primary site in the gastrointestinal tract typically continue to express guanylate cyclase receptors and therefore, these cells should be sensitive to apoptosis therapy mediated by intestinal guanylate cyclase receptors. Peptides having uroguanylin activity enhanced with a specific combination with specific

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