IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION

REQUEST FOR FILING APPLICATION
Under Rule 53(a), (b) & (f)
(No Filing Fee or Oath/Declaration)
(Do NOT use for Provisional or PCT Applications)
Use for Design or Utility Applications

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RULE 53(f) NO DECLARATION

Hon. Commissioner of Patents
Washington, DC 20231

Atty. Dkt. P 284943 (M#) | N/A (Client Ref)

Date: March 28, 2002

Sir:

1. This is a Request for filing a new Patent Application(☐ Design ☒ Utility) entitled:

2. (Complete) Title: Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis

without a filing fee or Oath/Declaration but for which is enclosed the following:

3. ☒ Abstract 1 page(s).

4. 24 Pages of Specification (only spec. and claims); 5. ☐ Specification in non-English language

6. 27 Numbered claim(s); and

7. ☐ Drawings: _____ sheet(s) ☐ 1 set informal; 8. ☐ formal of size: ☐A4 ☐11"

9. **DOMESTIC/INTERNATIONAL** priority is claimed under 35 USC 119(e)/120/365(c) based on the following provisional, nonprovisional and/or PCT international application(s):

Application No.	Filing Date	Application No.	Filing Date
(1) 60/279,438	March 29, 2001	(2) 60/279,437	March 29, 2001
(3) 60/300,850	June 27, 2001	(4) 60/303,806	July 10, 2001
(5) 60/307,358	July 25, 2001	(6) 60/348,646	January 17, 2002

10. **FOREIGN** priority is claimed under 35 USC 119(a)-(d)/365(b) based on filing in _____

Application No.	Filing Date	Application No.	Filing Date
(1)		(2)	
(3)		(4)	
(5)		☐ See 3rd page for additional priorities	

11. _____ (No.) Certified copy (copies): ☐ attached; ☐ previously filed (date) _____
in U.S. Application No. / _____ filed on _____

12. ☐ This is a reissue of Patent No. _____

13. ☐ See top first page re prior Provisional, National, International application(s) (X box only if info is there and do not complete item 14 or 15.)

14. This application claims benefit of the following prior US application(s), the contents of which are incorporated into this application by this reference:

No. / _____ filed _____
No. / _____ filed _____
No. / _____ filed _____
No. PCT/ / _____ filed _____, which designated the U.S. and that International Application ☐ was ☐ was not published under PCT Acticle 21(2) in English

15. ☐ See the attached Preliminary Amendment, which amends the specification to claim benefit of the above listed US applications

16. Extension to date: ☐ concurrently filed ☐ not needed ☐ previously filed

17. ☐ Small Entity Status is claimed (**pre**-filing confirmation **required**)

17(a) ☐ Attached: (No.) Small Entity Statement(s). (Since 9/8/00 Small Entity Statement not essential to make claim)

17(b) ☐ See **NONPUBLICATION REQUEST** under Rule 213(a) attached (Pat-258)

18. ☐ Assignee (optional): _____

19. ☒ **Attached: Paper copy of Sequence Listing (separately numbered as pages 1-17) and a 3.5 inch computer diskette containing a computer readable copy of Sequence Listing. In compliance with 37 C.F.R. § 1.821(f), Applicants' undersigned attorney hereby states that the content of the paper and computer readable copies of the Sequence Listing are the same.**

20. This application is made by the following named inventor(s) **(Double check instructions for accuracy.):**
(Listing of inventor(s) not a requirement, but list if known)

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Mailing Address			
(include Zip Code)			

21. NOTE: FOR ADDITIONAL INVENTORS, "X" box ☐ and list additional inventors on attached sheet (incorporated by reference)

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

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SCANNED, #12

APPLICATION UNDER UNITED STATES PATENT LAWS

Atty. Dkt. No. PW 284943
(M#)

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

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

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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

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 nos. 60/279,438, filed on March 29, 2001; 60/279,437, filed on March 29, 2001; 60/300,850, filed on June 27, 2001; 60/303,806, filed on July 10, 2001; 60/307,358, filed on July 25, 2001; and 60/348,646, filed on January 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; US patent 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 hyperplasia is the major promoter of gastrointestinal inflammation and carcinogenesis.

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^+ and influx of Ca^{++}, 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 CTFR 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 as anti-metastatic agents. The development of new agonists is therefore of substantial clinical importance.

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, antimetabolites, 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 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 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 pre-cancerous 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" of peptide, in this sense, refers to an amount sufficient to increase apoptosis in 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):

$$\underset{}{\text{Asn}^{1}}\ \underset{}{\text{Asp}^{2}}\ \underset{}{\text{Glu}^{3}}\ \underset{*}{\text{Cys}^{4}}\ \underset{}{\text{Glu}^{5}}\ \underset{}{\text{Leu}^{6}}\ \underset{**}{\text{Cys}^{7}}\ \underset{}{\text{Val}^{8}}\ \underset{}{\text{Asn}^{9}}\ \underset{}{\text{Val}^{10}}\ \underset{}{\text{Ala}^{11}}\ \underset{*}{\text{Cys}^{12}}\ \underset{}{\text{Thr}^{13}}\ \underset{}{\text{Gly}^{14}}\ \underset{**}{\text{Cys}^{15}}\ \underset{}{\text{Leu}^{16}}$$

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 $cPLA_2$, 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

may be used as a means of treating and controlling inflammatory bowel diseases such as ulcerative colitis and Crohn's 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^+ efflux, Ca^{++} 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 a 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, when used either alone or in combination with specific inhibitors of cGMP-phosphodiesterase, also retard the onset of carcinogenesis in gut epithelium by restoring a healthy balance between cell proliferation and apoptosis via a cGMP-mediated mechanism.

As used herein, the term "guanylate cyclase receptor" refers to the class of guanylate cyclase receptors on any cell type to which the inventive agonist peptides or natural agonists described herein bind.

As used herein, the term "guanylate cyclase receptor-agonist" refers to peptides and/or other compounds that bind to a guanylate cyclase receptor and stimulate cGMP production. The term also includes all peptides that have amino acid sequences substantially equivalent to at least a portion of the binding domain comprising amino acid residues 3-15 of SEQ ID NO:1. This term also covers fragments and pro-peptides that bind to guanylate cyclase receptor and stimulate cGMP production. The term "substantially equivalent" refers to a peptide that has an amino acid sequence equivalent to that of the binding domain where certain residues may be deleted or replaced with other amino acids without impairing the peptide's ability to bind to a guanylate cyclase receptor and stimulate cGMP production.

Strategy and design of novel guanylate cyclase receptor agonists

Uroguanylin is a peptide secreted by the goblet and other epithelial cells lining the gastrointestinal mucosa as pro-uroguanylin, a functionally inactive form. The human pro-peptide is subsequently converted to the functionally active 16 amino acid peptide set forth in SEQ ID NO:1 (human uroguanylin sequence, see Table 2) in the lumen of the intestine by endogenous proteases. Since uroguanylin is a heat-resistant, acid-resistant, and proteolysis-resistant peptide, oral or systemic administration of this peptide and/or other

peptides similar to the functionally active 16 amino acid peptide sequence of SEQ ID NO:1 may be effectively employed in treatment methods.

Peptides similar to, but distinct from, uroguanylin are described below, including some which produce superior cGMP enhancing properties and/or other beneficial characteristics (*e.g.*, improved temperature stability, enhanced protease stability, or superior activity at preferred pH's) compared to previously known uroguanylin peptides. The peptides may be used to inhibit GI inflammation and for treating or preventing the onset of polyp formation associated with gut inflammation. Epithelial tissues susceptible to cancer cell formation may also be treated. The guanylate cyclase receptor agonists described have the amino acid sequences shown in Tables 2 and 3. The "binding domain" for agonist-receptor interaction includes the amino acid residues from 3-15 of SEQ ID NO:1.

Molecular modeling was applied to the design of novel guanylate cyclase receptor agonists using methods detailed in (30). It consisted of energy calculations for three compounds known to interact with guanylate cyclase receptors, namely for human uroguanylin, bicyclo [4,12; 7,15]Asn^{1}-Asp^{2}-Asp^{3}-Cys^{4}-Glu^{5}-Leu^{6}-Cys^{7}-Val^{8}-Asn^{9}-Val^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15}-Leu^{16} (UG, SEQ ID NO:1); human guanylin, bicyclo [4,12; 7,15]Pro^{1}-Gly^{2}-Thr^{3}-Cys^{4}-Glu^{5}-Ile^{6}-Cys^{7}-Ala^{8}-Tyr^{9}-Ala^{10}-Ala^{11}-Cys^{12}-Thr^{13}-Gly^{14}-Cys^{15} (GU, SEQ ID NO:22); and *E. coli* small heat-stable enterotoxin, tricyclo [6,10; 7,15; 11-18] Asn^{1}-Ser^{2}-Ser^{3}-Asn^{4}-Tyr^{5}-Cys^{6}-Cys^{7}-Glu^{8}-Leu^{9}-Cys^{10}-Cys^{11}-Asn^{12}-Pro^{13}-Ala^{14}-Cys^{15}-Thr^{16}-Gly^{17}-Cys^{18}-Tyr^{19} (ST, SEQ ID NO:23). Geometrical comparisons of all possible low-energy conformations for these three compounds were used to reveal the common 3D structures that served as the "templates" for the bioactive conformation, i.e., for the conformation presumably adopted by GU, UG and ST during interaction with receptor. It allowed designing novel analogs with significantly increased conformational population of the bioactive conformation at the expense of other low-energy conformations by selecting individual substitutions for various amino acid residues.

Energy calculations were performed by use of build-up procedures (30). The ECEPP/2 potential field (31,32) was used assuming rigid valence geometry with planar *trans*-peptide bonds, including that for Pro^{13} in ST. The ω angle in Pro^{13} was allowed to

vary. Aliphatic and aromatic hydrogens were generally included in united atomic centers of CH_n type; H^{α}-atoms and amide hydrogens were described explicitly.

The main calculation scheme involved several successive steps. First, the sequences of the two monocyclic model fragments (three fragments for ST), Ac-*cyclo* (Cys^i -...-Cys^j) - NMe, were considered, where all residues except Cys, Gly and Pro were replaced by alanines; the i and j values corresponded to the sequences of GU, UG and ST. At this step, all possible combinations of local minima for the peptide backbone for each amino acid residue were considered, *i.e.*, the minima in the Ramachandran map of *E, F, C, D, A* and A^* types (according to the notation in (33)) for the Ala residue; of E^*, F^*, C^*, D^*, *A, E, F, C D* and A^* types for the Gly residue; and of *F, C* and *A* types for Pro. For each backbone conformation, one optimal possibility to close a cycle employing the parabolic potential functions, intrinsic to the ECEPP force field, was found by checking an energy profile of rotation around the dihedral angle $\chi 1$ for the D-Cys residue.

Totally, as many as *ca.* 180,000 conformations for each of the cyclic moieties were considered. Then, the conformers satisfying the $E - E_{min} < \Delta E = 15$ kcal/mol criterion and differing by more than 40° in at least one value of any backbone dihedral angle were selected (from *ca.* 3,000 to 8,000 conformations for different model fragments). At the next step, the selected conformations of the matching monocyclic fragments were overlapped to create possible conformations of the bicyclic model fragments (the tricyclic fragments in the case of ST). Typically, this procedure yielded *ca.* 20,000–30,000 conformations. All these conformations were submitted for a new cycle of energy calculations, which resulted in 191 conformations satisfying the $E - E_{min} < \Delta E = 20$ kcal/mol criterion for the ST model fragment and in 6,965 conformations satisfying the same criterion for the GU/UG model fragment. After that, the missing side chains in the model fragments were restored, and energy calculations were performed again, the dihedral angle values of side chain groups (except the $\chi 1$ angle for the Cys residues) and of the terminal groups of the backbone being optimized before energy minimization to achieve their most favorable spatial arrangements, employing an algorithm previously described (34). For the UG 4-15 fragment, 632 conformations satisfied the criterion of $\Delta E = 20$ kcal/mol; 164 of them satisfied the more stringent criterion of $\Delta E = 12$ kcal/mol, which corresponds to the accepted criterion of 1

kcal/mol/residue (30). Subsequent elongation of the UG 4-15 fragment to 3-16, and then to the entire UG molecule was performed by the same build-up procedure. Finally, 31 backbone conformations of UG were found as satisfying the criterion of $\Delta E = 16$ kcal/mol.

Geometrical comparison of conformers was performed in the following manner. The best fit in the superposition for the atomic centers in a pair of conformers was assessed to check the level of geometrical similarity between the two conformers, according to (35). The criterion for geometrical similarity was the rms value, which was calculated for a pair of conformations A and B as follows:

$$\text{rms} = (1/N)\,\Sigma^{N}_{i=1}\,[(x^{A}_{i} - x^{B}_{i})^2 + (y^{A}_{i} - y^{B}_{i})^2 + (z^{A}_{i} - z^{B}_{i})^2]^{1/2},$$

where N is the number of the C^{α}-atom pairs chosen for superposition, and x, y and z are the Cartesian coordinates. By the criterion of geometrical similarity of rms < 2.0 Å, low-energy conformations of the rigid conformational fragment UG 4-15 fell into seven conformational families. One of them consists of the same six conformers that are similar both to 1UYA and 1ETN; this family contains also the lowest-energy conformer of UG. (1UYA and 1ETN are the experimentally defined 3D structures of UG and ST, respectively, which are known to possess high biological activity (36,37); the 3D structures were available in the Protein Data Bank.)

Table 1. The values of dihedral angles (in degrees) for peptide backbone in the "template" conformation of UG

		Conformer's #					
Residue	Angle	1	3	9	22	25	27
Cys^4	ψ	-37	-41	-40	-55	-38	-54
Glu^5	ϕ	-71	-67	-72	-69	-68	-70
	ψ	-50	-47	-48	-33	-43	-22
Leu^6	ϕ	-86	-86	-85	-81	-88	-91
	ψ	163	165	160	153	160	156
Cys^7	ϕ	-79	-82	-79	-83	-79	-81
	ψ	74	68	78	67	75	72
Val^8	ϕ	-120	-114	-126	-124	-125	-128
	ψ	-65	-57	-62	-55	-60	-64
Asn^9	ϕ	-83	-95	-82	-88	-89	-82
	ψ	119	113	134	118	111	116

Val^{10}	ϕ	-84	-82	-97	-90	-82	-82
	ψ	-21	-13	-16	-4	-15	-16
Ala^{11}	ϕ	-79	-86	-87	-89	-85	-80
	ψ	-32	-21	-35	-35	-18	-27
Cys^{12}	ϕ	-86	-92	-78	-79	-95	-90
	ψ	-52	-53	-55	-57	-53	-54
Thr^{13}	ϕ	-129	-121	-127	-119	-118	-130
	ψ	111	153	141	155	141	119
Gly^{14}	ϕ	-64	-78	-78	-80	-78	-68
	ψ	83	64	68	62	67	78
Cys^{15}	ϕ	-139	-160	-150	-156	-78	-131

The dihedral angles ϕ and ψ, values that determine the overall 3D shape of this UG fragment, are similar (Table 1). It allowed performing preliminary design of new analogs aimed at stabilizing this particular family of conformations employing the known local conformational limitations imposed by various types of amino acids.

For instance, it is known that Gly is more conformationally flexible compared to any other L-amino acid residue, since Gly may adopt conformations with any of the four combinations of signs for ϕ and ψ, *i.e.*, -,+; -,-; +,+; and +,-. The last combination is sterically forbidden for the L-amino acids, as Ala. Therefore, substitution of Gly^{14} for Ala^{14} should limit conformational flexibility in position 14 preserving the conformations described in Table 1. Also, substitution for Aib (α-Me-Ala, di-α-methyl-alanine) should limit the local conformational flexibility by two regions only, namely for -,- and +,+, the first one being compatible with conformers of Ala^{11} in Table 1. Therefore, one more desirable substitution is Aib^{11}. In Pro, the ϕ value is fixed at -75°; this residue is also similar to valine by its hydrophobic properties. Therefore, Val^{10} may be replaced by Pro^{10}, which adds more local conformational constraints to the UG conformers in Table 1. Replacement by Pro also requires that the preceding residue possesses only positive ψ values; Asn^{9} in Table 1 fulfills this requirement. The Pro residue already exists in the corresponding position of ST. All suggested substitutions within SEQ ID NO:1 shown below (*e.g.*, Pro^{10}, Aib^{11} or Ala^{14}) do not change the chemical nature of the non-aliphatic amino acids (such as Asn, Asp or Thr), which may be important for the actual interaction with receptor. The

former substitutions should lead only to conformational limitations shifting conformational equilibrium in UG towards the suggested "template" 3-D shape.

Based on the 3D structures defined in Table 1, a three-dimensional pharmacophore for uroguanylin was defined, enabling the determination of distances between functional groups of uroguanylin thought to directly interact with the receptor. Those groups thought to directly interact with the receptor are side groups of residues in positions 3, 5, 9 and 13 of the backbone sequence. Preferably, the residues are Glu3, Glu5, Asn9, and Thr13, as shown in SEQ ID NO:2 and SEQ ID NO:20. Thus, a three dimensional pharmacophore of uroguanylin is described in which the spatial arrangement of the four side chains of the residues at positions 3, 5, 9 and 13 may be created such that the distances between these side chains enable optional biological activity. Those distances (measured as distances between Cβ atoms of corresponding residues) are as follows: from 5.7 to 7.6 Å for the 3-5 distance, from 4.0 to 6.0 Å for 3-9; from 7.7 to 8.3 Å for 3-13, from 9.4 to 9.5 Å for 5-9, from 9.4 to 9.5 Å for 5-13, and from 5.8 to 6.3 Å for 9-13.

The distances above depend only on conformations of the peptide backbone. In some cases, however, conformations of side chains themselves are also important. For instance, calculations showed that there is no conformational difference between the backbones of UG (SP301), [Glu^2]-UG (SP303), [Glu^3]-UG (SP304) and [Glu^2, Glu3]-UG (SP302) in terms of their low-energy conformations. However, there is a distinct difference in the spatial positions of the β-carboxyls of Asp and γ-carboxyls of Glu in position 3. Namely, γ-carboxyls of the Glu residues in position 3 are clearly stretched "outwards" of the bulk of the molecules farther than the corresponding β-carboxyls of the Asp residues. The above observation strongly suggests that the negatively charged carboxyl group of the side chain in position 3 specifically interacts with a positively charged binding site on the receptor; therefore, analogs containing Glu3 instead of Asp3 should be more active. At the same time, to ensure efficiency of this particular interaction, an entire system of the long-range electrostatic interactions between ligand and receptor should be well balanced. Since the Glu^2 side chain presents more conformational possibilities compared to the Asp^2 side chain, this balance may be slightly changed in SP302 (double substitution of Asp's for Glu's) compared to SP304 (single substitution of Asp^3 for Glu^3).

Compounds capable of adopting low-energy conformations described in Table 1 are listed in Table 2. All compounds are [4,12; 7,15] bicycles.

Table 2

1. Parent compound: uroguanylin

SEQ ID NO:1

Asn[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]

2. Compounds without modifications of cysteines:

Common sequence (SEQ ID NO:2):

Asn[1]-**Aaa**[2]-**Bbb**[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-**Xxx**[10]-**Yyy**[11]-Cys[12]-Thr[13]-**Zzz**[14]-Cys[15]-Leu[16]

where Aaa = Asp, Glu; Bbb = Asp, Glu

with the exception that Aaa and Bbb are not both Asp in same molecule

And where Xxx = Val, Pro; Yyy = Ala, Aib; Zzz = Gly, Ala

3. Compounds with mercaptoproline (Mpt) substituted for cysteine in position 7:

Common sequence (SEQ ID NO:3):

Asn[1]-**Aaa**[2]-**Bbb**[3]-Cys[4]-Glu[5]-Leu[6]-**Mpt**[7]-Val[8]-Asn[9]-**Xxx**[10]-**Yyy**[11]-Cys[12]-Thr[13]-**Zzz**[14]-Cys[15]-Leu[16]

where Aaa = Asp, Glu; Bbb = Asp, Glu

where Xxx = Val, Pro; Yyy = Ala, Aib; Zzz = Gly, Ala

4. Compounds with penicillamines (β,β-dimethylcysteines, Pen) substituted for cysteines:

Common sequence (SEQ ID NO:4):

Asn[1]-**Aaa**[2]-**Bbb**[3]-**Kkk**[4]-Glu[5]-Leu[6]-**Lll**[7]-Val[8]-Asn[9]-**Xxx**[10]-**Yyy**[11]-**Mmm**[12]-Thr[13]-**Zzz**[14]-**Nnn**[15]-Leu[16]

where Aaa = Asp, Glu; Bbb = Asp, Glu

where Xxx = Val, Pro; Yyy = Ala, Aib; Zzz = Gly, Ala

and Kkk, Lll, Mmm and Nnn are either Cys or Pen (except not all are Cys in the same conformer)

5. Compounds with lactam bridges substituted for disulfide bridges:

Common sequence (SEQ ID NO:5):

Asn[1]-**Aaa[2]-Bbb[3]-Kkk[4]**-Glu[5]-Leu[6]-**Lll[7]**-Val[8]-Asn[9]-**Xxx[10]-Yyy[11]-Mmm[12]**-Thr[13]-**Zzz[14]-Nnn[15]**-Leu[16]

where Aaa = Asp, Glu; Bbb = Asp, Glu

where Xxx = Val, Pro; Yyy = Ala, Aib; Zzz = Gly, Ala;

and all combinations of the following (Dpr is diaminopropionic acid):

Kkk is Dpr and Mmm is either Asp or Glu;

Kkk is either Asp or Glu, and Mmm is Dpr;

Lll is either Cys or Pen;

Nnn is either Cys or Pen;

or:

Lll is Dpr and Nnn is either Asp or Glu;

Lll is either Asp or Glu, and Nnn is Dpr;

Kkk is either Cys or Pen;

Mmm is either Cys or Pen;

Some of the peptides shown in Table 2 contain 16 amino acid residues in which cysteine residues form disulfide bridges between Cys[4] and Cys[12], and Cys[7] and Cys[15], respectively. These peptides differ from the peptide sequences described in WO 01/25266, and are designed on the basis of peptide conformation and energy calculations.

In addition, peptides, varying in length from 13 to 16 amino acids, shown in Table 3, are designed, based on energy calculations and three-dimensional structures, to promote stabilization of the biologically active conformer and minimize or eliminate interconversion to biologically inactive conformers. These peptides are also designed to promote stability against proteolysis and higher temperatures. The design of these peptides involves modifications of amino acid residues that contain ionic charges at lower pH values, such as glutamic and aspartic acids.

