A/PROV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
REQUEST FOR FILING PROVISIONAL PATENT APPLICATION
Under 35 USC 111(b)
(Not for DESIGN cases)

Box: PROVISIONAL APPLICATION

Hon. Commissioner of Patents
Washington, D.C. 20231

PROVISIONAL APPLICATION
Under Rule 53(c)

00909

Sir:

Herewith is a PROVISIONAL APPLICATION
Title: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS

Atty. Dkt. PW 284936 (M#) | (Client Ref)

Including:

Date: January 17, 2002

1. Specification: 31 pages 2. ☐ Specification in non-English language 3. ☐ Drawings: _____ sheet(s)
4. The invention ☐ was ☒ was not made by, or under a contract with, an agency of the U.S. Government.
If yes, Government agency/contact # = _____
5. ☐ Attached is an assignment and cover sheet. Please return the recorded assignment to the undersigned.
6. Small Entity Status ⌀ ☒ is Not claimed ☐ is claimed (**pre**-filing confirmation **required**)
NOTE: Do NOT File IDS!
7. ☐ Attached:
8. This application is made by the following named inventor(s) **(Double check instructions for accuracy.):**

(1) Inventor	Kunwar		**SHAILUBHAI**
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(5) Inventor			
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Residence			
	City	State/Foreign Country	Country of Citizenship

9. NOTE: FOR ADDITIONAL INVENTORS, check box ☐ and attach sheet (PAT102A) with same information regarding additional inventors.

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	Large/Small Entity		Fee Code
10. Filing Fee	$160/$80	+160	114/214
11. If "non-English" box 2 is X'd, add Rule 17(k) processing fee	$130	+0	139
12. If "assignment" box 5 is X'd, add recording fee.	$40	+0	581
13.	TOTAL FEE ENCLOSED =	$160	

Our Deposit Account No. 03-3975
Our Order No. 81361 (C#) | 284936 (M#)


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Pillsbury Winthrop LLP
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NOTE: File in duplicate with 2 post card receipts (PAT-103) & attachments

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APPLICATION UNDER UNITED STATES PATENT LAWS

Atty. Dkt. No. PW 284936
(M#)

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

Inventor (s): Kunwar SHAILUBHAI
Gregory V. NIKIFOROVICH
Gary S. JACOB

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Pillsbury Winthrop LLP

This is a:

- ☒ Provisional Application
- ☐ Regular Utility Application
- ☐ Continuing Application
  - ☒ The contents of the parent are incorporated by reference
- ☐ PCT National Phase Application
- ☐ Design Application
- ☐ Reissue Application
- ☐ Plant Application
- ☐ Substitute Specification
  Sub. Spec Filed ____________
  in App. No. ______/______
- ☐ Marked up Specification re
  Sub. Spec. filed ____________
  In App. No ______/______

SPECIFICATION

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Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis

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 and pre-cancerous growths, particularly in the gastrointestinal tract, pancreas and lungs. In addition, the agonists may be used in the treatment of inflammatory disorders and asthma.

Background of the Invention

Uroguanylin, guanylin and bacterial ST peptides are structurally related agonist peptides that bind to a guanylate cyclase receptor and stimulate intracellular production of cyclic guanosine monophosphate (cGMP) (8-13). This can result in activation of the cystic fibrosis transmembrane conductance regulator (CFTR), an apical membrane channel for efflux of chloride from enterocytes lining the intestinal tract (8-13). Activation of CFTR and the subsequent enhancement of transepithelial secretion of chloride leads to stimulation of sodium (Na^+) and water secretion into the intestinal lumen. Therefore, one of the physiological functions of these hormones is the regulation of fluid and electrolyte transport in the GI tract by serving as paracrine regulators of CFTR activity (8-13).

One of the major clinical manifestations of defective mutations in CFTR is excessive inflammation in airway passages (19), implying that CFTR is involved in control of proinflammatory signaling pathways, particularly via regulation of expression of NF-kB, chemokines and cytokines (20-22). Several lines of evidence suggest that CFTR dysfunction influences production of some of these molecules (23). Exactly how CFTR dysfunction contributes to the activation of and nuclear localization of NF-KB is unclear. One of the possible mechanisms could be via regulation of intracellular levels of K+/Na+ and via regulation of acidity (pH) of specific intracellular compartments affecting relevant kinase and phosphatase activities (24). Recent reports have noted that the CFTR channel is also involved in transport and maintenance of reduced glutathione, an antioxidant that plays an important role in protection against oxidative stress and free-radical mediated cell damage. It is also very

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well established that excessive oxidative stress is one of the primary reasons for activation of NF-KB and in pathogenesis of inflammatory diseases and cancer (25).

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 A1 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, as WO 01/25266 A1 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) (26). In contrast, uroguanylin was shown to activate K^+ conductance via a so far unknown receptor distinct from GC-C (27). This conclusion was 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. Taken together these data suggest that uroguanylin binds to a currently unknown receptor, which is distinct from GC-C (27).

Several lines of evidence have implicated efflux of K^+ and influx of Ca^{++} in the induction of apoptosis. First, staphylococcal α-toxin has been shown to induce apoptosis by selectively decreasing the intracellular concentrations of monovalent cations. Second, apoptotic and shrunken cells have been shown to contain reduced levels of intracellular K^+ as compared to those in normal cells. Third, an intracellular concentration of K^+ in excess of 150 mM has been shown to inhibit apoptosis by inhibiting proapoptotic nucleases such as caspase-3. Finally, activation of K^+ efflux and Ca^{++} influx has been shown to stimulate enzymatic activities of several nucleases that play critical roles in the induction of apoptosis (28-32).

The therapeutic benefits of non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of familial adenomatous polyposis, certain other cancers and in inflammatory diseases are well documented and impressive. However, the mechanisms by which NSAIDs act to reduce inflammatory signals and tumorigenesis remain unclear. NSAIDs are known to bind and inhibit the cyclooxygenase (COX) enzymes, COX-1 and COX-2, which produce prostaglandins (PGs). A role for PGs in promoting inflammation and tumorigenesis is very well supported by the observations that, relative to normal tissue, inflamed tissues and tumor

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