Table 3

SEQ ID NO:6	X1 Glu Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:7	X1 Glu Asp Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:8	X1 Asp Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:9	X1 Asp Asp Cys X2 X3 Cys X4 Tyr X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:10	X1 Glu Glu Cys X2 X3 Cys X4 Tyr X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:11	X1 Asp Glu Cys X2 X3 Cys X4 Tyr X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:12	X1 Glu Asp Cys X2 X3 Cys X4 Tyr X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:13	X1 Asp Asp Cys X2 X3 Cys X4 Gln X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:14	X1 Glu Glu Cys X2 X3 Cys X4 Gln X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:15	X1 Asp Glu Cys X2 X3 Cys X4 Gln X5 X6 Cys X7 X8 Cys X9
SEQ ID NO:16	X1 Glu Asp Cys X2 X3 Cys X4 Gln X5 X6 Cys X7 X8 Cys X9
SEQ ID NO: 17	Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9
SEQ ID NO: 18	Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys
SEQ ID NO: 19	X1 Glu Cys X2 X3 Cys X4 Asn X5 X6 Cys X7 X8 Cys X9
	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
SEQ ID NO:20	Asn Asp Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
SEQ ID NO:21	Glu Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

X1 to X9 can be any amino acid. The disulfide bridges are formed between Cys residues at 4 and 12 and between 7 and 15, respectively. SEQ ID NO:18 represents the minimum length requirement for these peptides to bind a guanylate cyclase receptor.

Pharmaceutical Compositions and Formulations

The guanylate cyclase receptor agonists of the present invention (Table 2; SEQ ID NOs:2-5 and Table 3; SEQ ID NOs:6-21), as well as uroguanylin, guanylin and/or bacterial enterotoxin ST, may be combined or formulated with various excipients, vehicles or adjuvants for oral, local or systemic administration. Peptide compositions may be administered in solutions, powders, suspensions, emulsions, tablets, capsules, transdermal patches, ointments, or other formulations. Formulations and dosage forms may be made

using methods well known in the art (see, *e.g.*, Remington's Pharmaceutical Sciences, 16th ed., A. Oslo ed., Easton, PA (1980)).

Inhibitors of cGMP-dependent phosphodiesterase may be small molecules, peptides, proteins or other compounds that specifically prevent the degradation of cGMP. Inhibitory compounds include suldinac sulfone, zaprinast, motapizone and other compounds that block the enzymatic activity of cGMP-specific phosphodiesterases. One or more of these compounds may be combined with a guanylate cyclase receptor agonist exemplified in SEQ ID NOs:2-21, uroguanylin, guanylin and *E. coli* ST peptide.

The selection of carriers (*e.g.*, phosphate-buffered saline or PBS) and other components suitable for use in compositions is well within the level of skill in this art. In addition to containing one or more guanylate cyclase receptor agonists, such compositions may incorporate pharmaceutically acceptable carriers and other ingredients known to facilitate administration and/or enhance uptake. Other formulations, such as microspheres, nanoparticles, liposomes, pegylated protein or peptide, and immunologically-based systems may also be used. Examples include formulations employing polymers (*e.g.*, 20% w/v polyethylene glycol) or cellulose, or enteric formulations and pegylated peptide analogs for increasing systemic half-life and stability.

Treatment Methods

The term "treatment" refers to reducing or alleviating symptoms in a subject, preventing symptoms from worsening or progressing, or preventing disease development. For a given subject, improvement in a symptom, its worsening, regression, or progression may be determined by any objective or subjective measure typically employed by one of skill in the art. Efficacy of the treatment in the case of cancer may be measured as an improvement in morbidity or mortality (*e.g.*, lengthening of the survival curve for a selected population). Thus, effective treatment would include therapy of existing disease, control of disease by slowing or stopping its progression, prevention of disease occurrence, reduction in the number or severity of symptoms, or a combination thereof. The effect may be shown in a controlled study using one or more statistically significant criteria.

Combination therapy with one or more medical/surgical procedures and/or at least one other chemotherapeutic agent may be practiced with the invention. Other suitable agents useful in combination therapy include anti-inflammatory drugs such as, for example,

steroids or non-steroidal anti-inflammatory drugs (NSAIDS), such as aspirin and the like. Prophylactic methods for preventing or reducing the incidence of relapse are also considered treatment.

Cancers expected to be responsive to compositions include breast, colorectal, lung, ovarian, pancreatic, prostatic, renal, stomach, bladder, liver, esophageal and testicular carcinoma. Further examples of diseases involving cancerous or precancerous tissues that should be responsive to a therapeutic comprising at least one guanylate cyclase receptor agonist include: carcinoma (*e.g.*, basal cell, basosquamous, Brown-Pearce, ductal, Ehrlich tumor, in situ, Krebs, Merkel cell, small or non-small cell lung, oat cell, papillary, bronchiolar, squamous cell, transitional cell, Walker), leukemia (*e.g.*, B-cell, T-cell, HTLV, acute or chronic lymphocytic, mast cell, myeloid), histiocytoma, histiocytosis, Hodgkin disease, non-Hodgkin lymphoma, plasmacytoma, reticuloendotheliosis, adenoma, adenocarcinoma, adenofibroma, adenolymphoma, ameloblastoma, angiokeratoma, angiolymphoid hyperplasia with eosinophilia, sclerosing angioma, angiomatosis, apudoma, branchioma, malignant carcinoid syndrome, carcinoid heart disease, carcinosarcoma, cementoma, cholangioma, cholesteatoma, chondrosarcoma, chondroblastoma, chondrosarcoma, chordoma, choristoma, craniopharyngioma, chrondroma, cylindroma, cystadenocarcinoma, cystadenoma, cystosarcoma phyllodes, dysgerminoma, ependymoma, Ewing sarcoma, fibroma, fibro-sarcoma, giant cell tumor, ganglioneuroma, glioblastoma, glomangioma, granulosa cell tumor, gynandroblastoma, hamartoma, hemangioendothelioma, hemangioma, hemangio-pericytoma, hemangiosarcoma, hepatoma, islet cell tumor, Kaposi sarcoma, leiomyoma, leiomyosarcoma, leukosarcoma, Leydig cell tumor, lipoma, liposarcoma, lymphangioma, lymphangiomyoma, lymphangiosarcoma, medulloblastoma, meningioma, mesenchymoma, mesonephroma, mesothelioma, myoblastoma, myoma, myosarcoma, myxoma, myxosarcoma, neurilemmoma, neuroma, neuroblastoma, neuroepithelioma, neurofibroma, neurofibromatosis, odontoma, osteoma, osteosarcoma, papilloma, paraganglioma, paraganglioma nonchromaffin, pinealoma, rhabdomyoma, rhabdomyosarcoma, Sertoli cell tumor, teratoma, theca cell tumor, and other diseases in which cells have become dysplastic, immortalized, or transformed.

A bolus of the inventive composition may be administered over a short time. Once a day is a convenient dosing schedule to treat, *inter alia*, one of the above-mentioned disease states. Alternatively, the effective daily dose may be divided into multiple doses for purposes of administration, for example, two to twelve doses per day. The dose level

selected for use will depend on the bioavailability, activity, and stability of the compound, the route of administration, the severity of the disease being treated, and the condition of the subject in need of treatment. It is contemplated that a daily dosage will typically be between about 10 μg and about 2 mg (*e.g.*, about 100 μg to 1 mg) of the compound per kilogram body weight. The amount of compound administered is dependent upon factors known to a person skilled in this art such as, for example, chemical properties of the compound, route of administration, location and type of cancer, and the like.

The subject mammal may be any animal or human patient. Thus, both veterinary and medical treatments are envisioned according to the invention.

The invention will be further described by the following non-limiting example.

EXAMPLE

Materials and Methods

Cell Culture: Human T84 colon carcinoma cells were obtained from the American Type Culture Collection at passage 52. Cells were grown in a 1:1 mixture of Ham's F-12 medium and Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 100 U penicillin/ml, and 100 μg/ml streptomycin. The cells were fed fresh medium every third day and split at a confluence of approximately 80%.

T84 cell-based assay for determining the intracellular levels of cGMP: Peptide analogs were custom synthesized by Multiple Peptide Systems, San Diego, CA., and by Princeton Biomolecules, Langhorne, PA. Biological activity of the synthetic peptides was assayed as previously reported (15). Briefly, the confluent monolayers of T-84 cells in 24-well plates were washed twice with 250 μl of DMEM containing 50 mM HEPES (pH 7.4), pre-incubated at 37°C for 10 min with 250 μl of DMEM containing 50 mM HEPES (pH 7.4) and 1 mM isobutylmethylxanthine (IBMX), followed by incubation with peptide analogs (0.1 nM to 10 μM) for 30 min. The medium was aspirated, and the reaction was terminated by the addition of 3% perchloric acid. Following centrifugation, and neutralization with 0.1 N NaOH, the supernatant was used directly for measurements of cGMP using an ELISA kit (Caymen Chemical, Ann Arbor, MI.).

Results

Peptides shown in Table 4 were custom synthesized and purified (>95% purity) using a published procedure (38). Peptide analogs were evaluated in the T84 cell-based assay for their ability to enhance intracellular levels of cGMP. As shown in Table 4, SP304 (SEQ ID NO:20) gave the greatest enhancement of intracellular cGMP of all the analogs tested. SP316 (SEQ ID NO:21) was second in effectiveness, whereas the biological activities of SP301, SP302 and SP303 were all somewhat weaker. The peptide analogs SP306 and SP310 were not active in this assay. These results indicate that SP304 is the most potent peptide for enhancing cGMP. These results also suggest that the cysteine residue at position 7 cannot be substituted with penicillamine as a component of the [7,15] disulfide linkage, and that the Asn residue at position 9 cannot be changed to a Gln.

Table 4: Peptide agonists evaluated for biological activity in the T84 cell bioassay.

SEQ ID NO.*	Compound Code	cGMP Level** (pmol/well)
1	SP 301	205
6	SP 302	225
7	SP 303	195
20	SP 304	315
14	SP 306	0
4	SP 310	0
21	SP 316	275

* SEQ ID's for SP301, SP304 and SP316 are the precise amino acid sequences for these analogs as given in the text.

** Intracellular cGMP level observed in T84 cells following treatment with 1 micromolar solution of the respective peptide agonist for 30 minutes. The value observed for SP304 was statistically significant with a $p > 0.5$.

To examine heat stability, 10 micromolar solutions of peptide analogs were heated at 95°C for up to 90 minutes. At specific times during the treatment, samples were tested for their biological activity in the T84 cell-based assay. Biological activity of SP301, SP302,

SP303 and SP304 did not change significantly after 60 minutes of heating. After 90 minutes, the activities of SP301, SP302 and SP303 were reduced to about 80% of their original values, whereas the biological activity of SP304 remained unaltered. This indicates that SP304 is more stable to heat denaturation compared to the other peptides tested. Based on energy calculations and 3D structure, we expected that the negatively charged carboxyl group of the side chain in position 3 of SEQ ID NO:1 specifically interacts with a positively charged binding site on the receptor. In the case where this interaction can be enhanced, analogs containing Glu3 instead of Asp3 should be more active, as was found to be the case with SP304. At the same time, to ensure efficiency of this particular interaction, an entire system of the long-range electrostatic interactions between ligand and receptor should be well balanced. Since the Glu^2 side chain presents more conformational possibilities compared to the Asp^2 side chain, this balance may be slightly changed in SP302 (double substitution of Asp's for Glu's) compared to SP304 (single substitution of Asp^3 for Glu^3). Indeed, biological activity of SP 304 is the best amongst the analogs evaluated.

Synthetic peptides SP301, SP302, SP303 and SP304 were also tested for their activities at different pH values of the T84 cell-based assay. Whereas all of these peptides showed enhanced intracellular production of cGMP at pH's ranging from 5 to 7, SP304 showed the greatest enhancement in the range between 6.5 and 7. It is important to note that the physiological pH of the large intestine is in a similar range, and, therefore, SP304 would be expected to be especially efficacious for colon cancer treatment.

We also evaluated peptides used either alone or in combination with inhibitors of cGMP dependent phosphodiesterase (*e.g.*, zaprinast or sulindac sulfone) in T84 cell-based assays for enhancement of intracellular levels of cGMP. Combinations of an inhibitor of cGMP dependent phosphodiesterase with SP304 displayed a dramatic effect in enhancing cGMP levels in these experiments. Synthetic peptide SP304 substantially increased the cGMP level over the level reached in the presence of either zaprinast or sulindac sulfone alone. Treatment of wells with SP304 in combination with either Zaprinast or sulindac sulfone resulted in synergistic increases in intracellular cGMP levels. These increases were statistically significant, with p values of <0.5. These data indicate that treatments combining a peptide agonist of a guanylate cyclase receptor with one or more inhibitors of cGMP dependent phosphodiesterase result in a greater than additive increase in cGMP concentrations.

While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to those of ordinary skill in the art that various changes and modifications can be made without departing from the spirit and scope of the invention.

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What is Claimed is:

1. A peptide consisting essentially of the amino acid sequence of any one of SEQ ID NO:2 - SEQ ID NO:21.

2. The peptide of claim 1, wherein said peptide is a (4,12; 7,15) bicycle having the sequence of SEQ ID NO:20.

3. The peptide of either claim 1 or claim 2, wherein said peptide consists of the amino acid sequence of any one of SEQ ID NO:2-SEQ ID NO:21.

4. A method for preventing or treating primary or metastatic cancer or polyps in a patient comprising administering to said patient an effective dosage of a guanylate cyclase receptor agonist having the sequence of any one of SEQ ID NO:2 - SEQ ID NO:21.

5. A method for treating metastatic cancer in a patient comprising administering to said patient an effective dosage of a guanylate cyclase receptor agonist selected from the group consisting of: uroguanylin; guanylin; and *E. coli* ST peptide.

6. A method for treating primary cancers other than colon cancer in a patient, comprising administering to said patient an effective dosage of a guanylate cyclase receptor agonist selected from the group consisting of: uroguanylin; guanylin; and *E. coli* ST peptide.

7. The method of claim 4, wherein said peptide is a (4,12; 7,15) bicyclic peptide having the sequence of SEQ ID NO:20.

8. The method of claim 4, wherein said primary cancer is a member selected from the group consisting of the breast, colon, rectum, lung, ovary, pancreas, bladder, prostate, kidney or testis.

9. The method of any one of claims 4-8, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

10. A method of treating a patient for colon cancer or polyps comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with uroguanylin, guanylin or *E. coli* ST peptide.

11. The method of claim 9 and 10, wherein said cGMP-dependent phosphodiesterase inhibitor is selected from the group consisting of suldinac sulfone, zaprinast, and motapizone.

12. A method for preventing or treating inflammation in a patient comprising administering to said patient an effective dosage of a guanylate cyclase receptor agonist having the sequence of any one of: SEQ ID NO:2 - SEQ ID NO:21; uroguanylin; guanylin; or *E. coli* ST peptide.

13. The method of claim 12, wherein said peptide is a (4,12; 7,15) bicyclic peptide having the sequence of SEQ ID NO:20.

14. The method of claim 12, wherein said inflammation is an inflammatory disaese selected from the group consisting of: asthma; nephritis, hepatitis, pancreatitis, bronchitis and cystic fibrosis.

15. The method of claim 12, wherein said patient is treated for an inflammatory disorder of the gastrointestinal tract.

16. The method of claim 15, wherein said inflammatory disorder of the gastrointestinal tract is an inflammatory bowel disease selected from the group consisting of: ulcerative colitis and Crohn's disease.

17. The method of claim 12, further comprising administering to said patient an effective dose of an inhibitor of cGMP-dependent phosphodiesterase either concurrently or sequentially with said guanylate cyclase receptor agonist.

18. The method of claim 17, wherein said cGMP-dependent phosphodiesterase is selected from the group consisting of suldinac sulfone, zaprinast, and motapizone.

19. A method of treating a patient for primary or metastatic cancer, polyps or inflammation comprising administering to said patient:

a) a guanylate cyclase receptor agonist peptide having the sequence of any one of: SEQ ID NOs:2-21; uroguanylin; guanylin; or *E. coli* ST peptide; and

b) at least one compound selected from the group consisting of: a cGMP-dependent phosphodiesterase inhibitor; an anti-inflammatory agent; an antiviral agent; and an anticancer agent;

wherein said guanylate cyclase receptor agonist and said compound are each administered in a therapeutically effective amount.

20. A pharmaceutical composition in unit dose comprising a guanylate cyclase receptor agonist peptide having the sequence of any one of SEQ ID NOs:2-21 present in a therapeutically effective amount.

21. A pharmaceutical composition in unit dose form comprising:

a) a guanylate cyclase receptor agonist peptide having the sequence of any one of: SEQ ID NOs:2-21; uroguanylin; guanylin; or *E. coli* ST peptide; and

b) at least one compound selected from the group consisting of: a cGMP-dependent phosphodiesterase inhibitor, an anti-inflammatory agent, an antiviral agent and an anticancer agent;

wherein said guanylate cyclase receptor agonist and said compound are each present in a therapeutically effective amount.

22. The pharmaceutical composition of either claim 20 or 21, wherein the unit dose form is selected from the group consisting of a tablet, a capsule, a solution or inhalation formulation.

23. The pharmaceutical composition of either claim 20 nor 21, further comprising one or more excipients.

24. A method of inducing apoptosis in the cells of a subject, comprising administering to said subject an effective amount of agonist peptide having the sequence of any one of SEQ ID NO:2 - SEQ ID NO:21.

25. A method of inducing apoptosis in the cells of a subject, comprising administering to said subject an effective amount of uroguanylin, guanylin or *E. coli* ST peptide for cancers other than colon cancer.

26. A peptide conjugate comprising polyethylene glycol (PEG) attached to a peptide having the sequence of any of: SEQ ID NO:2 - SEQ ID NO:21; uroguanylin; guanylin; or *E. coli* ST peptide.

27. A method of treating cancer, inflammation or polyps in a patient comprising administering to said patient a therapeutically effective amount of the peptide conjugate of claim 26.

Abstract

A method of treatment of inflamed, pre-cancerous or cancerous 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 degradation of cGMP. Without requiring a particular mechanism of action, this treatment may restore a healthy balance between proliferation and apoptosis in the subject's population of epithelial cells, and also suppress carcinogenesis. Thus, the method may be used to treat, *inter alia*, inflammation, including gastrointestinal inflammatory disorders, general organ inflammation and asthma, and carcinogenesis of the lung, gastrointestinal tract, bladder, testis, prostate and pancreas, or polyps.

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JACOB, GARY S.

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PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number

CLAIMS AS FILED - PART I

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TOTAL CLAIMS	27	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	34 minus 20=	* 14
INDEPENDENT CLAIMS	12 minus 3 =	* 9
MULTIPLE DEPENDENT CLAIM PRESENT		☒

* If the difference in column 1 is less than zero, enter "0" in column 2

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X42=		OR	X84=	756.00
+140=		OR	+280=	280.00
TOTAL		OR	TOTAL	~~2010.00~~ 2028.

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

CLAIMS ONLY

SERIAL NO.	FILING DATE
APPLICANT(S)	

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1					
2		1				
3		2				
4	1					
5	1					
6	1					
7		1				
8		1				
9		5				
10	1					
11		0				
12	1					
13		1				
14		1				
15		1				
16		1				
17		1				
18		1				
19	1					
20	1					
21	1					
22		2				
23		02				
24	1					
25	1					
26	1					
27		1				
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TOTAL IND.	12	↓		↓		↓
TOTAL DEP.	22					
TOTAL CLAIMS	34					

	*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
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100						
TOTAL IND.		↓		↓		↓
TOTAL DEP.						
TOTAL CLAIMS						

* MAY BE USED FOR ADDITIONAL CLAIMS OR ADMENDMENTS

FORM PTO-2022 (1-98)

U.S.DEPARTMENT OF COMMERCE
Patent and Trademark Office

*U.S. GPO 1998-443-593-89152

OIPE

RAW SEQUENCE LISTING
PATENT APPLICATION: US/10/107,814

DATE: 04/11/2002
TIME: 13:29:46

Input Set : A:\usseqlst.txt
Output Set: N:\CRF3\04112002\J107814.raw

P5

ENTERED

<110> APPLICANT: SHAILUBHAI, KUNWAR
NIKIFOROVICH, GREGORY
JACOB, GARY S.
<120> TITLE OF INVENTION: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS
<130> FILE REFERENCE: 81361/284943/MAS
C--> **<140> CURRENT APPLICATION NUMBER: US/10/107,814**
C--> **<141> CURRENT FILING DATE: 2002-03-28**
<160> NUMBER OF SEQ ID NOS: 23
<170> SOFTWARE: PatentIn Ver. 2.1
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<211> LENGTH: 16
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<223> OTHER INFORMATION: Asp or Glu
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RAW SEQUENCE LISTING DATE: 04/11/2002
PATENT APPLICATION: **US/10/107,814** TIME: 13:29:46

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Output Set: **N:\CRF3\04112002\J107814.raw**

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72 <223> OTHER INFORMATION: Ala or Aib
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77 <223> OTHER INFORMATION: Gly or Ala
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91 guanylate cyclase receptor agonist peptide
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RAW SEQUENCE LISTING DATE: 04/11/2002
PATENT APPLICATION: **US/10/107,814** TIME: 13:29:46

Input Set : **A:\usseqlst.txt**
Output Set: **N:\CRF3\04112002\J107814.raw**

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RAW SEQUENCE LISTING DATE: 04/11/2002
PATENT APPLICATION: US/10/107,814 TIME: 13:29:46

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Output Set: N:\CRF3\04112002\J107814.raw

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250 <220> FEATURE:
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RAW SEQUENCE LISTING DATE: 04/11/2002
PATENT APPLICATION: US/10/107,814 TIME: 13:29:46

Input Set : A:\usseqlst.txt
Output Set: N:\CRF3\04112002\J107814.raw

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262 <222> LOCATION: (15)
263 <223> OTHER INFORMATION: Dpr, Cys, Pen, Asp or Glu
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266 **Asn Xaa Xaa Xaa Glu Leu Xaa Val Asn Xaa Xaa Xaa Thr Xaa Xaa Leu**
267 1 5 10 15
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276 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
277 guanylate cyclase receptor agonist peptide
279 <220> FEATURE:
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283 <220> FEATURE:
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295 <223> OTHER INFORMATION: Any amino acid
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VERIFICATION SUMMARY DATE: 04/11/2002
PATENT APPLICATION: **US/10/107,814** TIME: 13:29:47

Input Set : **A:\usseqlst.txt**
Output Set: **N:\CRF3\04112002\J107814.raw**

L:12 M:270 C: Current Application Number differs, Replaced Application Number
L:13 M:271 C: Current Filing Date differs, Replaced Current Filing Date
L:80 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:2
L:132 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:3
L:199 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:4
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L:578 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:11
L:630 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:12
L:682 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:13
L:734 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:14
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L:838 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:16
L:885 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:17
L:926 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:18
L:950 M:283 W: Missing Blank Line separator, <220> field identifier
L:976 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:19

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/107,814	03/28/2002	Kunwar Shailubhai	P 284943

CONFIRMATION NO. 9117

00909
PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

FORMALITIES LETTER

OC000000008017091

Date Mailed: 05/03/2002

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit $ **740** *to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(l) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

Items Required To Avoid Processing Delays:

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- Additional claim fees of $**1288** as a non-small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is $**2158** for a Large Entity

- $**740** Statutory basic filing fee.

- **$130** Late oath or declaration Surcharge.
- Total additional claim fee(s) for this application is **$1288**
  - **$252** for **14** total claims over 20.
  - **$756** for **9** independent claims over 3.
  - **$280**for multiple dependent claim surcharge.

A copy of this notice MUST be returned with the reply.

V. G.

Customer Service Center
Initial Patent Examination Division (703) 308-1202

PART 3 - OFFICE COPY

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
10/107,814	03/28/2002	Kunwar Shailubhai	P 284943

CONFIRMATION NO. 9117

00909
PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

FORMALITIES LETTER

OC000000008017091

01 FC:102 256.00 CH
03 FC:103 252.00 CH
04 FC:104 280.00 CH
05 FC:105 130.00 CH
06 FC:133 130.00 CH

Date Mailed: 05/03/2002

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Adjustment date: 08/12/2002 YGIZAW
08/02/2002 HMARZI1 00000082 033975 10107814
06 FC:189 130.00 CR

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit $ **740** *to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(l) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

Items Required To Avoid Processing Delays:

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- Additional claim fees of $**1288** as a non-small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is $**2158** for a Large Entity

- $**740** Statutory basic filing fee.

- **$130** Late oath or declaration Surcharge.
- Total additional claim fee(s) for this application is **$1288**
  - **$252** for **14** total claims over 20.
  - **$756** for **9** independent claims over 3.
  - **$280**for multiple dependent claim surcharge.

A copy of this notice MUST be returned with the reply.

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 2 - COPY TO BE RETURNED WITH RESPONSE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

FILING COMPLETION UNDER RULE 53(f)

(NOT PCT Applications)
For Design, Provisional, or Utility Applications

PATENT
APPLICATION

COMPLETION Under
Rule 53(f)

In re PATENT APPLICATION of
Inventor(s): Shailubhai et al.

Attn: Application Division

Appln. No.:	10	107,814	Atty.Dkt.	P	0284943	
	Series Code ⇧	Serial No. ⇧			M#	Client Ref

Filed: March 28, 2002
Title: Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis

Hon. Commisioner of Patents
Washington,DC 20231

Date: August 1, 2002

Sir:

The following **completes the filing** under Rule 53(f) of the above-identified patent application:

1. **Notice to File Missing Parts** ☒ copy attached ☐ not yet received

2. ☒ Signed Declaration attached. ☒ Original ☐ Facsimile/Copy

(Always "X" box 2 if filling signed Declaration and
"X" box 2A only if top box of the Declaration is X'd and file application copy, or
"X" box 2B only if none of the top three boxes of the Declaration is X'd.)

2A. ☐ Attached: Original signed Declaration with attached specification (including claim(s)) which is a copy of specification and claim(s) originally filed to secure the above filing date.

2B. ☐ The original application as filed in the PTO on the above filing date is the application which each inventor executed by signing the attached Rule 63 Declaration.

3. ☐ Specification originally filed in non-English language; hence verified translation attached of:
   a. ☐ Abstract
   b. [#] pages of Specification(only spec. & claims)
   c. ☐ Drawing(s) _____ No of Sheets
      ☐ Fig(s). _____

4. ☐ Letter filing formal drawing attached.

5. ☒ Attached is an assignment and cover sheet. Please return the recorded assignment to the undersigned.

6. **DOMESTIC/INTERNATIONAL** priority is claimed under 35 USC 119(e)/120/365(c) based on the following provisional, nonprovisional and/or PCT international application(s):

Application No.		Filing Date	Application No.		Filing Date
(1)	60/279,438	29 March 2001	(2)	60/279,437	29 March 2001
(3)	60/300,850	27 June 2001	(4)	60/303,806	10 July 2001
(5)	60/307,358	25 July 2001	(6)	60/348,646	17 January 2002

7. **FOREIGN** priority is claimed under 35 USC 119(a)-(d)/365(b) based on filing in _____

8.

Application No.	Filing Date	Application No.	Filing Date
(1)		(2)	
(3)		(4)	
(5)		(6)	

08/12/2002 YGIZAW 00000008 033975 10107814
01 FC:115 110.00 CH

PAT-106 5/02

Completion Under Rule 53(f)

9. _____ (No.) Certified copy (copies): ☐ attached; ☐ previously filed (date) _____
in U.S. Application No. / _____ filed on _____

10. Small Entity Status ➡ ☒ is Not claimed ☐ is claimed (file PAT-256 if this is the first claim of Small Entity Status)

11. ☒ Attached: Information Disclosure Statement with PTO 1449 and references

12. ☐ Please see the attached Preliminary Amendment which reduces the number of claims for purposes of reducing the initial filing fee.

THE FOLLOWING FILING FEE IS BASED ON CLAIMS AS FILED LESS ANY CHANGED BY PRELIMINARY AMENDMENT PER ITEM 12 ABOVE

				Large/Small Entity		Fee Code
13 Basic Filing Fee				Design Application	$330/$165	106/26
				Not Design Application	$740/$370	+740	101/201
14 Total Effective Claims	34	minus 20 =	14	x $18/$9	+252	103/203
15 Independent Claims	12	minus 3 =	9	x $84/$42	+756	102/202
16 If any proper multiple dependent claim (ignore improper) is present, (Leave this line blank if this is a reissue application)				$280/$140	+280	104/204
17 Surcharge for filing Declaration/filing fee late				$130/$65	+130	105/205
18				FILING FEE =	$2158	
19 **Original due date:** July 3, 2002						
20. **Petition is hereby made** to extend the original due date to cover the date this response is filed for which the requisite fee is attached				(1 mo)	$110/$55 =	+110	115/215
				(2mos)	$400/$200 =		116/216
				(3mos)	$920/$460 =		117/217
				(4mos)	$1,440/$720 =		118/218
21 If "non-English" box 3 is X'd, add Rule 17(k) processing fee				$130	+0	139
22 If "assignment" box 5 is X'd, add recording fee.				$40	+40	581
23. Petition Fee for				$130	+0	
24.				TOTAL FEE =	$2308	

PLEASE CHARGE DEPOSIT ACCOUNT

CHARGE Deposit Account No. 03-3975

Our Order No. 081361 (C#) | 0284943 (M#)

CHARGE STATEMENT: The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 (missing or insufficiencies only) now or hereafter relative to this application and the resulting Official document under Rule 20, or credit any overpayment, to our Account/Order Nos. shown in the heading hereof for which purpose a duplicate copy of this sheet is attached. **This CHARGE STATEMENT does not authorize charge of the issue fee until/unless an issue fee transmittal form is filed.**

Pillsbury Winthrop LLP
Intellectual Property Group

P.O. Box 10500
McLean, VA 22102
Tel (703) 905-2000

By Atty: Richard A. Steinberg **Reg. No.** 26,588

Sig: Richard A. Steinberg

Fax: (703) 905-2500
Tel: (703) 905-2039

Atty/Sec. RAS/kmh

NOTE: File in duplicate with PTO receipt (PAT-103A) and attachments

FOR UTILITY/DESIGN CIP/PCT NATIONAL/PLANT ORIGINAL/SUBSTITUTE/SUPPLEMENTAL DECLARATIONS

RULE 63 (37 C.F.R. 1.63) DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PW FORM

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the **INVENTION ENTITLED** **Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis**

the specification of which (CHECK applicable BOX(ES))

X A. ☐ is attached hereto.

BOX(ES) → B. ☒ was filed on March 28, 2002 as U.S. Application No. 10/107,814

→ → C. ☐ was filed as PCT International Application No. PCT/ / on

and (if applicable to U.S. or PCT application) was amended on

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. Except as noted below, I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International Application which designated at least one other country than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International Application, filed by me or my assignee disclosing the subject matter claimed in this application and having a filing date (1) before that of the application on which priority is claimed, or (2) if no priority claimed, before the filing date of this application:

PRIOR FOREIGN APPLICATION(S) Number	Country	Day/MONTH/Year Filed	Date first Laid-open or Published	Date Patented or Granted	Priority NOT Claimed

If more prior foreign applications, X box *at bottom* and continue on attached page.

Except as noted below, I hereby claim domestic priority benefit under 35 U.S.C. 119(e) or 120 and/or 365(c) of the indicated United States applications listed below and PCT international applications listed above or below and, if this is a continuation-in-part (CIP) application, insofar as the subject matter disclosed and claimed in this application is in addition to that disclosed in such prior applications, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 which became available between the filing date of each such prior application and the national or PCT international filing date of this application:

PRIOR U.S. PROVISIONAL, NONPROVISIONAL AND/OR PCT APPLICATION(S) Application No. (series code/serial no.)	Day/MONTH/Year Filed	Status pending, abandoned, patented	Priority NOT Claimed
60/279,438	29/03/2001		
60/279,437	29/03/2001		
60/300,850	27/6/2001		
60/303,806	10/7/2001		
60/307,358	25/7/2001		
60/348,646	17/1/2002		

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

And I hereby appoint Pillsbury Winthrop LLP, Intellectual Property Group, telephone number (703) 905-2000 (to whom all communications are to be directed), and persons of that firm who are associated with USPTO Customer No. 909 (see below label) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent, and I hereby authorize them to delete from that Customer No. names of persons no longer with their firm, to add new persons of their Firm to that Customer No., and to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/ organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct the above Firm and/or an attorney of that Firm in writing to the contrary.

USE ONLY FOR PILLSBURY WINTHROP

00909

(1) **INVENTOR'S SIGNATURE:** Date: 6/18/02

Name	Kunwar		SHAILUBHAI
	First	Middle Initial	Family Name
Residence	Blue Bell	PA	USA
	City	State/Foreign Country	Country of Citizenship
Mailing Address	600 Wick Lane, Blue Bell, PA, USA		
(include Zip Code)	19422		

(2) **INVENTOR'S SIGNATURE:** Date: 6/19/02

Name	Gregory		NIKIFOROVICH
	First	Middle Initial	Family Name
Residence	St. Louis	MO	USA
	City	State/Foreign Country	Country of Citizenship
Mailing Address	751 Aramis Drive, St. Louis, MO. USA		
(include Zip Code)	63141		

☒ FOR ADDITIONAL INVENTORS see attached page.

☐ See additional foreign priorities on attached page (incorporated herein by reference).

Atty. Dkt. No. P284943

DECLARATION AND POWER OF ATTORNEY
(continued)
ADDITIONAL INVENTORS:

(3) **INVENTOR'S SIGNATURE:** **Date:**

	Gary	S.	JACOB
	First	Middle Initial	Family Name
Residence	Creve Coeur	MO	USA
	City	State/Foreign Country	Country of Citizenship
Mailing Address	12541 Mason Forest Drive. Creve Coeur. MO. USA		
(include Zip Code)	63141		

(4) **INVENTOR'S SIGNATURE:** **Date:**

	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

(5) **INVENTOR'S SIGNATURE:** **Date:**

	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

(6) **INVENTOR'S SIGNATURE:** **Date:**

	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

(7) **INVENTOR'S SIGNATURE:** **Date:**

	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

(8) **INVENTOR'S SIGNATURE:** **Date:**

	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

(9) **INVENTOR'S SIGNATURE:** **Date:**

	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Mailing Address			
(include Zip Code)			

Rule 56(a) & (b) = 37 C.F.R. 1.56(a) &
PATENT AND TRADEMARK CASES - RULES OF PRACTICE
DUTY OF DISCLOSURE

(a) ...Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the [Patent and Trademark] Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability...(b) information is material to patentability when it is not cumulative and (1) It also establishes by itself, or in combination with other information, a prima facie case of unpatentability of a claim or (2) refutes, or is inconsistent with, a position the applicant takes in: (i) Opposing an argument of unpatentability relied on by the Office, or (ii) Asserting an argument of patentability

PATENT LAWS 35 U.S.C.

§102. Conditions for patentability; novelty and loss of right to patent

A person shall be entitled to a patent unless--

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent or

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

(c) he has abandoned the invention, or

(d) the invention was first patented or caused to be patented, or was the subject of an inventor's certificate, by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application for patent or inventor's certificate filed more than twelve months* before the filing of the application in the United States, or

(e) the invention was described in

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or

(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a); or

(f) he did not himself invent the subject matter sought to be patented, or

(g) (1) during the course of an interference conducted under section 135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed, or

(2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

§103. Condition for patentability; non-obvious subject matter

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made. . . .

(c) Subject matter developed by another person, which qualified as prior art only under one or more of subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

* Six months for Design Applications (35 U.S.C. 172).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

K. Shailubhai et al.

Application Serial No. 10/107,814

Filed: March 28, 2002

Confirmation No. 9117

Group Art Unit: 1646

Examiner: unassigned

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

* * * * *

INFORMATION DISCLOSURE STATEMENT

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

Sir:

Applicants respectfully submit herewith prior art as cited on the attached PTO Form-1449 for consideration by the Examiner in the above-identified application.

This Information Disclosure Statement is intended to be in full compliance with the rules, but should the Examiner find any part of its required content to have been omitted, prompt notice to that effect is earnestly solicited to enable Applicants to comply fully.

Any deficiencies in the fees may be charged to Deposit Account No. 03-3975 under Order No. 081361/0284943.

Consideration of the foregoing and enclosures plus the return of a copy of the enclosed Form PTO-1449 with the Examiner's initials in the left column per MPEP 609 are earnestly solicited along with an early action on the merits.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: Richard A. Steinberg

Richard A. Steinberg
Registration No. 26,588

1600 Tysons Boulevard
McLean, VA 22102
(703) 905-2000 Telephone
(703) 905-2500 Facsimile

Attorney Reference: 081361/0284943
Date: August 1, 2002

FORM PTO-1449 (modified)
To: U.S. Department of Commerce
(PW FORM PAT-1449)
Patent and Trademark Office

Atty. Dkt. No.	M#	Client Ref.
	0284943	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Applicant: Shailubhai et al.

Application Serial No. 10/107,814

Filing Date: March 28, 2002

Date: August 1, 2002 Page 1 of 1

Examiner: unassigned | Group Art Unit: unassigned

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR	5,489,670	Feb 1996	Currie et al.			
	BR	5,518,888	May 1996	Waldman			
	CR	5,601,990	Feb 1997	Waldman			
	DR	5,731,159	Mar 1998	Waldman			
	ER	5,879,656	Mar 1999	Waldman			
	FR	5,928,873	Jul 1999	Waldman			
	GR	5,969,097	Oct 1999	Wiegand et al.			
	HR						
	IR						
	JR						
	KR						
	LR						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclosed	No
	MR									
	NR									
	OR									
	PR									
	QR									
	RR									
	SR									

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

	TR	Shailubhai et al., "Uroguanylin Treatment Suppresses Polyp Formation in the Apc Min/+ Mouse and Induces Apoptosis in Human Colon Adenocarcinoma Cells via Cyclic GMP" *Cancer Research* 60 (September 15, 2000) 5151-5157.
	UR	Carrithers et al., "Guanylyl cyclase C is a selective marker for metastatic colorectal tumors in human extraintestinal tissues" *Proc. Natl. Acad. Sci. USA* 93 (December 1996) 14827-14832.
	VR	Hill et al., "Analysis of the human guanylin gene and the processing and cellular localization of the peptide" *Proc. Natl. Acad. Sci. USA* 92 (March 1995) 2046-2050.
	WR	Hamra et al., "Uroguanylin: Structure and activity of a second endogenous peptide that stimulates intestinal guanylate cyclase" *Proc. Natl. Acad. Sci. USA* 90 (November 1993) 10464-10468.
	XR	De Sauvage et al., "Precursor structure, expression and tissue distribution of human guanylin" *Proc. Natl. Acad. Sci. USA* 89 (October 1992) 9089-9093.
	YR	Currie et al., "Guanylin: An endogenous activator of intestinal guanylate cyclase" *Proc. Natl. Acad. Sci. USA* 89 (February 1992) 947-951.

Examiner | Date Considered:

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Image

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Application Number	:	10/107,814	Confirmation No. 9117
Applicant	:	Kunwar Shailubhai et al.	
Filed	:	March 28, 2002	
Tech Cntr/AU	:	1646	
Examiner	:	(unknown)	
Entitled	:	Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis	
Attorney Reference	:	019089-0284943	
Customer Number	:	00909	

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

STATUS REQUEST

Sir:

Please advise, in writing, of the status of the above-identified application for patent in that no initial Official Action has been received by our office.

Respectfully submitted,

PILLSBURY WINTHROP L.L.P.

By: _____
Paul L. Sharer
Registration No. 36,004

1600 Tysons Boulevard
McLean, Virginia 22102
(703) 905-2000 Telephone
(703) 905-2500 Facsimile

Date: November 24, 2003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number	:	10/107,814	Confirmation No. 9117
Applicant	:	Kunwar Shailubhai et al.	
Filed	:	March 28, 2002	
Tech Cntr/AU	:	1642	
Examiner	:	Stephen L. Rawlings	
Entitled	:	GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT OF TISSUE INFLAMMATION AND CARCINOGENESIS	
Attorney Reference	:	121634-40284943	
Customer No.	:	43569	

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

STATUS REQUEST

Sir:

Please advise, in writing, of the status of the above-identified application for patent in that no initial Official Action has been received by our office.

Filed concurrently herewith is a Change of Correspondence Address (PTO/SB/122).

Respectfully submitted,

MAYER BROWN ROWE & MAW LLP

By: _____
Paul L. Sharer
Registration No. 36,004
Direct No. (202) 263-3340

Intellectual Property Group
Mayer Brown Rowe & Maw LLP
1909 K Street, N.W.
Washington, D.C. 20006-1101
(202) 263-3000 Telephone
(202) 263-3300 Facsimile

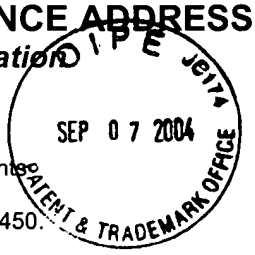
Date: September 7, 2004

PTO/SB/122 (09-03)
Approved for use through 11/30/2005. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

CHANGE OF CORRESPONDENCE ADDRESS

Application

Address to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450



Application Number	10/107,814
Filing Date	March 28, 2002
First Named Inventor	Kunwar Shailubhai et al.
Art Unit	1642
Examiner Name	Stephen L. Rawlings
Attorney Docket Number	121634-40284943

Please change the Correspondence Address for the above-identified patent application to:

☑ Customer Number : 43569

OR

☐ **Firm or Individual Name**					
Address					
Address					
City		**State**		**Zip**	
Country					
Telephone		**Fax**			

This form cannot be used to change the data associated with a Customer Number. To change the data associated with an existing Customer Number use "Request for Customer Number Data Change" (PTO/SB/124).

I am the:

☐ Applicant/Inventor

☐ Assignee of record of the entire interest.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☑ Attorney or Agent of record. Registration Number 36,004.

☐ Registered practitioner named in the application transmittal letter in an application without an executed oath or declaration. See 37 CFR 1.33(a)(1). Registration Number_____.

Typed or Printed Name	Paul L. Sharer
Signature	
Date September 7, 2004	Telephone (202) 263-3340

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____forms are submitted.

This collection of information is required by 37 CFR 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/107,814	03/28/2002	Kunwar Shailubhai	P 0284943	9117

43569 7590 12/13/2004

MAYER, BROWN, ROWE & MAW LLP
1909 K STREET, N.W.
WASHINGTON, DC 20006

EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 12/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/107,814	SHAILUBHAI ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-27 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-27 are pending in the application and are currently subject to restriction.

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claims 1-3, 20-23, and 26, insofar as the claims are drawn to a peptide and/or a composition thereof, and a conjugate thereof further comprising polyethylene glycol attached to said peptide, wherein said peptide consists essentially of the amino acid sequence of any one of SEQ ID NOs: 2-21 or wherein the peptide is uroguanylin, guanylin, or *E. coli* ST peptide, classified, for example, in class 530, subclass 317.

Group II. Claims 4-11, 19, 24, 25, and 27, insofar as the claims are drawn to a method for preventing or treating cancer or polyps in a patient comprising administering to the patient a composition comprising a guanylate cyclase receptor agonist, or a conjugate thereof, selected from the group consisting of a peptide having any one of the amino acid sequences set forth as SEQ ID NOs: 2-21, uroguanylin, guanylin, and *E. coli* ST peptide, wherein said conjugate further comprises polyethylene glycol attached to said peptide, classified, for example, in class 514, subclass 10.

Group III. Claims 12-19, 24, 25, and 27, insofar as the claims are drawn to a method for preventing or treating inflammation in a patient comprising administering to the patient a composition comprising a guanylate cyclase receptor agonist, or a conjugate thereof, selected from the group consisting of a peptide having any one of the amino acid sequences set forth as SEQ ID NOs: 2-21, uroguanylin, guanylin, and *E. coli* ST peptide,

wherein said conjugate further comprises polyethylene glycol attached to said peptide, classified, for example, in class 514, subclass 10.

3. The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups II and III are methods, whereas the inventions of Group I are products.

Inventions in Group I and inventions in Groups II and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the product as claimed, namely the peptide or conjugate thereof can be used in a materially different process of using that product, such as the process of using the peptide or conjugate thereof as an immunogen to produce antibodies that bind to said peptide or conjugate thereof; or alternatively, where the product is a composition comprising said peptide or conjugate thereof, which further comprises a cGMP-dependent phosphodiesterase inhibitor, an anti-inflammatory agent, an antiviral agent, or an anticancer agent, the product as claimed is disclosed as useful in materially different processes for treating different diseases or conditions (e.g., cancer and cystic fibrosis).

Groups II and III are patentably distinct inventions, since the inventions are methods for treating or preventing etiologically and pathologically distinct diseases or conditions. The inventions of Group II are methods for treating or preventing cancer or polyps (i.e., usually benign, but possibly precancerous protuberances of a mucous membrane). "Cancer" is a general term for more than 100 diseases that are characterized by uncontrolled, abnormal growth of cells. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body.

In contrast, the inventions of Group III are method for treating or preventing inflammatory diseases, including asthma, nephritis, pancreatitis, bronchitis, cystic fibrosis, ulcerative colitis, and Crohn's disease. Although Crohn's disease and

ulcerative colitis, for example, are chronic, non-specific disorders of unknown etiology, which among other inflammatory bowel diseases have extracolonic manifestations that are often associated and involve the liver, joints and skin.

Accordingly, the objective to practicing the claimed methods in each group differs. As such, the outcome or endpoint determined or measured in practicing the claimed methods in each group differs. Furthermore, the probability of success in practicing the claimed methods in each group differs, such that each group has achieved a different status in the art and the examination of any one group would require considerations not required for examination of any other.

In addition, the methods of Groups II and III are disclosed as materially different methods, since the methods of Groups II are disclosed as comprising administering to a patient diagnosed with cancer a composition comprising an anticancer agent; whereas the methods of Groups III are disclosed as comprising administering to a patient diagnosed with cancer a composition comprising an anti-inflammatory agent. While one might administer an anti-inflammatory agent to a cancer patient, one would not typically administer an anticancer agent to a patient afflicted with cystic fibrosis, for example.

Because of the different products, and their different modes of action, used in practicing the different methods for treating different diseases or conditions, the search required to consider any one of the inventions of Group II and any one of the inventions of Group III is not the same, nor is it coextensive with the search necessary to consider any of the others.

Since any one of the inventions of Group II and any one of the inventions of Group III are patentably distinct, each from the other, and because the examination of more than one of the inventions could not be made without serious burden, it is proper to restrict each from the other. See MPEP § 803.

4. Because these inventions are distinct for the reasons given above and also because the search required for any one group is not required for any other group and/or the inventions have acquired a separate status in the art as shown by their different classification or their recognized divergent subject matter, searching more than

one invention encompassed by the claim would constitute a serious burden; therefore, restriction for examination purposes as indicated is proper.

5. This application is further subject a requirement to elect a single species of invention, since the inventions of each of the above groups include patentably distinct species of invention.

The claims of each group of inventions are directed to patentably distinct species of the claimed inventions, wherein said peptide consists essentially of, or comprises the amino acid sequence of any one of SEQ ID NOs: 2-21 or wherein the peptide is uroguanylin, guanylin, or *E. coli* ST peptide. Claims 1, 20-23, and 26 of Group I are generic; claims 4-6, 8-11, 19, 24, 25, and 27 of Group II are generic; and claims 12, 14-19, 24, 25, and 27 of Group III are generic. Notably, many of the sequence identification numbers specified in the claims correspond to a genus of amino acid sequences, so the generic claims link a multitude of different species of invention.

Each peptide having an amino acid sequence that differs from that of the others is distinct in structure from the others. Therefore, each species of invention comprising one of these peptides is distinct from the others comprising one of the other peptides.

Accordingly, the examination of each species of invention would require a unique search that is not required for examination of any of the other species, because the search of any one peptide will not provide adequate information regarding any other. Moreover, the search required to consider any one of the species of invention is not the same, nor is it coextensive with the search necessary to consider any of the others. Since each species of invention is patentably distinct from the others, and because the examination of more than one species could not be made without serious burden, it is proper to require election of a single species. See MPEP § 809.

Applicant is required under 35 U.S.C. 121 to specifically elect a single species of invention by identifying one amino acid sequence of which the peptide comprises or consists, which species of invention will be considered for prosecution on the merits and to which the claims shall be restricted if no generic claim is finally held to be allowable. The Examiner notes that a novel and nonobvious species of invention, although

allowable over the prior art, may not necessarily be allowable over the requirements set forth in 35 U.S.C. §§ 101 and 112.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species, which are written in dependent form, or otherwise, include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should Applicant traverse on the ground that the species are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103(a) of the other invention.

6. Claims 4-11, 19, 24, 25, and 27 of Group II are generic to a plurality of disclosed patentably distinct species of invention, wherein said cancer is of an organ selected from the group consisting of (a) breast, (b) colon, (c) rectum, (d) lung, (e) ovary, (f) pancreas, (g) bladder, (h) prostate, (i) kidney, and (j) testis.

Recognizing that the claims are drawn to a method for treating or preventing a primary cancer, or a metastasis thereof, the claims are drawn to patentably distinct species of invention for treating or preventing primary or metastatic cancer or polyps of (a) breast, (b) colon, (c) rectum, (d) lung, (e) ovary, (f) pancreas, (g) bladder, (h) prostate, (i) kidney, or (j) testis. Each of the different organs listed in the Markush group has unique biologic and physiologic properties. Each different type of cancer or benign or precancerous growth affecting a different organ has unique pathologic properties.

Accordingly, the search required to examine the species of invention, for example, wherein the organ is breast, would not be the same as, or coextensive with the search necessary to examine the species of invention, wherein the organ is colon. Each species of invention requires a separate search. Searching more than one species of invention would therefore be burdensome.

Claims 12-19, 24, 25, and 27 of Group III are generic to a plurality of disclosed patentably distinct species of invention, wherein said inflammatory disease is (a) asthma, (b) nephritis, (c) pancreatitis, (d) bronchitis, (d) cystic fibrosis, (e) ulcerative colitis, and (f) Crohn's disease.

Recognizing that the claims are drawn to a method for treating or preventing an inflammatory disease, the claims are drawn to patentably distinct species of invention for treating or preventing (a) asthma, (b) nephritis, (c) pancreatitis, (d) bronchitis, (d) cystic fibrosis, (e) ulcerative colitis, or (f) Crohn's disease. Each different type of inflammatory disease affects a different tissue or organ and has unique pathologic and etiologic properties. Accordingly, the search required to examine the species of invention, for example, wherein disease is asthma, would not be the same as, or coextensive with the search necessary to examine the species of invention, wherein the disease is Crohn's disease. Each species of invention requires a separate search. Searching more than one species of invention would therefore be burdensome.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed. See MPEP § 803.02.

Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable over the prior art, examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration. Should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species

held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

7. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

8. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

9. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
December 9, 2004

Index of Claims

Application No.	Applicant(s)	
10/107,814	SHAILUBHAI ET AL.	
Examiner	**Art Unit**	
Stephen L. Rawlings, Ph.D.	1642	

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	12/9/04
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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Application Number	:	10/107,814	Confirmation No. 9117
Applicant	:	Kunwar Shailubhai et al.	
Filed	:	March 28, 2002	
Tech Cntr/AU	:	1642	
Examiner	:	Stephen L. Rawlings	
Entitled	:	Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis	
Attorney Reference	:	121634-40284943	
Customer Number	:	43569	

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

AMENDMENT/RESPONSE TRANSMITTAL

Transmitted herewith is an amendment/response for this application.

EXTENSION OF TIME

A petition for extension of time under 37 C.F.R. 1.136 is not believed necessary.

CLAIM FEES

The claim fees have been calculated as follows:

	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO. PREVIOUSLY PAID FOR		PRESENT EXTRA		RATE		ADDITIONAL FEE
Total	34	–	34	=	0	x $	50.00	=	$ 0.00
Independent	12	–	12	=	0	x $	200.00	=	$ 0.00
						FIRST PRESENTATION OF MULTIPLE DEP. CLAIM+ $	360.00	=	$ 0.00
						TOTAL ADDITIONAL CLAIM FEE DUE			**$ 0.00**

FEE PAYMENT

Authorization is given herein to charge the any deficiencies in the fees not specifically authorized herein, or to further credit any overpayments, to Deposit Account No. 503-121 in order to maintain the pendency of this application.

Intellectual Property Department
Mayer Brown Rowe & Maw LLP
1909 K Street, N.W.
Washington, D.C. 20006-1101
(202) 263-3000 Telephone
(202) 263-3300 Facsimile

Christopher M. Beck
Registration No. 52,603

Date: January 13, 2005

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Application Number	:	10/107,814	Confirmation No. 9117
Applicant	:	Kunwar Shailubhai et al.	
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Customer Number	:	43569	

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

RESPONSE TO RESTRICTION/ELECTION REQUIREMENT

Sir:

In response to the Official Action [Restriction/Election Requirement] mailed December 13, 2004 for the above-identified application, amendments and/or remarks submitted herewith include:

- Remarks and arguments.

REMARKS/ARGUMENTS

In response to the Restriction Requirement dated December 13, 2004, Applicants elect Group I (claims 1-3, 20-23 and 26).

With respect to the required species election, Applicants elect the species of Sequence ID NO: 20. Claims 1-3, 20-23 and 26 read on the elected species.

In view of the foregoing, the claims are now believed to be in form for allowance, and such action is hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned at the telephone number listed below.

All objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Respectfully submitted,

MAYER BROWN ROWE & MAW LLP

By: _____

Christopher M. Beck
Registration No. 52,603
Direct No. (202) 263-3374

Paul L. Sharer
Registration No. 36,004
Direct No. (202) 263-3340

Intellectual Property Group
1909 K Street, N.W.
Washington, D.C. 20006-1101
(202) 263-3000 Telephone
(202) 263-3300 Facsimile

Date: January 13, 2005

GenCore version 5.1.6

OM protein - nucleic search, using frame_plus_p2n model

Run on: February 11, 2005, 21:36:32 ; Search time 2132 Seconds
(without alignments)
285.661 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
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Ygapop 10.0 , Ygapext 0.5
Fgapop 6.0 , Fgapext 7.0
Delop 6.0 , Delext 7.0

Searched: 34239544 seqs, 19032134700 residues

Total number of hits satisfying chosen parameters: 68479088

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
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Listing first 45 summaries

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-FGAPEXT=7 -YGAPOP=10 -YGAPEXT=0.5 -DELOP=6 -DELEXT=7

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7: gb_est6:*
8: gb_gss1:*
9: gb_gss2:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

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c	2	92	96.8	302	1	AI721056	AI721056 as69e05.x
	3	92	96.8	339	9	AY410925	AY410925 Homo sapi
	4	92	96.8	367	5	BX092859	BX092859 BX092859
c	5	92	96.8	455	2	AW009510	AW009510 ws83f10.x
c	6	92	96.8	496	5	BQ027704	BQ027704 UI-H-CO0-
	7	92	96.8	703	7	CO581337	CO581337 ILLUMIGEN
	8	92	96.8	716	7	CO580213	CO580213 ILLUMIGEN
	9	90	94.7	316	1	AA689133	AA689133 vq52b01.r
	10	88	92.6	427	4	BM446293	BM446293 1IL6A7.ab
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	12	84	88.4	268	1	AV061512	AV061512 AV061512
	13	84	88.4	281	1	AV062212	AV062212 AV062212
	14	84	88.4	286	1	AV061769	AV061769 AV061769
c	15	84	88.4	291	5	BX640323	BX640323 BX640323
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	36	84	88.4	465	1	AA463144	AA463144 vg85e05.r
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	40	84	88.4	553	1	AA929498	AA929498 vt40a07.r
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	44	84	88.4	605	4	BG969327	BG969327 602836804
	45	84	88.4	608	7	CF423670	CF423670 lac97h04.

ALIGNMENTS

RESULT 1
AY410926
LOCUS AY410926 194 bp DNA linear GSS 16-DEC-2003
DEFINITION Pan troglodytes GUCA2B gene, VIRTUAL TRANSCRIPT, partial sequence, genomic survey sequence.
ACCESSION AY410926
VERSION AY410926.1 GI:39766894
KEYWORDS GSS.
SOURCE Pan troglodytes (chimpanzee)
ORGANISM Pan troglodytes
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Pan.
REFERENCE 1 (bases 1 to 194)
AUTHORS Clark,A.G., Glanowski,S., Nielson,R., Thomas,P., Kejariwal,A., Todd,M.A., Tanenbaum,D.M., Civello,D.R., Lu,F., Murphy,B., Ferriera,S., Wang,G., Zheng,X.H., White,T.J., Sninsky,J.J., Adams,M.D. and Cargill,M.
TITLE Inferring nonneutral evolution from human-chimp-mouse orthologous gene trios
JOURNAL Science 302 (5652), 1960-1963 (2003)
PUBMED 14671302
REFERENCE 2 (bases 1 to 194)
AUTHORS Clark,A.G., Glanowski,S., Nielson,R., Thomas,P., Kejariwal,A., Todd,M.A., Tanenbaum,D.M., Civello,D.R., Lu,F., Murphy,B., Ferriera,S., Wang,G., Zheng,X.H., White,T.J., Sninsky,J.J., Adams,M.D. and Cargill,M.
TITLE Direct Submission
JOURNAL Submitted (16-NOV-2003) Celera Genomics, 45 West Gude Drive, Rockville, MD 20850, USA
COMMENT This sequence was made by sequencing genomic exons and ordering them based on alignment.
FEATURES Location/Qualifiers
source 1. .194

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                     /organism="Pan troglodytes"
                     /mol_type="genomic DNA"
                     /db_xref="taxon:9598"
     gene            <1. .>194
                     /gene="GUCA2B"
                     /locus_tag="HCM4053"
ORIGIN

Alignment Scores:
Pred. No.:                0.000186       Length:          194
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Percent Similarity:       100.00%        Conservative:    1
Best Local Similarity:    93.75%         Mismatches:      0
Query Match:              96.84%         Indels:          0
DB:                       9              Gaps:            0

US-10-107-814-20 (1-16) x AY410926 (1-194)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db        144 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 191

RESULT 2
AI721056/c
LOCUS       AI721056                302 bp    mRNA    linear   EST 10-JUN-1999
DEFINITION  as69e05.x1 Barstead colon HPLRB7 Homo sapiens cDNA clone
            IMAGE:2333984 3' similar to SW:GUAU_HUMAN Q16661 UROGUANYLIN
            PRECURSOR ;, mRNA sequence.
ACCESSION   AI721056
VERSION     AI721056.1  GI:5038312
KEYWORDS    EST.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 302)
  AUTHORS   Hillier,L., Allen,M., Bowles,L., Dubuque,T., Geisel,G., Jost,S.,
            Krizman,D., Kucaba,T., Lacy,M., Le,N., Lennon,G., Marra,M.,
            Martin,J., Moore,B., Schellenberg,K., Steptoe,M., Tan,F.,
            Theising,B., White,Y., Wylie,T., Waterston,R. and Wilson,R.
  TITLE     WashU-NCI human EST Project
  JOURNAL   Unpublished (1997)
COMMENT     Contact: Wilson RK
            Washington University School of Medicine
            4444 Forest Park Parkway, Box 8501, St. Louis, MO 63108
            Tel: 314 286 1800
            Fax: 314 286 1810
            Email: est@watson.wustl.edu
            This clone is available royalty-free through LLNL ; contact the
            IMAGE Consortium (info@image.llnl.gov) for further information.
            Seq primer: -40UP from Gibco.
FEATURES             Location/Qualifiers
     source          1. .302
                     /organism="Homo sapiens"
                     /mol_type="mRNA"
                     /db_xref="taxon:9606"
                     /clone="IMAGE:2333984"
                     /sex="male"
                     /dev_stage="adult, age 25"
                     /lab_host="DH10B (phage resistant)"
                     /clone_lib="Barstead colon HPLRB7"
                     /note="Organ: colon; Vector: pT7T3D-Pac (Pharmacia) with a
                     modified polylinker; Site_1: EcoRI; Site_2: NotI; 1st
                     strand cDNA was primed with a Not I - oligo(dT) primer [5'
                     TGTTACGAATCTGAAGTGGGAGCGGCCGCCCTTTTTTTTTTTTTTTTTTTTTTTT
                     3']; double-stranded cDNA was ligated to Eco RI adaptors
                     [5' AATTCACTAGTAAT 3' and 5' ATTACTAGTG 3'], digested
                     with Not I and cloned into the Not I and Eco RI sites of
                     the modified pT7T3 vector. Library constructed by Bob
                     Barstead."
ORIGIN

Alignment Scores:
Pred. No.:                0.000304       Length:          302
Score:                    92.00          Matches:         15
Percent Similarity:       100.00%        Conservative:    1
Best Local Similarity:    93.75%         Mismatches:      0
Query Match:              96.84%         Indels:          0
DB:                       1              Gaps:            0

US-10-107-814-20 (1-16) x AI721056 (1-302)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db        268 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 221

RESULT 3
AY410925
LOCUS       AY410925                339 bp    DNA     linear   GSS 16-DEC-2003
DEFINITION  Homo sapiens GUCA2B gene, VIRTUAL TRANSCRIPT, partial sequence,
            genomic survey sequence.
ACCESSION   AY410925
VERSION     AY410925.1  GI:39766893
KEYWORDS    GSS.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 339)
  AUTHORS   Clark,A.G., Glanowski,S., Nielson,R., Thomas,P., Kejariwal,A.,
            Todd,M.A., Tanenbaum,D.M., Civello,D.R., Lu,F., Murphy,B.,
            Ferriera,S., Wang,G., Zheng,X.H., White,T.J., Sninsky,J.J.,
            Adams,M.D. and Cargill,M.
  TITLE     Inferring nonneutral evolution from human-chimp-mouse orthologous
            gene trios
  JOURNAL   Science 302 (5652), 1960-1963 (2003)
   PUBMED   14671302
REFERENCE   2  (bases 1 to 339)
  AUTHORS   Clark,A.G., Glanowski,S., Nielson,R., Thomas,P., Kejariwal,A.,
            Todd,M.A., Tanenbaum,D.M., Civello,D.R., Lu,F., Murphy,B.,
            Ferriera,S., Wang,G., Zheng,X.H., White,T.J., Sninsky,J.J.,
            Adams,M.D. and Cargill,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (16-NOV-2003) Celera Genomics, 45 West Gude Drive,
            Rockville, MD 20850, USA
COMMENT     This sequence was made by sequencing genomic exons and ordering
            them based on alignment.
FEATURES             Location/Qualifiers
     source          1. .339
                     /organism="Homo sapiens"
                     /mol_type="genomic DNA"
                     /db_xref="taxon:9606"
     gene            <1. .>339
                     /gene="GUCA2B"
                     /locus_tag="HCM4053"
ORIGIN

Alignment Scores:
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Score:                    92.00          Matches:         15
Percent Similarity:       100.00%        Conservative:    1
Best Local Similarity:    93.75%         Mismatches:      0
Query Match:              96.84%         Indels:          0
DB:                       9              Gaps:            0

US-10-107-814-20 (1-16) x AY410925 (1-339)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db        289 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 336

RESULT 4
BX092859
LOCUS       BX092859                367 bp    mRNA    linear   EST 23-JAN-2003
DEFINITION  BX092859 Barstead colon HPLRB7 Homo sapiens cDNA clone
            IMAGp998G095790 ; IMAGE:2333984, mRNA sequence.
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GenCore version 5.1.6

OM protein - nucleic search, using frame_plus_p2n model

Run on: February 11, 2005, 22:26:42 ; Search time 375 Seconds
(without alignments)
251.753 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
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Ygapop 10.0 , Ygapext 0.5
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Searched: 5378673 seqs, 2950229984 residues

Total number of hits satisfying chosen parameters: 10757346

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

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-LOOPCL=0 -LOOPEXT=0 -UNITS=bits -START=1 -END=-1 -MATRIX=blosum62
-TRANS=human40.cdi -LIST=45 -DOCALIGN=200 -THR_SCORE=pct -THR_MAX=100
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Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.		Score	% Query Match	Length	DB	ID	Description
1		92	96.8	596	18	US-10-335-053-281	Sequence 281, App
2		84	88.4	651	9	US-09-917-800A-1700	Sequence 1700, Ap
3		63	66.3	69	18	US-10-766-735-62	Sequence 62, Appl
4	c	63	66.3	69	18	US-10-766-735-63	Sequence 63, Appl
5		63	66.3	69	19	US-10-796-719-62	Sequence 62, Appl
6	c	63	66.3	69	19	US-10-796-719-63	Sequence 63, Appl
7		63	66.3	214	18	US-10-425-821-88	Sequence 88, Appl
8		60	63.2	325	16	US-10-262-473-15	Sequence 15, Appl
9		58	61.1	57	17	US-10-621-684-1	Sequence 1, Appli
10		58	61.1	57	17	US-10-621-684-4	Sequence 4, Appli
11		58	61.1	57	18	US-10-775-481A-1	Sequence 1, Appli
12		58	61.1	57	18	US-10-775-481A-4	Sequence 4, Appli
13		58	61.1	69	18	US-10-766-735-64	Sequence 64, Appl
14	c	58	61.1	69	18	US-10-766-735-65	Sequence 65, Appl
15		58	61.1	69	19	US-10-796-719-64	Sequence 64, Appl
16	c	58	61.1	69	19	US-10-796-719-65	Sequence 65, Appl
17		56	58.9	65	10	US-09-908-975-3802	Sequence 3802, Ap
18		56	58.9	367	16	US-10-262-473-13	Sequence 13, Appl
19		56	58.9	409	16	US-10-262-473-11	Sequence 11, Appl
20		56	58.9	567	17	US-10-152-319A-1607	Sequence 1607, Ap
21		56	58.9	571	10	US-09-873-367C-174	Sequence 174, App
22		56	58.9	571	18	US-10-335-053-44	Sequence 44, Appl
23		56	58.9	650	14	US-10-158-646-41	Sequence 41, Appl
24		56	58.9	655	9	US-09-981-353-60	Sequence 60, Appl
25		56	58.9	655	15	US-10-235-994-21	Sequence 21, Appl
26	c	54	56.8	1603	17	US-10-424-599-44415	Sequence 44415, A
27	c	53	55.8	94720	17	US-10-052-482-160	Sequence 160, App
28	c	52.5	55.3	935	18	US-10-425-115-21919	Sequence 21919, A
29	c	52	54.7	252907	18	US-10-417-375-66	Sequence 66, Appl
30		51	53.7	663	18	US-10-767-701-25585	Sequence 25585, A
31	c	51	53.7	1689	18	US-10-425-115-105712	Sequence 105712,
32	c	51	53.7	157090	18	US-10-672-764A-34	Sequence 34, Appl
33		50	52.6	440	13	US-10-027-632-278769	Sequence 278769,
34		50	52.6	440	17	US-10-027-632-278769	Sequence 278769,
35		50	52.6	476	10	US-09-918-995-442	Sequence 442, App
36	c	50	52.6	598	13	US-10-027-632-202413	Sequence 202413,
37	c	50	52.6	598	13	US-10-027-632-202414	Sequence 202414,
38	c	50	52.6	598	13	US-10-027-632-202415	Sequence 202415,
39	c	50	52.6	598	17	US-10-027-632-202413	Sequence 202413,
40	c	50	52.6	598	17	US-10-027-632-202414	Sequence 202414,
41	c	50	52.6	598	17	US-10-027-632-202415	Sequence 202415,
42		50	52.6	1396	9	US-09-764-864-408	Sequence 408, App
43		50	52.6	2040	18	US-10-425-115-63378	Sequence 63378, A
44	c	50	52.6	2145	17	US-10-108-260A-9	Sequence 9, Appli
45		50	52.6	3134	18	US-10-723-860-5849	Sequence 5849, Ap

ALIGNMENTS

RESULT 1
US-10-335-053-281
; Sequence 281, Application US/10335053
; Publication No. US20040241653A1
; GENERAL INFORMATION:
; APPLICANT: Quark Biotech, Inc.
; TITLE OF INVENTION: Methods for identifying marker genes for cancer
; FILE REFERENCE: 68733-A; 070/US1
; CURRENT APPLICATION NUMBER: US/10/335,053
; CURRENT FILING DATE: 2003-03-27
; PRIOR APPLICATION NUMBER: 60/345,317
; PRIOR FILING DATE: 2001-12-31
; NUMBER OF SEQ ID NOS: 319
; SOFTWARE: PatentIn version 3.2
; SEQ ID NO 281
; LENGTH: 596
; TYPE: DNA
; ORGANISM: Homo sapiens
US-10-335-053-281

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Pred. No.:                4.14e-05        Length:         596
Score:                    92.00           Matches:        15
Percent Similarity:       100.00%         Conservative:   1
Best Local Similarity:    93.75%          Mismatches:     0
Query Match:              96.84%          Indels:         0
DB:                       18              Gaps:           0

US-10-107-814-20 (1-16) x US-10-335-053-281 (1-596)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||||||||||||||||||||||||||||||||||||||
Db        318 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 365

RESULT 2
US-09-917-800A-1700
; Sequence 1700, Application US/09917800A
; Patent No. US20020119462A1
; GENERAL INFORMATION:
;  APPLICANT: Mendrick, Donna
;  APPLICANT:  Porter, Mark
;  APPLICANT:  Johnson, Kory
;  APPLICANT:  Castle, Arthur
;  APPLICANT:  Elashoff, Michael
;  APPLICANT:  Gene Logic, Inc.
;  TITLE OF INVENTION: Molecular Toxicology Modeling
;  FILE REFERENCE: 44921-5038-US
;  CURRENT APPLICATION NUMBER: US/09/917,800A
;  CURRENT FILING DATE:  2001-07-31
;  PRIOR APPLICATION NUMBER: US 60/222,040
;  PRIOR FILING DATE: 2000-07-31
;  PRIOR APPLICATION NUMBER: US 60/222,880
;  PRIOR FILING DATE: 2000-11-02
;  PRIOR APPLICATION NUMBER: US 60/290,029
;  PRIOR FILING DATE: 2001-05-11
;  PRIOR APPLICATION NUMBER: US 60/290,645
;  PRIOR FILING DATE: 2001-05-15
;  PRIOR APPLICATION NUMBER: US 60/292,336
;  PRIOR FILING DATE: 2001-05-22
;  PRIOR APPLICATION NUMBER: US 60/295,798
;  PRIOR FILING DATE: 2001-06-06
;  PRIOR APPLICATION NUMBER: US 60/297,457
;  PRIOR FILING DATE: 2001-06-13
;  PRIOR APPLICATION NUMBER: US 60/298,884
;  PRIOR FILING DATE: 2001-06-19
;  PRIOR APPLICATION NUMBER: US 60/303,459
;  PRIOR FILING DATE: 2001-07-09
;  NUMBER OF SEQ ID NOS: 1740
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 1700
;   LENGTH: 651
;   TYPE: DNA
;   ORGANISM: Rattus norvegicus
;   FEATURE:
;   OTHER INFORMATION: Genbank Accession No. US20020119462A1 NM_022284
US-09-917-800A-1700

Alignment Scores:
Pred. No.:                0.000814        Length:         651
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Percent Similarity:       100.00%         Conservative:   1
Best Local Similarity:    92.86%          Mismatches:     0
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DB:                       9               Gaps:           0

US-10-107-814-20 (1-16) x US-09-917-800A-1700 (1-651)

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              ||||||||||||||||||:::||||||||||||||||||||
Db        440 GATGAATGTGAGCTGTGTATAAATGTTGCCTGTACGGGCTGC 481

RESULT 3
US-10-766-735-62
; Sequence 62, Application US/10766735
; Publication No. US20040266989A1
; GENERAL INFORMATION:
;  APPLICANT: Currie,  Mark G.
;  APPLICANT:  Mahajan-Miklos, Shalina
;  TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR THE
;  TITLE OF INVENTION:  TREATMENT OF GASTROINTESTINAL DISORDERS
;  FILE REFERENCE: 14184-039001
;  CURRENT APPLICATION NUMBER: US/10/766,735
;  CURRENT FILING DATE:  2004-01-28
;  PRIOR APPLICATION NUMBER: US 60/443,098
;  PRIOR FILING DATE: 2003-01-28
;  PRIOR APPLICATION NUMBER: US 60/471,288
;  PRIOR FILING DATE: 2003-05-15
;  PRIOR APPLICATION NUMBER: US 60/519,460
;  PRIOR FILING DATE: 2003-11-12
;  NUMBER OF SEQ ID NOS: 124
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 62
;   LENGTH: 69
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Synthetically generated oligonucleotide
US-10-766-735-62

Alignment Scores:
Pred. No.:                0.125           Length:         69
Score:                    63.00           Matches:        10
Percent Similarity:       83.33%          Conservative:   0
Best Local Similarity:    83.33%          Mismatches:     2
Query Match:              66.32%          Indels:         0
DB:                       18              Gaps:           0

US-10-107-814-20 (1-16) x US-10-766-735-62 (1-69)

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Db         24 TGTGAATTGTGTTGTAATCCTGCTTGTACCGGGTGC 59

RESULT 4
US-10-766-735-63/c
; Sequence 63, Application US/10766735
; Publication No. US20040266989A1
; GENERAL INFORMATION:
;  APPLICANT: Currie,  Mark G.
;  APPLICANT:  Mahajan-Miklos, Shalina
;  TITLE OF INVENTION: METHODS AND COMPOSITIONS FOR THE
;  TITLE OF INVENTION:  TREATMENT OF GASTROINTESTINAL DISORDERS
;  FILE REFERENCE: 14184-039001
;  CURRENT APPLICATION NUMBER: US/10/766,735
;  CURRENT FILING DATE:  2004-01-28
;  PRIOR APPLICATION NUMBER: US 60/443,098
;  PRIOR FILING DATE: 2003-01-28
;  PRIOR APPLICATION NUMBER: US 60/471,288
;  PRIOR FILING DATE: 2003-05-15
;  PRIOR APPLICATION NUMBER: US 60/519,460
;  PRIOR FILING DATE: 2003-11-12
;  NUMBER OF SEQ ID NOS: 124
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 63
;   LENGTH: 69
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Synthetically generated oligonucleotide
US-10-766-735-63

Alignment Scores:
Pred. No.:                0.125           Length:         69
Score:                    63.00           Matches:        10
Percent Similarity:       83.33%          Conservative:   0
Best Local Similarity:    83.33%          Mismatches:     2
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GenCore version 5.1.6

OM protein - nucleic search, using frame_plus_p2n model

Run on: February 11, 2005, 21:44:07 ; Search time 365 Seconds
(without alignments)
71.727 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
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Ygapop 10.0 , Ygapext 0.5
Fgapop 6.0 , Fgapext 7.0
Delop 6.0 , Delext 7.0

Searched: 1202784 seqs, 818138359 residues

Total number of hits satisfying chosen parameters: 2405568

Minimum DB seq length: 0
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Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

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-LIST=45 -DOCALIGN=200 -THR_SCORE=pct -THR_MAX=100 -THR_MIN=0 -ALIGN=40
-MODE=LOCAL -OUTFMT=pto -NORM=ext -HEAPSIZE=500 -MINLEN=0 -MAXLEN=2000000000
-USER=US10107814_@CGN_1_1_69_@runat_07022005_155155_21829 -NCPU=6 -ICPU=3
-NO_MMAP -LARGEQUERY -NEG_SCORES=0 -WAIT -DSPBLOCK=100 -LONGLOG
-DEV_TIMEOUT=120 -WARN_TIMEOUT=30 -THREADS=1 -XGAPOP=10 -XGAPEXT=0.5 -FGAPOP=6
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5: /cgn2_6/ptodata/1/ina/PCTUS_COMB.seq:*
6: /cgn2_6/ptodata/1/ina/backfiles1.seq:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	58	61.1	57	1	US-08-141-892A-1	Sequence 1, Appli
2	58	61.1	57	1	US-08-141-892A-4	Sequence 4, Appli
3	58	61.1	57	2	US-08-583-447A-1	Sequence 1, Appli
4	58	61.1	57	2	US-08-583-447A-4	Sequence 4, Appli
5	58	61.1	57	2	US-08-467-920-1	Sequence 1, Appli
6	58	61.1	57	2	US-08-467-920-4	Sequence 4, Appli
7	58	61.1	57	3	US-08-635-930-1	Sequence 1, Appli
8	58	61.1	57	3	US-08-635-930-4	Sequence 4, Appli
9	58	61.1	57	3	US-09-193-997-1	Sequence 1, Appli
10	58	61.1	57	3	US-09-193-997-4	Sequence 4, Appli
11	58	61.1	57	3	US-09-138-237A-1	Sequence 1, Appli
12	58	61.1	57	3	US-09-138-237A-4	Sequence 4, Appli
13	56	58.9	45	2	US-07-903-029-3	Sequence 3, Appli
14	56	58.9	589	2	US-07-903-029-2	Sequence 2, Appli
c 15	53	55.8	1119	4	US-09-543-681A-3299	Sequence 3299, Ap
c 16	53	55.8	78720	4	US-09-949-016-12710	Sequence 12710, A
c 17	53	55.8	78720	4	US-09-949-016-17283	Sequence 17283, A
18	52	54.7	136917	4	US-09-949-016-16369	Sequence 16369, A
19	50	52.6	74527	4	US-09-949-016-12339	Sequence 12339, A
20	50	52.6	74528	4	US-09-949-016-13275	Sequence 13275, A
21	49	51.6	4894	4	US-09-976-594-155	Sequence 155, App
c 22	49	51.6	134890	4	US-09-949-016-15602	Sequence 15602, A
c 23	48	50.5	601	4	US-09-949-016-158933	Sequence 158933,
c 24	48	50.5	601	4	US-09-949-016-158934	Sequence 158934,
25	48	50.5	789	4	US-09-627-536-11	Sequence 11, Appl
26	48	50.5	2419	4	US-09-627-536-10	Sequence 10, Appl
27	48	50.5	62354	4	US-09-949-016-16188	Sequence 16188, A
28	47.5	50.0	3318	4	US-09-949-016-3755	Sequence 3755, Ap
29	47.5	50.0	37030	4	US-08-311-731A-25	Sequence 25, Appl
30	47.5	50.0	245286	4	US-09-949-016-15497	Sequence 15497, A
31	47	49.5	601	4	US-09-949-016-40527	Sequence 40527, A
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35	47	49.5	809	4	US-09-270-767-12276	Sequence 12276, A
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c 37	47	49.5	69062	4	US-09-949-016-13609	Sequence 13609, A
c 38	47	49.5	69687	4	US-09-949-016-12890	Sequence 12890, A
39	47	49.5	90724	4	US-09-949-016-16601	Sequence 16601, A
40	47	49.5	325034	4	US-09-949-016-14957	Sequence 14957, A
41	47	49.5	389504	4	US-09-949-016-11774	Sequence 11774, A
42	47	49.5	4403765	3	US-09-103-840A-2	Sequence 2, Appli
43	47	49.5	4411529	3	US-09-103-840A-1	Sequence 1, Appli
44	46.5	48.9	87629	4	US-09-949-016-15262	Sequence 15262, A
45	46.5	48.9	87629	4	US-09-949-016-15263	Sequence 15263, A

ALIGNMENTS

RESULT 1
US-08-141-892A-1
; Sequence 1, Application US/08141892A
; Patent No. 5518888
; GENERAL INFORMATION:
; APPLICANT: Waldman, Scott A.
; TITLE OF INVENTION: ST Receptor Binding Compounds and Methods
; TITLE OF INVENTION: of Using the Same
; NUMBER OF SEQUENCES: 54
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz and No. 5518888ris
; STREET: One Liberty Place - 46th Floor
; CITY: Philadelphia
; STATE: Pennsylvania
; COUNTRY: U.S.A.
; ZIP: 19103
; COMPUTER READABLE FORM:
; MEDIUM TYPE: 3.5 inch disk, 720 Kb
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: WordPerfect 5.1
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/08/141,892A
; FILING DATE: 26-OCT-1993
; CLASSIFICATION: 435
; PRIOR APPLICATION DATA:
; APPLICATION NUMBER:
; FILING DATE:
; ATTORNEY/AGENT INFORMATION:
; NAME: DeLuca, Mark
; REGISTRATION NUMBER: 33,229
; REFERENCE/DOCKET NUMBER: TJU-0903
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: 215-568-3100
; TELEFAX: 215-568-3439
; INFORMATION FOR SEQ ID NO: 1:

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;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  57 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  both
;    MOLECULE TYPE:  cDNA
;    FEATURE:
;      NAME/KEY:  CDS
;      LOCATION:  1..57
US-08-141-892A-1

Alignment Scores:
Pred. No.:                0.152          Length:         57
Score:                    58.00          Matches:        9
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Best Local Similarity:    75.00%         Mismatches:     3
Query Match:              61.05%         Indels:         0
DB:                       1              Gaps:           0

US-10-107-814-20 (1-16) x US-08-141-892A-1 (1-57)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
Db         19 TGTGAACTTTGTTGTAATCCTGCCTGTGCTGGATGT 54

RESULT 2
US-08-141-892A-4
; Sequence 4, Application US/08141892A
; Patent No. 5518888
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and Methods
;    TITLE OF INVENTION:  of Using the Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz and No. 5518888ris
;      STREET:  One Liberty Place - 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  U.S.A.
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  3.5 inch disk, 720 Kb
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  WordPerfect 5.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/141,892A
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:
;      FILING DATE:
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-0903
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  4:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  57 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  both
;    MOLECULE TYPE:  cDNA
;    FEATURE:
;      NAME/KEY:  CDS
;      LOCATION:  1..57
US-08-141-892A-4

Alignment Scores:
Pred. No.:                0.152          Length:         57
Score:                    58.00          Matches:        9
Percent Similarity:       75.00%         Conservative:   0
Best Local Similarity:    75.00%         Mismatches:     3
Query Match:              61.05%         Indels:         0
DB:                       1              Gaps:           0

US-10-107-814-20 (1-16) x US-08-141-892A-4 (1-57)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
Db         19 TGTGAATTGTGTTGTAATCCTGCTTGTAACGGGTGC 54

RESULT 3
US-08-583-447A-1
; Sequence 1, Application US/08583447A
; Patent No. 5879656
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and
;    TITLE OF INVENTION:  Methods of Using the Same
;    NUMBER OF SEQUENCES:  56
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz & No. 5879656ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  Windows
;      SOFTWARE:  WordPerfect 6.1
;    CURRENT APPLICATION DATA:
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;      FILING DATE:  05-JAN-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US 08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1702
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  1:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  57 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  double
;      TOPOLOGY:  both
;    MOLECULE TYPE:  cDNA
;    FEATURE:
;      NAME/KEY:  CDS
;      LOCATION:  1..57
US-08-583-447A-1

Alignment Scores:
Pred. No.:                0.152          Length:         57
Score:                    58.00          Matches:        9
Percent Similarity:       75.00%         Conservative:   0
Best Local Similarity:    75.00%         Mismatches:     3
Query Match:              61.05%         Indels:         0
DB:                       2              Gaps:           0

US-10-107-814-20 (1-16) x US-08-583-447A-1 (1-57)

Qy          4 CysGluLeuCysValAsnValAlaCysThrGlyCys 15
              ||||||||||||   |||   ||||||   ||||||
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GenCore version 5.1.6

OM protein - nucleic search, using frame_plus_p2n model

Run on: February 11, 2005, 21:33:16 ; Search time 360 Seconds
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Perfect score: 95
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Ygapop 10.0 , Ygapext 0.5
Fgapop 6.0 , Fgapext 7.0
Delop 6.0 , Delext 7.0

Searched: 4390206 seqs, 2959870667 residues

Total number of hits satisfying chosen parameters: 8780412

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Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

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-FGAPEXT=7 -YGAPOP=10 -YGAPEXT=0.5 -DELOP=6 -DELEXT=7

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Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	92	96.8	583	2	AAT65115	Aat65115 Human GCA
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4	84	88.4	651	6	ABK63793	Abk63793 Rat seque
5	84	88.4	651	12	ADP72757	Adp72757 Renal tox
6	63	66.3	62	4	ABA01874	Aba01874 Human the
7	63	66.3	65	4	ABA01870	Aba01870 Human the
c 8	63	66.3	66	4	ABA01873	Aba01873 Human the
9	63	66.3	68	4	ABA01866	Aba01866 Human the
c 10	63	66.3	68	4	ABA01869	Aba01869 Human the
c 11	63	66.3	69	4	ABA01865	Aba01865 Human the
12	63	66.3	69	4	ABA01862	Aba01862 Human the
c 13	63	66.3	69	13	ADR48400	Adr48400 Oligonucl
14	63	66.3	69	13	ADR48399	Adr48399 Oligonucl
15	63	66.3	72	4	ABA01860	Aba01860 Human the
c 16	63	66.3	73	4	ABA01861	Aba01861 Human the
17	63	66.3	236	2	AAQ23866	Aaq23866 Heat-stab
18	63	66.3	433	2	AAQ20050	Aaq20050 Sequence
19	63	66.3	433	2	AAQ89260	Aaq89260 E. coli s
20	63	66.3	950	8	ACC79521	Acc79521 ST gene a
21	63	66.3	1183	8	ACC79524	Acc79524 3' flanki
22	60	63.2	325	8	ACC85777	Acc85777 Human NOV
23	58	61.1	57	2	AAZ07540	Aaz07540 ST recept
24	58	61.1	57	2	AAZ07541	Aaz07541 ST recept
25	58	61.1	57	13	ADR45821	Adr45821 Nucleotid
26	58	61.1	57	13	ADR45824	Adr45824 Nucleotid
27	58	61.1	69	13	ADR48402	Adr48402 Oligonucl
c 28	58	61.1	69	13	ADR48403	Adr48403 Oligonucl
29	58	61.1	243	2	AAQ23865	Aaq23865 Heat-stab
30	57	60.0	69	4	ABA01896	Aba01896 ClpG-STh
31	57	60.0	102	4	ABA01876	Aba01876 Human the
32	56	58.9	65	6	ABN31054	Abn31054 Rat splic
33	56	58.9	367	8	ACC85776	Acc85776 Human NOV
34	56	58.9	367	11	ADJ18913	Adj18913 Human NOV
35	56	58.9	409	8	ACC85775	Acc85775 Human NOV
36	56	58.9	567	10	ABT41905	Abt41905 Toxicity
37	56	58.9	567	12	ADP72737	Adp72737 Renal tox
38	56	58.9	571	6	ABL61837	Abl61837 Colon ade
39	56	58.9	571	10	ADD29595	Add29595 Human tum
40	56	58.9	589	2	AAZ22677	Aaz22677 Human gua
41	56	58.9	649	4	AAH57434	Aah57434 Human int
42	56	58.9	650	10	AAD59154	Aad59154 Human gua
43	56	58.9	655	9	ADA10942	Ada10942 Human cDN
44	56	58.9	655	12	ADG47982	Adg47982 Human gua
45	56	58.9	4595	2	AAT65123	Aat65123 Human GCA

ALIGNMENTS

RESULT 1
AAT65115
ID AAT65115 standard; cDNA; 583 BP.
XX
AC AAT65115;
XX
DT 22-APR-1998 (first entry)
XX
DE Human GCAP-II precursor cDNA.
XX
KW Guanyl cyclase C activating peptide II; GCAP-II; insulinotropic;
KW diabetes; endocrine disorder; diagnosis; treatment; human; ds.
XX
OS Homo sapiens.
XX
FH Key Location/Qualifiers
FT CDS 22. .360
FT /*tag= a
FT /product= "GCAP-II precursor"
XX
PN DE19543628-A1.
XX
PD 28-MAY-1997.
XX
PF 24-NOV-1995; 95DE-01043628.
XX
PR 24-NOV-1995; 95DE-01043628.
XX
PA (FORS/) FORSSMANN W.

```
XX
PI   Forssmann W,  Kist A,  Kruhoeffer M,  Meyer M,  Pardigol A,  Heine G;
XX
DR   WPI; 1997-290350/27.
DR   P-PSDB; AAW18498.
XX
PT   New guanyl cyclase C activating peptide fragments - have insulinotropic
PT   activity, useful for treating diabetes, etc.
XX
PS   Example 6; Fig 11; 33pp; German.
XX
CC   This cDNA sequence encodes a precursor of the guanyl cyclase C activating
CC   peptide, GCAP-II, which affects insulin secretion by the beta cells in
CC   the pancreas. This peptide is useful for treating pancreatic endocrine
CC   disorders, especially diabetes mellitus type II, renal and intestinal
CC   disorders, disorders of the gastrointestinal, respiratory and urogenital
CC   apparatus, disorders of the cardiovascular and nervous systems, disorders
CC   of the integuments and sense organs and diseases associated with GCAP-II
CC   (89-112) deficiency. This peptide can be used for treatment of
CC   electrolyte effects on bone reconstruction (osteoporosis) or the dental
CC   apparatus. Antibodies to GCAP-II (89-112) can be used to treat diseases
CC   associated with overproduction of GCAP-II (89-112). Human GCAP-II (89-
CC   112) and GCAP-I (99-15) cDNA are useful for diagnosis and treatment of
CC   the above disorders e.g. gene therapy for diabetes
XX
SQ   Sequence 583 BP; 115 A; 198 C; 167 G; 103 T; 0 U; 0 Other;

Alignment Scores:
Pred. No.:                9.8e-05        Length:          583
Score:                    92.00          Matches:         15
Percent Similarity:       100.00%        Conservative:    1
Best Local Similarity:    93.75%         Mismatches:      0
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US-10-107-814-20 (1-16) x AAT65115 (1-583)

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RESULT 2
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ID   AAT60819 standard; cDNA; 583 BP.
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AC   AAT60819;
XX
DT   29-OCT-1997  (first entry)
XX
DE   Guanylate cyclase activating peptide II cDNA.
XX
KW   Human; guanylate cyclase; activating peptide; GCAP-II; cGMP;
KW   transepithelial transport; treatment; kidney; intestinal; respiratory;
KW   urogenital; circulatory; nervous system; disorder; disease; endocrine;
KW   sensory; system; osteoporosis; dental; pancreas; diabetes; hypophysis;
KW   gastrointestinal tract; diarrhoea; gene therapy; probe;
KW   recombinant production; transgenic animal; antibody; immunoassay reagent;
KW   ss.
XX
OS   Homo sapiens.
XX
FH   Key             Location/Qualifiers
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FT   sig_peptide     22. .285
FT                   /*tag=  b
FT   mat_peptide     286. .357
FT                   /*tag=  c
FT                   /product= "guanylate_cyclase_activating_peptide_II"
FT   primer_bind     complement(328. .345)
FT                   /*tag=  d
FT                   /bound_moiety= "primer HUGU-5 (AAT60814)"
FT   primer_bind     complement(346. .366)
FT                   /*tag=  e
FT                   /bound_moiety= "primer HUGU-8 (AAT60816)"
FT   primer_bind     442. .461
FT                   /*tag=  f
FT                   /bound_moiety= "primer HUGU-10 (AAT60818)"
FT   primer_bind     462. .482
FT                   /*tag=  g
FT                   /bound_moiety= "primer HUGU-9 (AAT60817)"
FT   primer_bind     558. .583
FT                   /*tag=  h
FT                   /bound_moiety= "primer HUGU-7 (AAT60815)"
XX
PN   DE19528544-A1.
XX
PD   06-FEB-1997.
XX
PF   03-AUG-1995;   95DE-01028544.
XX
PR   03-AUG-1995;   95DE-01028544.
XX
PA   (FORS/) FORSSMANN W.
XX
PI   Forssmann W;
XX
DR   WPI; 1997-110032/11.
DR   P-PSDB; AAW10595.
XX
PT   Guanylate cyclase activating peptide II - increases cGMP formation, and
PT   controls transport of water and electrolytes across epithelial cells.
XX
PS   Claim 2; Page 4; 15pp; German.
XX
CC   The present sequence encodes the human guanylate cyclase activating
CC   peptide II (GCAP-II), which increases cGMP formation, and is involved in
CC   the control of transepithelial water and electrolyte transport. GCAP-II
CC   can be used to treat a variety of kidney, intestinal, respiratory,
CC   urogenital, circulatory and nervous system disorders, diseases of the
CC   endocrine and sensory systems (e.g. osteoporosis, and dental disease),
CC   disorders of the pancreas (e.g. diabetes, and hypophysis) or the
CC   endocrine gastrointestinal tract and for the long term treatment of
CC   diarrhoea, without inducing an immune response. The GCAP-II cDNA can be
CC   used to treat the same conditions, clone the GCAP-II-encoding gene for
CC   use in gene therapy, as a hybridisation probe and for the production of
CC   recombinant GCAP-II or transgenic animal creation. Antibodies raised
CC   against GCAP-II are useful as immunoassay reagents. GCAP-II is
CC   administered at, e.g. 100-1200 microg/day by intravenous or intramuscular
CC   injection or 300-1200 microg/day subcutaneously. It may also be given
CC   orally, intranasally or by inhalation, in typical unit doses of 0.3-30
CC   mg. GCAP-II was chemically synthesised, or isolated by chromatography
CC   from transformed eukaryotic or prokaryotic cells, or human blood. When
CC   T84 cells were incubated with synthetic GCAP-II, generation of cGMP was
CC   increased in a dose dependent manner. GCAP-II influences cGMP production
CC   via a known receptor for heat stable enterotoxin. Other stomach,
CC   intestinal, pancreatic and liver cells also responded to GCAP-II, e.g.
CC   via changes in intracellular Ca2+ ion concentration
XX
SQ   Sequence 583 BP; 115 A; 198 C; 167 G; 103 T; 0 U; 0 Other;

Alignment Scores:
Pred. No.:                9.8e-05        Length:          583
Score:                    92.00          Matches:         15
Percent Similarity:       100.00%        Conservative:    1
Best Local Similarity:    93.75%         Mismatches:      0
Query Match:              96.84%         Indels:          0
DB:                       2              Gaps:            0

US-10-107-814-20 (1-16) x AAT60819 (1-583)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::||||||||||||||||||||||||||||||||||||||||
Db        310 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 357

RESULT 3
```

GenCore version 5.1.6

OM protein - nucleic search, using frame_plus_p2n model

Run on: February 11, 2005, 21:37:01 ; Search time 6778 Seconds
(without alignments)
114.382 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Xgapop 10.0 , Xgapext 0.5
Ygapop 10.0 , Ygapext 0.5
Fgapop 6.0 , Fgapext 7.0
Delop 6.0 , Delext 7.0

Searched: 4708233 seqs, 24227607955 residues

Total number of hits satisfying chosen parameters: 9416466

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Command line parameters:
-MODEL=frame+_p2n.model -DEV=xlh
-Q=/cgn2_1/USPTO_spool/US10107814/runat_07022005_155154_21811/app_query.fasta_1.199
-DB=GenEmbl -QFMT=fastap -SUFFIX=rge -MINMATCH=0.1 -LOOPCL=0 -LOOPEXT=0
-UNITS=bits -START=1 -END=-1 -MATRIX=blosum62 -TRANS=human40.cdi -LIST=45
-DOCALIGN=200 -THR_SCORE=pct -THR_MAX=100 -THR_MIN=0 -ALIGN=40 -MODE=LOCAL
-OUTFMT=pto -NORM=ext -HEAPSIZE=500 -MINLEN=0 -MAXLEN=2000000000
-USER=US10107814_@CGN_1_1_3731_@runat_07022005_155154_21811 -NCPU=6 -ICPU=3
-NO_MMAP -LARGEQUERY -NEG_SCORES=0 -WAIT -DSPBLOCK=100 -LONGLOG
-DEV_TIMEOUT=120 -WARN_TIMEOUT=30 -THREADS=1 -XGAPOP=10 -XGAPEXT=0.5 -FGAPOP=6
-FGAPEXT=7 -YGAPOP=10 -YGAPEXT=0.5 -DELOP=6 -DELEXT=7

Database : GenEmbl:*
1: gb_ba:*
2: gb_htg:*
3: gb_in:*
4: gb_om:*
5: gb_ov:*
6: gb_pat:*
7: gb_ph:*
8: gb_pl:*
9: gb_pr:*
10: gb_ro:*
11: gb_sts:*
12: gb_sy:*
13: gb_un:*
14: gb_vi:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	92	96.8	72	6	A79703	A79703 Sequence 37
2	92	96.8	336	6	A79702	A79702 Sequence 36
3	92	96.8	414	9	BC069301	BC069301 Homo sapi
4	92	96.8	583	6	A60251	A60251 Sequence 3
5	92	96.8	583	6	A79701	A79701 Sequence 35
6	92	96.8	583	9	HSGCAPII	Z50753 H.sapiens m
7	92	96.8	596	9	HSU34279	U34279 Human urogu
8	92	96.8	597	6	CQ720645	CQ720645 Sequence
9	92	96.8	3371	9	HSU55058	U55058 Human urogu
10	92	96.8	3600	9	HSGCAP2	Z70295 H.sapiens G
11	92	96.8	141677	9	AC114492	AC114492 Homo sapi
12	90	94.7	522	10	CPUGUMRNA	Z74738 C.porcellus
13	84	88.4	358	10	AF469496	AF469496 Notomys a
14	84	88.4	526	10	RNU41322	U41322 Rattus norv
15	84	88.4	548	10	RNU73898	U73898 Rattus norv
16	84	88.4	554	10	MMU67800	U67800 Mus musculu
17	84	88.4	590	10	MMU90727	U90727 Mus musculu
18	84	88.4	605	10	BC024373	BC024373 Mus muscu
19	84	88.4	651	6	AX402024	AX402024 Sequence
20	84	88.4	651	10	RNU75186	U75186 Rattus norv
21	84	88.4	3703	10	AF006668	AF006668 Mus muscu
22	84	88.4	7274	10	MMU95182	U95182 Mus musculu
23	84	88.4	214456	10	AL645563	AL645563 Mouse DNA
c 24	84	88.4	217927	2	AL606911	AL606911 Mus muscu
c 25	84	88.4	232814	2	BX324150	BX324150 Mus muscu
c 26	84	88.4	243164	2	AC132173	AC132173 Rattus no
27	84	88.4	253902	2	AC095908	AC095908 Rattus no
28	82	86.3	472	4	SDGCAPII	Z83746 S.domestica
29	77	81.1	1003	4	DVU49353	U49353 Didelphis v
30	73	76.8	920	5	AB080642	AB080642 Anguilla
31	73	76.8	941	5	AAN301672	AJ301672 Anguilla
32	73	76.8	1037	5	AAN301673	AJ301673 Anguilla
33	73	76.8	194209	5	BX248318	BX248318 Zebrafish
34	67	70.5	1009	5	AB080640	AB080640 Anguilla
35	64	67.4	433	1	AF302048	AF302048 Vibrio mi
36	63	66.3	62	6	AX252197	AX252197 Sequence
37	63	66.3	65	6	AX252193	AX252193 Sequence
c 38	63	66.3	66	6	AX252196	AX252196 Sequence
c 39	63	66.3	68	6	AX252192	AX252192 Sequence
40	63	66.3	69	6	AX252185	AX252185 Sequence
c 41	63	66.3	69	6	AX252188	AX252188 Sequence
42	63	66.3	69	6	AX252189	AX252189 Sequence
c 43	63	66.3	72	6	AX252182	AX252182 Sequence
44	63	66.3	72	6	AX252183	AX252183 Sequence
c 45	63	66.3	73	6	AX252184	AX252184 Sequence

ALIGNMENTS

RESULT 1
A79703
LOCUS A79703 72 bp DNA linear PAT 20-OCT-1999
DEFINITION Sequence 37 from Patent WO9720049.
ACCESSION A79703
VERSION A79703.1 GI:6092631
KEYWORDS .
SOURCE unidentified
ORGANISM unidentified
unclassified.
REFERENCE 1 (bases 1 to 72)
AUTHORS Forssmann,W. and Kist,A.
TITLE HUMAN PEPTIDE CIRCULATING IN THE BLOOD AND POSSESSING INSULINOTROPIC PROPERTIES
JOURNAL Patent: WO 9720049-A 37 05-JUN-1997;
FORSSMANN WOLF GEORG (DE); KIST ANDREAS (DE)
FEATURES Location/Qualifiers
source 1. .72
/organism="unidentified"
/mol_type="unassigned DNA"
/db_xref="taxon:32644"
ORIGIN

Alignment Scores:
Pred. No.: 1.05e-06 Length: 72
Score: 92.00 Matches: 15
Percent Similarity: 100.00% Conservative: 1
Best Local Similarity: 93.75% Mismatches: 0

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Query Match:            96.84%      Indels:        0
DB:                     6           Gaps:          0

US-10-107-814-20 (1-16) x A79703 (1-72)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||||||||||||||||||||||||||||||||||||||
Db         25 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 72

RESULT 2
A79702
LOCUS       A79702                   336 bp    DNA     linear   PAT 20-OCT-1999
DEFINITION  Sequence 36 from Patent WO9720049.
ACCESSION   A79702
VERSION     A79702.1  GI:6092630
KEYWORDS    .
SOURCE      unidentified
  ORGANISM  unidentified
            unclassified.
REFERENCE   1  (bases 1 to 336)
  AUTHORS   Forssmann,W. and Kist,A.
  TITLE     HUMAN PEPTIDE CIRCULATING IN THE BLOOD AND POSSESSING
            INSULINOTROPIC PROPERTIES
  JOURNAL   Patent: WO 9720049-A 36 05-JUN-1997;
            FORSSMANN WOLF GEORG (DE); KIST ANDREAS (DE)
FEATURES             Location/Qualifiers
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                     /db_xref="taxon:32644"
ORIGIN

Alignment Scores:
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Score:                  92.00       Matches:       15
Percent Similarity:     100.00%     Conservative:  1
Best Local Similarity:  93.75%      Mismatches:    0
Query Match:            96.84%      Indels:        0
DB:                     6           Gaps:          0

US-10-107-814-20 (1-16) x A79702 (1-336)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||||||||||||||||||||||||||||||||||||||
Db        289 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 336

RESULT 3
BC069301
LOCUS       BC069301                 414 bp    mRNA    linear   PRI 30-JUN-2004
DEFINITION  Homo sapiens guanylate cyclase activator 2B (uroguanylin), mRNA
            (cDNA clone MGC:97480 IMAGE:7262756), complete cds.
ACCESSION   BC069301
VERSION     BC069301.1  GI:47481402
KEYWORDS    MGC.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 414)
  AUTHORS   Strausberg,R.L., Feingold,E.A., Grouse,L.H., Derge,J.G.,
            Klausner,R.D., Collins,F.S., Wagner,L., Shenmen,C.M., Schuler,G.D.,
            Altschul,S.F., Zeeberg,B., Buetow,K.H., Schaefer,C.F., Bhat,N.K.,
            Hopkins,R.F., Jordan,H., Moore,T., Max,S.I., Wang,J., Hsieh,F.,
            Diatchenko,L., Marusina,K., Farmer,A.A., Rubin,G.M., Hong,L.,
            Stapleton,M., Soares,M.B., Bonaldo,M.F., Casavant,T.L.,
            Scheetz,T.E., Brownstein,M.J., Usdin,T.B., Toshiyuki,S.,
            Carninci,P., Prange,C., Raha,S.S., Loquellano,N.A., Peters,G.J.,
            Abramson,R.D., Mullahy,S.J., Bosak,S.A., McEwan,P.J.,
            McKernan,K.J., Malek,J.A., Gunaratne,P.H., Richards,S.,
            Worley,K.C., Hale,S., Garcia,A.M., Gay,L.J., Hulyk,S.W.,
            Villalon,D.K., Muzny,D.M., Sodergren,E.J., Lu,X., Gibbs,R.A.,
            Fahey,J., Helton,E., Ketteman,M., Madan,A., Rodrigues,S.,
            Sanchez,A., Whiting,M., Madan,A., Young,A.C., Shevchenko,Y.,
            Bouffard,G.G., Blakesley,R.W., Touchman,J.W., Green,E.D.,
            Dickson,M.C., Rodriguez,A.C., Grimwood,J., Schmutz,J., Myers,R.M.,
            Butterfield,Y.S., Krzywinski,M.I., Skalska,U., Smailus,D.E.,
            Schnerch,A., Schein,J.E., Jones,S.J. and Marra,M.A.
  TITLE     Generation and initial analysis of more than 15,000 full-length
            human and mouse cDNA sequences
  JOURNAL   Proc. Natl. Acad. Sci. U.S.A. 99 (26), 16899-16903 (2002)
   PUBMED   12477932
REFERENCE   2  (bases 1 to 414)
  AUTHORS   Strausberg,R.
  TITLE     Direct Submission
  JOURNAL   Submitted (29-APR-2004) National Institutes of Health, Mammalian
            Gene Collection (MGC), Cancer Genomics Office, National Cancer
            Institute, 31 Center Drive, Room 11A03, Bethesda, MD 20892-2590,
            USA
  REMARK    NIH-MGC Project URL: http://mgc.nci.nih.gov
COMMENT     Contact: MGC help desk
            Email: cgapbs-r@mail.nih.gov
            Tissue Procurement: Baylor Human Genome Sequencing Center
            cDNA Library Preparation: Baylor Human Genome Sequencing Center
            cDNA Library Arrayed by: The I.M.A.G.E. Consortium (LLNL)
            DNA Sequencing by: Baylor College of Medicine Human Genome
            Sequencing Center
            Center code: BCM-HGSC
            Web site: http://www.hgsc.bcm.tmc.edu/cdna/
            Contact: amg@bcm.tmc.edu
            Gunaratne, P.H., Garcia, A.M., Lu, X., Hulyk, S.W., Loulseged, H.,
            Kowis, C.R., Sneed, A.J., Martin, R.G., Muzny, D.M., Nanavati,
            A.N., Gibbs, R.A.

            Clone distribution: MGC clone distribution information can be found
            through the I.M.A.G.E. Consortium/LLNL at: http://image.llnl.gov
            Series: IRBR Plate: 7 Row: h Column: 6.
FEATURES             Location/Qualifiers
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                     /protein_id="AAH69301.1"
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                     /db_xref="LocusID:2981"
                     /db_xref="MIM:601271"
                     /translation="MGCRAASGLLPGVAVVLLLLLQSTQSVYIQYQGFRVQLESMKKL
                     SDLEAQWAPSPRLQAQSLLPAVCHHPALPQDLQPVCASQEASSIFKTLRTIANDDCEL
                     CVNVACTGCL"
ORIGIN

Alignment Scores:
Pred. No.:              5.77e-06    Length:        414
Score:                  92.00       Matches:       15
Percent Similarity:     100.00%     Conservative:  1
Best Local Similarity:  93.75%      Mismatches:    0
Query Match:            96.84%      Indels:        0
DB:                     9           Gaps:          0

US-10-107-814-20 (1-16) x BC069301 (1-414)

Qy          1 AsnAspGluCysGluLeuCysValAsnValAlaCysThrGlyCysLeu 16
              ||||||:::|||||||||||||||||||||||||||||||||||||||
Db        317 AACGACGACTGTGAGCTGTGTGTGAACGTTGCGTGTACCGGCTGCCTC 364
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GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: February 11, 2005, 20:58:55 ; Search time 38 Seconds
(without alignments)
215.612 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 1612378 seqs, 512079187 residues

Total number of hits satisfying chosen parameters: 1612378

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : UniProt_03:*
1: uniprot_sprot:*
2: uniprot_trembl:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	92	96.8	112	1	GUAU_HUMAN	Q16661 homo sapien
2	90	94.7	111	1	GUAU_CAVPO	P70107 cavia porce
3	84	88.4	106	1	GUAU_MOUSE	O09051 mus musculu
4	84	88.4	106	1	GUAU_RAT	P70668 rattus norv
5	84	88.4	106	2	Q9QUQ3	Q9quq3 mus musculu
6	84	88.4	107	2	Q8R5G8	Q8r5g8 notomys ale
7	82	86.3	113	1	GUAU_PIG	O13009 sus scrofa
8	77	81.1	109	1	GUAU_DIDMA	Q28358 didelphis m
9	73	76.8	108	2	Q98TI0	Q98ti0 anguilla an
10	73	76.8	108	2	Q7ZZS0	Q7zzs0 anguilla ja
11	73	76.8	116	2	Q98TH9	Q98th9 anguilla an
12	67	70.5	109	2	Q7ZZS2	Q7zzs2 anguilla ja
13	64	67.4	78	2	Q93G01	Q93g01 vibrio mimi
14	63	66.3	61	2	Q6VEG7	Q6veg7 escherichia
15	63	66.3	61	2	Q6VEG8	Q6veg8 escherichia
16	63	66.3	72	1	HST2_ECOLI	Q47185 escherichia
17	63	66.3	72	1	HST3_ECOLI	P07965 escherichia
18	62	65.3	110	2	Q7ZZS1	Q7zzs1 anguilla ja
19	60	63.2	17	2	Q9R581	Q9r581 vibrio chol
20	60	63.2	18	2	Q9R580	Q9r580 vibrio chol
21	60	63.2	19	2	Q9R579	Q9r579 vibrio chol
22	60	63.2	28	2	Q9R578	Q9r578 vibrio chol
23	60	63.2	78	1	HSTN_VIBCH	P04429 vibrio chol
24	60	63.2	78	1	HSTO_VIBCH	Q07425 vibrio chol
25	58	61.1	18	2	Q7M0U3	Q7m0u3 citrobacter
26	58	61.1	71	1	HSTB_YEREN	P74977 yersinia en
27	58	61.1	72	1	HST1_ECOLI	P01559 escherichia
28	56	58.9	72	1	HSTC_YEREN	O50319 yersinia en
29	56	58.9	115	1	GUAN_HUMAN	Q02747 homo sapien
30	56	58.9	115	1	GUAN_RAT	P28902 rattus norv
31	56	58.9	115	2	Q8R5G9	Q8r5g9 notomys ale
32	56	58.9	116	1	GUAN_MOUSE	P33680 mus musculu
33	55	57.9	66	1	HST_YERKR	P31518 yersinia kr
34	54	56.8	71	1	HSTA_YEREN	P07593 yersinia en
35	51	53.7	106	1	FSHB_STRCA	P80663 struthio ca
36	51	53.7	107	1	GUAN_CAVPO	P70664 cavia porce
37	51	53.7	109	1	GUAN_PIG	P79897 sus scrofa
38	51	53.7	131	2	Q8QGF8	Q8qgf8 gallus gall
39	50	52.6	15	1	GUAN_DIDMA	P55936 didelphis m
40	50	52.6	18	1	HSTB_ECOLI	P01560 escherichia
41	50	52.6	61	2	Q6VEG9	Q6veg9 escherichia
42	50	52.6	339	2	Q8NC41	Q8nc41 homo sapien
43	50	52.6	509	2	Q96SQ1	Q96sq1 homo sapien
44	50	52.6	510	2	Q6IE84	Q6ie84 mus musculu
45	50	52.6	702	2	Q96JL8	Q96jl8 homo sapien

ALIGNMENTS

RESULT 1
GUAU_HUMAN
ID GUAU_HUMAN STANDARD; PRT; 112 AA.
AC Q16661;
DT 01-NOV-1997 (Rel. 35, Created)
DT 01-NOV-1997 (Rel. 35, Last sequence update)
DT 25-OCT-2004 (Rel. 45, Last annotation update)
DE Uroguanylin precursor (UGN) (Guanylate cyclase activator 2B)
DE (Guanylate cyclase C activating peptide II) (GCAP-II).
GN Name=GUCA2B;
OS Homo sapiens (Human).
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX NCBI_TaxID=9606;
RN [1]
RP SEQUENCE FROM N.A.
RC TISSUE=Colon;
RX MEDLINE=96193705; PubMed=8605041; DOI=10.1006/bbrc.1996.0287;
RA Miyazato M., Nakazato M., Yamaguchi H., Date Y., Kojima M.,
RA Kangawa K., Matsuo H., Matsukura S.;
RT "Cloning and characterization of a cDNA encoding a precursor for human
RT uroguanylin.";
RL Biochem. Biophys. Res. Commun. 219:644-648(1996).
RN [2]
RP SEQUENCE FROM N.A.
RC TISSUE=Colon;
RX MEDLINE=96106424; PubMed=8519795; DOI=10.1016/0167-4838(95)00204-4;
RA Hill O., Cetin Y., Cieslak A., Maegert H.-J., Forssmann W.-G.;
RT "A new human guanylate cyclase-activating peptide (GCAP-II,
RT uroguanylin): precursor cDNA and colonic expression.";
RL Biochim. Biophys. Acta 1253:146-149(1995).
RN [3]
RP SEQUENCE FROM N.A.
RC TISSUE=Placenta;
RA Maegert H.-J., Hill O., Forssmann W.-G.;
RL Submitted (AUG-1996) to the EMBL/GenBank/DDBJ databases.
RN [4]
RP SEQUENCE FROM N.A.
RX MEDLINE=97422613; PubMed=9268639; DOI=10.1006/geno.1997.4808;
RA Miyazato M., Nakazato M., Matsukura S., Kangawa K., Matsuo H.;
RT "Genomic structure and chromosomal localization of human
RT uroguanylin.";
RL Genomics 43:359-365(1997).
RN [5]
RP SEQUENCE OF 89-112, AND DISULFIDE BONDS.
RC TISSUE=Blood;
RX MEDLINE=96049550; PubMed=7589507; DOI=10.1016/0014-5793(95)01075-P;
RA Hess R., Kuhn M., Schulz-Knappe P., Raida M., Fuchs M., Klodt J.,
RA Adermann K., Kaever V., Cetin Y., Forssmann W.-G.;
RT "GCAP-II: isolation and characterization of the circulating form of
RT human uroguanylin.";
RL FEBS Lett. 374:34-38(1995).
RN [6]
RP SEQUENCE OF 97-112, AND DISULFIDE BONDS.

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RX   MEDLINE=94189775; PubMed=8141334;
RA   Kita T., Smith C.E., Fok K.F., Duffin K.L., Moore W.M.,
RA   Karabatsos P.J., Kachur J.F., Hamra F.K., Pidhorodeckyj N.V.,
RA   Forte L.R., Currie M.G.;
RT   "Characterization of human uroguanylin: a member of the guanylin
RT   peptide family.";
RL   Am. J. Physiol. 266:F342-F348(1994).
RN   [7]
RP   STRUCTURE BY NMR OF 97-112.
RX   MEDLINE=98445220; PubMed=9774236;
RA   Marx U.C., Klodt J., Meyer M., Gerlach H., Roesch P., Forssmann W.-G.,
RA   Adermann K.;
RT   "One peptide, two topologies: structure and interconversion dynamics
RT   of human uroguanylin isomers.";
RL   J. Pept. Res. 52:229-240(1998).
CC   -!- FUNCTION: Endogenous activator of intestinal guanylate cyclase. It
CC       stimulates this enzyme through the same receptor binding region as
CC       the heat-stable enterotoxins. May be a potent physiological
CC       regulator of intestinal fluid and electrolyte transport. May be an
CC       autocrine/paracrine regulator of intestinal salt and water
CC       transport.
CC   -!- SUBCELLULAR LOCATION: Secreted.
CC   -!- TISSUE SPECIFICITY: Stomach and intestine.
CC   -!- SIMILARITY: Belongs to the guanylin family.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
CC   the European Bioinformatics Institute. There are no restrictions on its
CC   use by non-profit institutions as long as its content is in no way
CC   modified and this statement is not removed. Usage by and for commercial
CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; U34279; AAC50416.1; -.
DR   EMBL; Z50753; CAA90629.1; -.
DR   EMBL; Z70295; CAA94311.1; -.
DR   EMBL; U55058; AAC51729.1; -.
DR   PIR; JC4651; JC4651.
DR   PDB; 1UYA; NMR; @=97-112.
DR   PDB; 1UYB; NMR; @=97-112.
DR   Genew; HGNC:4683; GUCA2B.
DR   MIM; 601271; -.
DR   GO; GO:0008048; F:calcium sensitive guanylate cyclase activat. . .; TAS.
DR   GO; GO:0007588; P:excretion; TAS.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PIRSF; PIRSF001849; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
KW   3D-structure; Direct protein sequencing; Signal.
FT   SIGNAL       1     26       Potential.
FT   PROPEP      27     88
FT   PEPTIDE     89    112       GCAP-II.
FT   PEPTIDE     97    112       Uroguanylin.
FT   DISULFID    67     80       Potential.
FT   DISULFID   100    108
FT   DISULFID   103    111
FT   TURN       109    110
SQ   SEQUENCE   112 AA;  12069 MW;  AA3030BC3D4EE412 CRC64;

  Query Match             96.8%;  Score 92;  DB 1;  Length 112;
  Best Local Similarity   93.8%;  Pred. No. 4.6e-06;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db         97 NDDCELCVNVACTGCL 112


RESULT 2
GUAU_CAVPO
ID   GUAU_CAVPO     STANDARD;      PRT;   111 AA.
AC   P70107;
DT   01-NOV-1997 (Rel. 35, Created)
DT   01-NOV-1997 (Rel. 35, Last sequence update)
DT   25-OCT-2004 (Rel. 45, Last annotation update)
DE   Uroguanylin precursor (UGN) (Guanylate cyclase activator 2B).
GN   Name=GUCA2B;
OS   Cavia porcellus (Guinea pig).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Rodentia; Hystricognathi; Caviidae; Cavia.
OX   NCBI_TaxID=10141;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   TISSUE=Stomach;
RA   Kruhoeffer M., Meyer M.F., Schlatter E., Kaempf U., Cetin Y.,
RA   Forssmann W.-G.;
RL   Submitted (AUG-1996) to the EMBL/GenBank/DDBJ databases.
CC   -!- FUNCTION: Endogenous activator of intestinal guanylate cyclase. It
CC       stimulates this enzyme through the same receptor binding region as
CC       the heat-stable enterotoxins. May be a potent physiological
CC       regulator of intestinal fluid and electrolyte transport. May be an
CC       autocrine/paracrine regulator of intestinal salt and water
CC       transport.
CC   -!- SUBCELLULAR LOCATION: Secreted.
CC   -!- SIMILARITY: Belongs to the guanylin family.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
CC   the European Bioinformatics Institute. There are no restrictions on its
CC   use by non-profit institutions as long as its content is in no way
CC   modified and this statement is not removed. Usage by and for commercial
CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; Z74738; CAA98994.1; -.
DR   HSSP; Q16661; 1UYA.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PIRSF; PIRSF001849; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
KW   Signal.
FT   SIGNAL       1     26       Potential.
FT   PROPEP      27     96
FT   PEPTIDE     97    111       Uroguanylin.
FT   DISULFID    67     80       Potential.
FT   DISULFID   100    108       By similarity.
FT   DISULFID   103    111       By similarity.
SQ   SEQUENCE   111 AA;  12125 MW;  7C3366A721FE0411 CRC64;

  Query Match             94.7%;  Score 90;  DB 1;  Length 111;
  Best Local Similarity   93.3%;  Pred. No. 9e-06;
  Matches   14;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGC 15
              |||||||||:|||||
Db         97 NDECELCVNIACTGC 111


RESULT 3
GUAU_MOUSE
ID   GUAU_MOUSE     STANDARD;      PRT;   106 AA.
AC   O09051;
DT   01-NOV-1997 (Rel. 35, Created)
DT   16-OCT-2001 (Rel. 40, Last sequence update)
DT   05-JUL-2004 (Rel. 44, Last annotation update)
DE   Uroguanylin precursor (UGN) (Guanylate cyclase activator 2B).
GN   Name=Guca2b;
OS   Mus musculus (Mouse).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
OX   NCBI_TaxID=10090;
RN   [1]
RP   SEQUENCE FROM N.A.
RX   MEDLINE=97434109; PubMed=9287995;
```

GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: February 11, 2005, 20:58:35 ; Search time 22 Seconds
(without alignments)
69.976 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 283416 seqs, 96216763 residues

Total number of hits satisfying chosen parameters: 283416

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : PIR_79:*
1: pir1:*
2: pir2:*
3: pir3:*
4: pir4:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	92	96.8	112	2	JC4651	uroguanylin precur
2	73	76.8	116	2	JC7620	guanylin precursor
3	63	66.3	72	1	QHEC4	heat-stable entero
4	63	66.3	72	1	QHECIB	heat-stable entero
5	60	63.2	17	2	A54534	heat-stable entero
6	60	63.2	78	1	QHVC1	heat-stable entero
7	58	61.1	18	2	A60103	heat-stable entero
8	58	61.1	72	1	QHEC1	heat-stable entero
9	56	58.9	53	2	S68705	heat-stable entero
10	56	58.9	115	1	A46279	guanylin precursor
11	56	58.9	115	1	JN0318	guanylin precursor
12	56	58.9	116	1	B46279	guanylin precursor
13	55	57.9	66	2	S31652	enterotoxin - Yers
14	54	56.8	71	2	S25659	heat-stable entero
15	51	53.7	106	2	S74084	follitropin beta c
16	50	52.6	18	1	QHEC2	heat-stable entero
17	45	47.4	240	2	T27629	hypothetical prote
18	44.5	46.8	892	2	T40040	GTPase-activator p
19	44	46.3	1016	2	T00375	hypothetical prote
20	43.5	45.8	334	2	G75344	probable polyferre
21	43.5	45.8	1548	2	S34583	serine proteinase
22	43	45.3	65	2	S34671	heat-stable entero
23	43	45.3	153	2	S52605	probable membrane
24	43	45.3	282	1	YPDOD1	prestalk D11 prote
25	42.5	44.7	1052	2	T14343	zinc finger RNA bi
26	42	44.2	84	2	B69014	ferredoxin 2[4Fe-4
27	42	44.2	128	2	S74085	lutropin beta chai
28	42	44.2	159	2	I51373	luteinizing hormon
29	42	44.2	201	2	A48827	zinc finger protei
30	42	44.2	268	2	T04787	hypothetical prote
31	42	44.2	275	2	T21933	hypothetical prote
32	42	44.2	342	2	T27785	hypothetical prote
33	42	44.2	495	2	G82371	FixG-related prote
34	42	44.2	618	2	G72281	glutamate synthase
35	42	44.2	698	2	T23469	hypothetical prote
36	42	44.2	937	2	A45082	neurotrophic recep
37	42	44.2	1253	2	T45787	disease resistance
38	42	44.2	1664	2	F84485	probable retroelem
39	41.5	43.7	187	2	F88124	protein T12C9.5 [i
40	41.5	43.7	410	2	T24020	hypothetical prote
41	41.5	43.7	1274	2	T42017	cysteine rich prot
42	41	43.2	129	1	FTHUB	follitropin beta c
43	41	43.2	129	1	FTPGB	follitropin beta c
44	41	43.2	129	1	FTSHB	follitropin beta c
45	41	43.2	130	2	JC4526	follitropin beta c

ALIGNMENTS

RESULT 1
JC4651
uroguanylin precursor - human
N;Alternate names: guanylyl cyclase activating peptide II
C;Species: Homo sapiens (man)
C;Date: 10-May-1996 #sequence_revision 19-Jul-1996 #text_change 09-Jul-2004
C;Accession: JC4651; S63702; S68052
R;Miyazato, M.; Nakazato, M.; Yamaguchi, H.; Date, Y.; Kojima, M.; Kangawa, K.; Matsuo,
Biochem. Biophys. Res. Commun. 219, 644-648, 1996
A;Title: Cloning and characterization of a cDNA encoding a precursor for human uroguanyl
A;Reference number: JC4651; MUID:96193705; PMID:8605041
A;Accession: JC4651
A;Molecule type: mRNA
A;Residues: 1-112 <MIY>
A;Cross-references: UNIPROT:Q16661; GB:U34279; NID:g1236798; PIDN:AAC50416.1; PID:g12367
R;Hill, O.; Cetin, Y.; Cieslak, A.; Maegert, H.J.; Forssmann, W.G.
Biochim. Biophys. Acta 1253, 146-149, 1995
A;Title: A new human guanylate cyclase-activating peptide (GCAP-II, uroguanylin): precur
A;Reference number: S63702; MUID:96106424; PMID:8519795
A;Accession: S63702
A;Molecule type: mRNA
A;Residues: 1-112 <HIL>
A;Cross-references: EMBL:Z50753; NID:g974823; PIDN:CAA90629.1; PID:g974824
A;Experimental source: tissue colon
R;Hess, R.; Kuhn, M.; Schulz-Knappe, P.; Raida, M.; Fuchs, M.; Klodt, J.; Adermann, K.;
FEBS Lett. 374, 34-38, 1995
A;Title: GCAP-II: isolation and characterization of the circulating form of human urogua
A;Reference number: S68052; MUID:96049550; PMID:7589507
A;Accession: S68052
A;Molecule type: protein
A;Residues: 89-99,'X',101-102,'X',104-107,'X',109-110,'X',112 <HES>
C;Comment: This protein, a member of the guanylin peptide family, is an endogenous activ
.
C;Superfamily: guanylin
C;Keywords: intestine
F;1-26/Domain: signal sequence #status predicted <SIG>
F;27-112/Product: uroguanylin #status predicted <MAT>

Query Match 96.8%; Score 92; DB 2; Length 112;
Best Local Similarity 93.8%; Pred. No. 9.6e-06;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db         97 NDDCELCVNVACTGCL 112
```

RESULT 2
JC7620
guanylin precursor, long form - European eel
C;Species: Anguilla anguilla (European eel)
C;Date: 30-Jun-2001 #sequence_revision 30-Jun-2001 #text_change 03-Aug-2001

C;Accession: JC7620
R;Comrie, M.M.; Cutler, C.P.; Cramb, G.
Biochem. Biophys. Res. Commun. 281, 1078-1085, 2001
A;Title: Cloning and expression of guanylin from the European eel (Anguilla anguilla).
A;Reference number: JC7620; MUID:21139737; PMID:11243845
A;Accession: JC7620
A;Molecule type: mRNA
A;Residues: 1-116 <COM>
A;Cross-references: GB:AJ301673
C;Comment: This protein, a member of a family of heat-stable peptides, is a potent extra
axis. This peptide signalling system plays a role in osmoregulation in euryhaline telec
C;Superfamily: guanylin
C;Keywords: heat-stable protein; osmoregulation
F;1-28/Domain: signal sequence #status predicted <SIG>
F;29-116/Product: guanylin precursor, long form #status predicted <MAT>
F;33-39/Region: homologous #status predicted
F;69-114/Region: highly conserved #status predicted

Query Match 76.8%; Score 73; DB 2; Length 116;
Best Local Similarity 73.3%; Pred. No. 0.0036;
Matches 11; Conservative 1; Mismatches 3; Indels 0; Gaps 0;

Qy 2 DECELCVNVACTGCL 16
| ||:| | ||||||
Db 102 DPCEICANAACTGCL 116

RESULT 3
QHEC4
heat-stable enterotoxin STA4 precursor - Escherichia coli
C;Species: Escherichia coli
C;Date: 31-Mar-1992 #sequence_revision 31-Mar-1992 #text_change 09-Jul-2004
C;Accession: JT0373; A35978
R;Stieglitz, H.; Cervantes, L.; Robledo, R.; Fonseca, R.; Covarrubias, L.; Bolivar, F.;
Plasmid 20, 42-53, 1988
A;Title: Cloning, sequencing, and expression in ficoll-generated minicells of an Escheri
A;Reference number: JT0373; MUID:89202548; PMID:3071819
A;Accession: JT0373
A;Molecule type: DNA
A;Residues: 1-72 <STI>
A;Cross-references: UNIPROT:P07965; GB:J03311; NID:g147875; PIDN:AAA24652.1; PID:g147876
R;Zhou, X.; Shen, L.P.; Chi, C.W.
Toxicon 28, 453-456, 1990
A;Title: Isolation and nucleotide sequence determination of a gene encoding a heat-stabl
A;Reference number: A35978; MUID:90273381; PMID:2190361
A;Accession: A35978
A;Molecule type: DNA
A;Residues: 1-72 <ZHO>
C;Genetics:
A;Gene: estA4
C;Superfamily: heat-stable enterotoxin ST
C;Keywords: enterotoxin; heat-stable protein
F;1-19/Domain: signal sequence #status predicted <SIG>
F;20-53/Domain: propeptide #status predicted <PRO>
F;54-72/Product: heat-stable enterotoxin #status predicted <MAT>
F;59-64,60-68,63-71/Disulfide bonds: #status predicted

Query Match 66.3%; Score 63; DB 1; Length 72;
Best Local Similarity 83.3%; Pred. No. 0.057;
Matches 10; Conservative 0; Mismatches 2; Indels 0; Gaps 0;

Qy 4 CELCVNVACTGC 15
|||| | |||||
Db 60 CELCCNPACTGC 71

RESULT 4
QHECIB
heat-stable enterotoxin ST-Ib precursor - Escherichia coli
N;Alternate names: heat-stable enterotoxin ST-A2
C;Species: Escherichia coli
C;Date: 30-Jun-1991 #sequence_revision 30-Jun-1991 #text_change 09-Jul-2004
C;Accession: JS0292; A33068; A33067; A30567
R;Moseley, S.L.; Hardy, J.W.; Huq, M.I.; Echeverria, P.; Falkow, S.
Infect. Immun. 39, 1167-1174, 1983
A;Title: Isolation and nucleotide determination of a gene encoding a heat-stable enteroto
A;Reference number: JS0292; MUID:83184648; PMID:6341230
A;Accession: JS0292
A;Molecule type: DNA
A;Residues: 1-72 <MOS>
A;Cross-references: UNIPROT:Q47185; UNIPROT:P07965; GB:M34916; NID:g146407; PIDN:AAA2399(
R;Dwarakanath, P.; Visweswariah, S.S.; Subrahmanyam, Y.V.B.K.; Shanthi, G.; Jagannatha, F
Gene 81, 219-226, 1989
A;Title: Cloning and hyperexpression of a gene encoding the heat-stable toxin of Escheric
A;Reference number: A33068; MUID:90034194; PMID:2680769
A;Accession: A33068
A;Molecule type: DNA
A;Residues: 1-18,'A',20-72 <DWA>
A;Cross-references: GB:M29255; NID:g148029; PIDN:AAA24686.1; PID:g148030
A;Note: the authors translated the codon AAG for residue 2 as Val and CTA for residue 34
R;Aimoto, S.; Takao, T.; Shimonishi, Y.; Hara, S.; Takeda, T.; Takeda, Y.; Miwatani, T.
Eur. J. Biochem. 129, 257-263, 1982
A;Title: Amino acid sequence of heat-stable enterotoxin produced by human enterotoxigenic
A;Reference number: A33067; MUID:83105138; PMID:6759126
A;Accession: A33067
A;Molecule type: protein
A;Residues: 54-72 <AIM>
R;Guzman-Verduzco, L.M.; Kupersztoch, Y.M.
Infect. Immun. 57, 645-648, 1989
A;Title: Rectification of two Escherichia coli heat-stable enterotoxin allele sequences a
A;Reference number: A30567; MUID:89108616; PMID:2643580
A;Accession: A30567
A;Molecule type: DNA
A;Residues: 1-18,'A',20-24,'AG',27-41,'V',43-44,'N',46,'E',48,'S',50-72 <GUZ>
A;Cross-references: GB:M18345; NID:g145862; PIDN:AAA23729.1; PID:g145863
C;Comment: This is one of the type I heat-stable enterotoxins that are methanol-soluble.
C;Genetics:
A;Gene: st
C;Superfamily: heat-stable enterotoxin ST
C;Keywords: enterotoxin; heat-stable protein
F;1-53/Domain: signal sequence and propeptide #status predicted <SIG>
F;54-72/Product: heat-stable enterotoxin ST-Ib #status experimental <MAT>
F;59-64,60-68,63-71/Disulfide bonds: #status experimental

Query Match 66.3%; Score 63; DB 1; Length 72;
Best Local Similarity 83.3%; Pred. No. 0.057;
Matches 10; Conservative 0; Mismatches 2; Indels 0; Gaps 0;

Qy 4 CELCVNVACTGC 15
|||| | |||||
Db 60 CELCCNPACTGC 71

RESULT 5
A54534
heat-stable enterotoxin - Vibrio mimicus (fragment)
C;Species: Vibrio mimicus
C;Date: 06-Jan-1995 #sequence_revision 06-Jan-1995 #text_change 03-May-1996
C;Accession: A54534
R;Arita, M.; Honda, T.; Miwatani, T.; Takeda, T.; Takao, T.; Shimonishi, Y.
FEMS Microbiol. Lett. 79, 105-110, 1991
A;Title: Purification and characterization of a heat-stable enterotoxin of Vibrio mimicus
A;Reference number: A54534
A;Accession: A54534
A;Status: preliminary
A;Molecule type: protein
A;Residues: 1-17 <ARI>
C;Superfamily: heat-stable enterotoxin ST

Query Match 63.2%; Score 60; DB 2; Length 17;
Best Local Similarity 66.7%; Pred. No. 0.048;
Matches 10; Conservative 1; Mismatches 4; Indels 0; Gaps 0;

Qy 2 DECELCVNVACTGCL 16
| ||:| | || |||
Db 2 DCCEICCNPACFGCL 16

GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: February 11, 2005, 21:32:26 ; Search time 34 Seconds
(without alignments)
153.764 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 1376875 seqs, 326749119 residues

Total number of hits satisfying chosen parameters: 1376875

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : Published_Applications_AA:*
1: /cgn2_6/ptodata/1/pubpaa/US07_PUBCOMB.pep:*
2: /cgn2_6/ptodata/1/pubpaa/PCT_NEW_PUB.pep:*
3: /cgn2_6/ptodata/1/pubpaa/US06_NEW_PUB.pep:*
4: /cgn2_6/ptodata/1/pubpaa/US06_PUBCOMB.pep:*
5: /cgn2_6/ptodata/1/pubpaa/US07_NEW_PUB.pep:*
6: /cgn2_6/ptodata/1/pubpaa/PCTUS_PUBCOMB.pep:*
7: /cgn2_6/ptodata/1/pubpaa/US08_NEW_PUB.pep:*
8: /cgn2_6/ptodata/1/pubpaa/US08_PUBCOMB.pep:*
9: /cgn2_6/ptodata/1/pubpaa/US09A_PUBCOMB.pep:*
10: /cgn2_6/ptodata/1/pubpaa/US09B_PUBCOMB.pep:*
11: /cgn2_6/ptodata/1/pubpaa/US09C_PUBCOMB.pep:*
12: /cgn2_6/ptodata/1/pubpaa/US09_NEW_PUB.pep:*
13: /cgn2_6/ptodata/1/pubpaa/US10A_PUBCOMB.pep:*
14: /cgn2_6/ptodata/1/pubpaa/US10B_PUBCOMB.pep:*
15: /cgn2_6/ptodata/1/pubpaa/US10C_PUBCOMB.pep:*
16: /cgn2_6/ptodata/1/pubpaa/US10D_PUBCOMB.pep:*
17: /cgn2_6/ptodata/1/pubpaa/US10_NEW_PUB.pep:*
18: /cgn2_6/ptodata/1/pubpaa/US11_NEW_PUB.pep:*
19: /cgn2_6/ptodata/1/pubpaa/US60_NEW_PUB.pep:*
20: /cgn2_6/ptodata/1/pubpaa/US60_PUBCOMB.pep:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	95	100.0	16	14	US-10-107-814-20	Sequence 20, Appl
2	92	96.8	16	14	US-10-107-814-1	Sequence 1, Appli
3	92	96.8	16	14	US-10-197-954-141	Sequence 141, App
4	92	96.8	16	15	US-10-621-684-56	Sequence 56, Appl
5	83	87.4	14	14	US-10-107-814-21	Sequence 21, Appl
6	77	81.1	15	15	US-10-621-684-55	Sequence 55, Appl
7	66	69.5	16	14	US-10-107-814-2	Sequence 2, Appli
8	64	67.4	17	17	US-10-796-719-15	Sequence 15, Appl
9	63	66.3	13	15	US-10-621-684-32	Sequence 32, Appl
10	63	66.3	14	15	US-10-621-684-31	Sequence 31, Appl
11	63	66.3	14	15	US-10-621-684-37	Sequence 37, Appl
12	63	66.3	14	17	US-10-796-719-29	Sequence 29, Appl
13	63	66.3	15	15	US-10-371-966-3	Sequence 3, Appli
14	63	66.3	15	15	US-10-621-684-30	Sequence 30, Appl
15	63	66.3	15	15	US-10-621-684-36	Sequence 36, Appl
16	63	66.3	15	17	US-10-796-719-32	Sequence 32, Appl
17	63	66.3	16	15	US-10-621-684-29	Sequence 29, Appl
18	63	66.3	16	15	US-10-621-684-35	Sequence 35, Appl
19	63	66.3	16	17	US-10-796-719-46	Sequence 46, Appl
20	63	66.3	17	15	US-10-621-684-28	Sequence 28, Appl
21	63	66.3	17	15	US-10-621-684-34	Sequence 34, Appl
22	63	66.3	17	17	US-10-796-719-53	Sequence 53, Appl
23	63	66.3	18	15	US-10-621-684-27	Sequence 27, Appl
24	63	66.3	18	15	US-10-621-684-33	Sequence 33, Appl
25	63	66.3	19	14	US-10-107-814-23	Sequence 23, Appl
26	63	66.3	19	15	US-10-371-966-1	Sequence 1, Appli
27	63	66.3	19	15	US-10-371-966-2	Sequence 2, Appli
28	63	66.3	19	17	US-10-796-719-1	Sequence 1, Appli
29	63	66.3	19	17	US-10-796-719-26	Sequence 26, Appl
30	63	66.3	21	17	US-10-796-719-39	Sequence 39, Appl
31	63	66.3	72	17	US-10-796-719-21	Sequence 21, Appl
32	61	64.2	13	17	US-10-796-719-135	Sequence 135, App
33	61	64.2	13	17	US-10-796-719-137	Sequence 137, App
34	61	64.2	14	17	US-10-796-719-102	Sequence 102, App
35	61	64.2	14	17	US-10-796-719-104	Sequence 104, App
36	61	64.2	19	17	US-10-796-719-84	Sequence 84, Appl
37	61	64.2	19	17	US-10-796-719-86	Sequence 86, Appl
38	60	63.2	13	17	US-10-796-719-143	Sequence 143, App
39	60	63.2	14	15	US-10-621-684-53	Sequence 53, Appl
40	60	63.2	14	17	US-10-796-719-110	Sequence 110, App
41	60	63.2	17	17	US-10-796-719-9	Sequence 9, Appli
42	60	63.2	17	17	US-10-796-719-10	Sequence 10, Appl
43	60	63.2	17	17	US-10-796-719-14	Sequence 14, Appl
44	60	63.2	18	15	US-10-621-684-40	Sequence 40, Appl
45	60	63.2	19	17	US-10-796-719-92	Sequence 92, Appl

ALIGNMENTS

RESULT 1
US-10-107-814-20
; Sequence 20, Application US/10107814
; Publication No. US20030073628A1
; GENERAL INFORMATION:
; APPLICANT: SHAILUBHAI, KUNWAR
; APPLICANT: NIKIFOROVICH, GREGORY
; APPLICANT: JACOB, GARY S.
; TITLE OF INVENTION: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT
; TITLE OF INVENTION: OF TISSUE INFLAMMATION AND CARCINOGENESIS
; FILE REFERENCE: 81361/284943/MAS
; CURRENT APPLICATION NUMBER: US/10/107,814
; CURRENT FILING DATE: 2002-03-28
; NUMBER OF SEQ ID NOS: 23
; SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 20
; LENGTH: 16
; TYPE: PRT
; ORGANISM: Artificial Sequence
; FEATURE:
; OTHER INFORMATION: Description of Artificial Sequence: Synthetic
; OTHER INFORMATION: guanylate cyclase receptor agonist peptide
; NAME/KEY: DISULFID
; LOCATION: (4)..(12)
; NAME/KEY: DISULFID
; LOCATION: (7)..(15)
US-10-107-814-20

Query Match 100.0%; Score 95; DB 14; Length 16;
Best Local Similarity 100.0%; Pred. No. 3.2e-06;
Matches 16; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Db          1 NDECELCVNVACTGCL 16
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RESULT 2
US-10-107-814-1
; Sequence 1, Application US/10107814
; Publication No. US20030073628A1
; GENERAL INFORMATION:
;  APPLICANT: SHAILUBHAI, KUNWAR
;  APPLICANT:  NIKIFOROVICH, GREGORY
;  APPLICANT:  JACOB, GARY S.
;  TITLE OF INVENTION: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT
;  TITLE OF INVENTION:  OF TISSUE INFLAMMATION AND CARCINOGENESIS
;  FILE REFERENCE: 81361/284943/MAS
;  CURRENT APPLICATION NUMBER: US/10/107,814
;  CURRENT FILING DATE:  2002-03-28
;  NUMBER OF SEQ ID NOS: 23
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 1
;   LENGTH: 16
;   TYPE: PRT
;   ORGANISM: Homo sapiens
;   FEATURE:
;   NAME/KEY: DISULFID
;   LOCATION: (4)..(12)
;   NAME/KEY: DISULFID
;   LOCATION: (7)..(15)
US-10-107-814-1

  Query Match             96.8%;  Score 92;  DB 14;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 8.1e-06;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          1 NDDCELCVNVACTGCL 16


RESULT 3
US-10-197-954-141
; Sequence 141, Application US/10197954
; Publication No. US20030119021A1
; GENERAL INFORMATION:
;  APPLICANT: K"ster, Hubert
;  APPLICANT:  Siddiqi, Suhaib
;  APPLICANT:  Little, Daniel
;  TITLE OF INVENTION: Capture Compounds, Collections Thereof
;  TITLE OF INVENTION:  And Methods For Analyzing The Proteome And Complex
;  TITLE OF INVENTION:  Compositions
;  FILE REFERENCE: 24743-2305
;  CURRENT APPLICATION NUMBER: US/10/197,954
;  CURRENT FILING DATE:  2002-07-16
;  PRIOR APPLICATION NUMBER: 60/306,019
;  PRIOR FILING DATE: 2001-07-16
;  PRIOR APPLICATION NUMBER: 60/314,123
;  PRIOR FILING DATE: 2001-08-21
;  PRIOR APPLICATION NUMBER: 60/363,433
;  PRIOR FILING DATE: 2002-03-11
;  NUMBER OF SEQ ID NOS: 149
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 141
;   LENGTH: 16
;   TYPE: PRT
;   ORGANISM: Homo Sapien
US-10-197-954-141

  Query Match             96.8%;  Score 92;  DB 14;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 8.1e-06;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          1 NDDCELCVNVACTGCL 16
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```
RESULT 4
US-10-621-684-56
; Sequence 56, Application US/10621684
; Publication No. US20040029182A1
;   GENERAL INFORMATION:
;        APPLICANT: Waldman, Scott A.
;        TITLE OF INVENTION: ST Receptor Binding Compounds and
;                            Methods of Using the Same
;        NUMBER OF SEQUENCES: 56
;        CORRESPONDENCE ADDRESS:
;             ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz & No. US20040029182A1ris
;             STREET: One Liberty Place, 46th Floor
;             CITY: Philadelphia
;             STATE: Pennsylvania
;             COUNTRY: USA
;             ZIP: 19103
;        COMPUTER READABLE FORM:
;             MEDIUM TYPE: Floppy disk
;             COMPUTER: IBM PC compatible
;             OPERATING SYSTEM: Windows
;             SOFTWARE: WordPerfect 6.1
;        CURRENT APPLICATION DATA:
;             APPLICATION NUMBER: US/10/621,684
;             FILING DATE: 17-Jul-2003
;             CLASSIFICATION: 435
;        PRIOR APPLICATION DATA:
;             APPLICATION NUMBER: US/08/583,447A
;             FILING DATE: 05-JAN-1996
;             APPLICATION NUMBER: US 08/141,892
;             FILING DATE: 26-OCT-1993
;        ATTORNEY/AGENT INFORMATION:
;             NAME: DeLuca, Mark
;             REGISTRATION NUMBER: 33,229
;             REFERENCE/DOCKET NUMBER: TJU-1702
;        TELECOMMUNICATION INFORMATION:
;             TELEPHONE: 215-568-3100
;             TELEFAX: 215-568-3439
;   INFORMATION FOR SEQ ID NO: 56:
;        SEQUENCE CHARACTERISTICS:
;             LENGTH: 16 amino acids
;             TYPE: amino acid
;             TOPOLOGY: linear
;        MOLECULE TYPE: peptide
;        SEQUENCE DESCRIPTION: SEQ ID NO: 56:
US-10-621-684-56

  Query Match             96.8%;  Score 92;  DB 15;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 8.1e-06;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          1 NDDCELCVNVACTGCL 16


RESULT 5
US-10-107-814-21
; Sequence 21, Application US/10107814
; Publication No. US20030073628A1
; GENERAL INFORMATION:
;  APPLICANT: SHAILUBHAI, KUNWAR
;  APPLICANT:  NIKIFOROVICH, GREGORY
;  APPLICANT:  JACOB, GARY S.
;  TITLE OF INVENTION: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT
;  TITLE OF INVENTION:  OF TISSUE INFLAMMATION AND CARCINOGENESIS
;  FILE REFERENCE: 81361/284943/MAS
;  CURRENT APPLICATION NUMBER: US/10/107,814
;  CURRENT FILING DATE:  2002-03-28
;  NUMBER OF SEQ ID NOS: 23
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 21
;   LENGTH: 14
;   TYPE: PRT
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GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: February 11, 2005, 21:21:52 ; Search time 44 Seconds
(without alignments)
140.640 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 2105692 seqs, 386760381 residues

Total number of hits satisfying chosen parameters: 2105692

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : A_Geneseq_16Dec04:*
1: geneseqp1980s:*
2: geneseqp1990s:*
3: geneseqp2000s:*
4: geneseqp2001s:*
5: geneseqp2002s:*
6: geneseqp2003as:*
7: geneseqp2003bs:*
8: geneseqp2004s:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	95	100.0	16	6	AAO16201	Aao16201 Guanylate
2	92	96.8	16	2	AAR90204	Aar90204 Uroguanyl
3	92	96.8	16	2	AAY02390	Aay02390 Heat stab
4	92	96.8	16	2	AAY29612	Aay29612 Uroguanyl
5	92	96.8	16	2	AAY06976	Aay06976 Heat stab
6	92	96.8	16	2	AAY02402	Aay02402 Heat stab
7	92	96.8	16	4	AAB92073	Aab92073 Guanylin
8	92	96.8	16	4	AAB83214	Aab83214 Human uro
9	92	96.8	16	6	AAO16182	Aao16182 Human uro
10	92	96.8	16	6	ABG74820	Abg74820 Human uro
11	92	96.8	16	8	ADN03414	Adn03414 Exemplary
12	92	96.8	16	8	ADR42249	Adr42249 Uroguanyl
13	92	96.8	19	2	AAW18470	Aaw18470 Human GCA
14	92	96.8	19	2	AAW18483	Aaw18483 Human GCA
15	92	96.8	19	2	AAW23224	Aaw23224 GCAP-II C
16	92	96.8	22	2	AAW18482	Aaw18482 Human GCA
17	92	96.8	22	2	AAW18473	Aaw18473 Human GCA
18	92	96.8	22	2	AAW23227	Aaw23227 GCAP-II C
19	92	96.8	23	2	AAW18487	Aaw18487 Human GCA
20	92	96.8	23	2	AAW23235	Aaw23235 GCAP-II C
21	92	96.8	24	2	AAW18465	Aaw18465 Human GCA
22	92	96.8	24	5	AAM47256	Aam47256 Guanylate
23	92	96.8	28	2	AAW18494	Aaw18494 Human GCA
24	92	96.8	28	2	AAW23241	Aaw23241 GCAP-II C
25	92	96.8	37	2	AAW18493	Aaw18493 Human GCA
26	92	96.8	37	2	AAW23240	Aaw23240 GCAP-II C
27	92	96.8	38	2	AAW18475	Aaw18475 Human GCA
28	92	96.8	38	2	AAW23229	Aaw23229 GCAP-II C
29	92	96.8	43	2	AAW18489	Aaw18489 Human GCA
30	92	96.8	43	2	AAW23236	Aaw23236 GCAP-II C
31	92	96.8	56	2	AAW18469	Aaw18469 Human GCA
32	92	96.8	56	2	AAW23223	Aaw23223 GCAP-II C
33	92	96.8	64	2	AAW18492	Aaw18492 Human GCA
34	92	96.8	64	2	AAW23239	Aaw23239 GCAP-II C
35	92	96.8	66	2	AAW18491	Aaw18491 Human GCA
36	92	96.8	66	2	AAW23238	Aaw23238 GCAP-II C
37	92	96.8	67	2	AAW18474	Aaw18474 Human GCA
38	92	96.8	67	2	AAW23228	Aaw23228 GCAP-II C
39	92	96.8	69	2	AAW18472	Aaw18472 Human GCA
40	92	96.8	69	2	AAW18481	Aaw18481 Human GCA
41	92	96.8	69	2	AAW18488	Aaw18488 Human GCA
42	92	96.8	69	2	AAW23226	Aaw23226 GCAP-II C
43	92	96.8	70	2	AAW18471	Aaw18471 Human GCA
44	92	96.8	70	2	AAW18480	Aaw18480 Human GCA
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ALIGNMENTS

RESULT 1
AAO16201
ID AAO16201 standard; peptide; 16 AA.
XX
AC AAO16201;
XX
DT 28-MAR-2003 (first entry)
XX
DE Guanylate cyclase receptor agonist peptide, SEQ ID No 20.
XX
KW Guanylate cyclase receptor agonist; apoptosis induction; cancer; polyps;
KW inflammation; asthma; nephritis; hepatitis; bronchitis; cystic fibrosis;
KW inflammatory bowel disease; pancreatitis; ulcerative colitis;
KW Crohn's disease; Kaposi's sarcoma.
XX
OS Unidentified.
XX
FH Key Location/Qualifiers
FT Disulfide-bond 4. .12
FT Disulfide-bond 7. .15
XX
PN WO200278683-A1.
XX
PD 10-OCT-2002.
XX
PF 28-MAR-2002; 2002WO-US009551.
XX
PR 29-MAR-2001; 2001US-0279437P.
PR 29-MAR-2001; 2001US-0279438P.
PR 27-JUN-2001; 2001US-0300850P.
PR 10-JUL-2001; 2001US-0303806P.
PR 25-JUL-2001; 2001US-0307358P.
PR 17-JAN-2002; 2002US-0348646P.
XX
PA (SYNE-) SYNERGY PHARM INC.
XX
PI Shailubhai K, Nikiforovich G, Jacob GS;
XX
DR WPI; 2003-148251/14.
XX
PT Novel guanylate cyclase receptor agonist peptide useful for preventing or
PT treating primary or metastatic cancer and polyps in a patient, and for
PT inducing apoptosis in the cells of a subject.
XX
PS Claim 1; Page 6; 47pp; English.
XX
CC The invention comprises guanylate cyclase receptor agonist peptides that
CC are useful for inducing apoptosis in the cells of a subject. The peptides

```
CC   of the invention may be used to treat: cancer; polyps; inflammation;
CC   asthma; nephritis; hepatitis; pancreatitis; bronchitis; cystic fibrosis;
CC   inflammatory bowel disease; ulcerative colitis; Crohn's disease; and
CC   Kaposi's sarcoma. The present amino acid sequence represents a guanylate
CC   cyclase receptor agonist peptide of the invention
XX
SQ   Sequence 16 AA;

  Query Match             100.0%;  Score 95;  DB 6;  Length 16;
  Best Local Similarity   100.0%;  Pred. No. 3.3e-06;
  Matches   16;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||||||||||||||||
Db          1 NDECELCVNVACTGCL 16


RESULT 2
AAR90204
ID   AAR90204 standard; peptide; 16 AA.
XX
AC   AAR90204;
XX
DT   01-AUG-1996  (first entry)
XX
DE   Uroguanylin.
XX
KW   intestinal guanylate cyclase regulator; laxative; constipation.
XX
OS   Homo sapiens.
XX
FH   Key             Location/Qualifiers
FT   Disulfide-bond  4. .12
FT                   /note= "this bond is absent in the non-active form of the
FT                   peptide"
FT   Disulfide-bond  7. .15
FT                   /note= "this bond is absent in the non-active form of the
FT                   peptide"
XX
PN   US5489670-A.
XX
PD   06-FEB-1996.
XX
PF   29-OCT-1993;   93US-00145940.
XX
PR   29-OCT-1993;   93US-00145940.
XX
PA   (SEAR ) SEARLE & CO G D.
XX
PI   Smith CE,  Fok KF,  Currie MG,  Kita T;
XX
DR   WPI; 1996-115663/12.
XX
PT   New isolated human uroguanylin peptide - an endogenous stimulator of
PT   intestinal guanylate cyclase, used for the control of intestinal
PT   absorption.
XX
PS   Claim 1; Col 7; 9pp; English.
XX
CC   The peptide, designated human uroguanylin, has been isolated from human
CC   urine. It is an endogenous stimulator of intestinal guanylate cyclase and
CC   acts to increase cyclic GMP levels, to control intestinal absorption, to
CC   regulate fluid and electrolyte transport, to displace heat stable
CC   enterotoxins, to elicit chloride secretion and to decrease water
CC   absorption. It may thus act as a laxative and be useful in patients
CC   suffering from constipation, e.g. cystic fibrosis patients who suffer
CC   with severe intestinal complications from constipation
XX
SQ   Sequence 16 AA;

  Query Match             96.8%;  Score 92;  DB 2;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 8.5e-06;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          1 NDDCELCVNVACTGCL 16


RESULT 3
AAY02390
ID   AAY02390 standard; peptide; 16 AA.
XX
AC   AAY02390;
XX
DT   09-JUL-1999  (first entry)
XX
DE   Heat stable ST enterotoxin uroguanylin peptide.
XX
KW   Selection; candidate drug; cell receptor binding; affinity;
KW   biological receptor; rational drug design; combinatorial drug design;
KW   receptor antagonist; receptor agonist; ST enterotoxin; beta turn mimetic;
KW   gamma-turn mimetic; beta sheet mimetic; disulphide bridge mimetic.
XX
OS   Unidentified.
XX
PN   WO9909416-A2.
XX
PD   25-FEB-1999.
XX
PF   20-AUG-1998;   98WO-GB002504.
XX
PR   20-AUG-1997;   97GB-00017652.
XX
PA   (NYCO-) NYCOMED IMAGING AS.
PA   (COCK/) COCKBAIN J.
XX
PI   Wolfe HR;
XX
DR   WPI; 1999-181156/15.
XX
PT   Method of drug selection - and use of an acetamidomethyl-protected
PT   polymer as a substrate in the solid state synthesis of an oligopeptide.
XX
PS   Disclosure; Page 2; 38pp; English.
XX
CC   The specification describes a method for selecting a candidate drug
CC   compound having affinity for biological receptors. The method uses a
CC   combination of rational and combinatorial drug design techniques. At
CC   least 1 residue in the original cell receptor binding peptide is modified
CC   to a non-natural amino acid, preferably a beta turn mimetic, a gamma-turn
CC   mimetic, a beta sheet mimetic or a disulphide bridge mimetic. The method
CC   is used for identification of a candidate receptor antagonist or agonist.
CC   The present peptide is a cell receptor binding peptide, and can thus be
CC   used as a starting point for identification of candidate drug compounds,
CC   using the method of the invention
XX
SQ   Sequence 16 AA;

  Query Match             96.8%;  Score 92;  DB 2;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 8.5e-06;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          1 NDDCELCVNVACTGCL 16


RESULT 4
AAY29612
ID   AAY29612 standard; peptide; 16 AA.
XX
AC   AAY29612;
XX
DT   15-OCT-1999  (first entry)
XX
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GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: February 11, 2005, 21:23:16 ; Search time 23 Seconds
(without alignments)
51.930 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 513545 seqs, 74649064 residues

Total number of hits satisfying chosen parameters: 513545

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : Issued_Patents_AA:*
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3: /cgn2_6/ptodata/1/iaa/6A_COMB.pep:*
4: /cgn2_6/ptodata/1/iaa/6B_COMB.pep:*
5: /cgn2_6/ptodata/1/iaa/PCTUS_COMB.pep:*
6: /cgn2_6/ptodata/1/iaa/backfiles1.pep:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	92	96.8	16	1	US-08-145-940-1	Sequence 1, Appli
2	92	96.8	16	2	US-08-583-447A-56	Sequence 56, Appl
3	86	90.5	15	1	US-08-145-940-2	Sequence 2, Appli
4	77	81.1	15	2	US-08-583-447A-55	Sequence 55, Appl
5	63	66.3	13	1	US-08-141-892A-32	Sequence 32, Appl
6	63	66.3	13	2	US-08-583-447A-32	Sequence 32, Appl
7	63	66.3	13	2	US-08-467-920-32	Sequence 32, Appl
8	63	66.3	13	3	US-08-635-930-32	Sequence 32, Appl
9	63	66.3	13	3	US-09-193-997-32	Sequence 32, Appl
10	63	66.3	13	3	US-09-138-237A-32	Sequence 32, Appl
11	63	66.3	14	1	US-08-141-892A-31	Sequence 31, Appl
12	63	66.3	14	1	US-08-141-892A-37	Sequence 37, Appl
13	63	66.3	14	2	US-08-583-447A-31	Sequence 31, Appl
14	63	66.3	14	2	US-08-583-447A-37	Sequence 37, Appl
15	63	66.3	14	2	US-08-467-920-31	Sequence 31, Appl
16	63	66.3	14	2	US-08-467-920-37	Sequence 37, Appl
17	63	66.3	14	3	US-08-635-930-31	Sequence 31, Appl
18	63	66.3	14	3	US-08-635-930-37	Sequence 37, Appl
19	63	66.3	14	3	US-09-193-997-31	Sequence 31, Appl
20	63	66.3	14	3	US-09-193-997-37	Sequence 37, Appl
21	63	66.3	14	3	US-09-138-237A-31	Sequence 31, Appl
22	63	66.3	14	3	US-09-138-237A-37	Sequence 37, Appl
23	63	66.3	15	1	US-08-141-892A-30	Sequence 30, Appl
24	63	66.3	15	1	US-08-141-892A-36	Sequence 36, Appl
25	63	66.3	15	2	US-08-583-447A-30	Sequence 30, Appl
26	63	66.3	15	2	US-08-583-447A-36	Sequence 36, Appl
27	63	66.3	15	2	US-08-467-920-30	Sequence 30, Appl
28	63	66.3	15	2	US-08-467-920-36	Sequence 36, Appl
29	63	66.3	15	3	US-08-635-930-30	Sequence 30, Appl
30	63	66.3	15	3	US-08-635-930-36	Sequence 36, Appl
31	63	66.3	15	3	US-09-193-997-30	Sequence 30, Appl
32	63	66.3	15	3	US-09-193-997-36	Sequence 36, Appl
33	63	66.3	15	3	US-09-138-237A-30	Sequence 30, Appl
34	63	66.3	15	3	US-09-138-237A-36	Sequence 36, Appl
35	63	66.3	16	1	US-08-141-892A-29	Sequence 29, Appl
36	63	66.3	16	1	US-08-141-892A-35	Sequence 35, Appl
37	63	66.3	16	2	US-08-583-447A-29	Sequence 29, Appl
38	63	66.3	16	2	US-08-583-447A-35	Sequence 35, Appl
39	63	66.3	16	2	US-08-467-920-29	Sequence 29, Appl
40	63	66.3	16	2	US-08-467-920-35	Sequence 35, Appl
41	63	66.3	16	3	US-08-635-930-29	Sequence 29, Appl
42	63	66.3	16	3	US-08-635-930-35	Sequence 35, Appl
43	63	66.3	16	3	US-09-193-997-29	Sequence 29, Appl
44	63	66.3	16	3	US-09-193-997-35	Sequence 35, Appl
45	63	66.3	16	3	US-09-138-237A-29	Sequence 29, Appl

ALIGNMENTS

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RESULT 1
US-08-145-940-1
; Sequence 1, Application US/08145940
; Patent No. 5489670
;  GENERAL INFORMATION:
;    APPLICANT:  Currie, Mark G.
;    APPLICANT:  Kita, Toshihiro
;    APPLICANT:  Smith, Christine E.
;    APPLICANT:  Fok, Kam F.
;    TITLE OF INVENTION:  Human Uroguanylin
;    NUMBER OF SEQUENCES:  2
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Dennis A. Bennett, G.D. Searle & Co.,
;      ADDRESSEE:  Corporate Patent Dept.
;      STREET:  P. O. Box 5110
;      CITY:  Chicago
;      STATE:  Illinois
;      COUNTRY:  USA
;      ZIP:  60680
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.25
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/145,940
;      FILING DATE:
;      CLASSIFICATION:  530
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Bennett, Dennis A.
;      REGISTRATION NUMBER:  34,547
;      REFERENCE/DOCKET NUMBER:  07-21(808)A
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (708)470-6501
;      TELEFAX:  (708)470-6881
;  INFORMATION FOR SEQ ID NO:  1:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  16 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-145-940-1

  Query Match             96.8%;  Score 92;  DB 1;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 2.9e-06;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          1 NDDCELCVNVACTGCL 16
```

RESULT 2
US-08-583-447A-56
; Sequence 56, Application US/08583447A
; Patent No. 5879656
; GENERAL INFORMATION:
; APPLICANT: Waldman, Scott A.
; TITLE OF INVENTION: ST Receptor Binding Compounds and
; TITLE OF INVENTION: Methods of Using the Same
; NUMBER OF SEQUENCES: 56
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz & No. 5879656ris
; STREET: One Liberty Place, 46th Floor
; CITY: Philadelphia
; STATE: Pennsylvania
; COUNTRY: USA
; ZIP: 19103
; COMPUTER READABLE FORM:
; MEDIUM TYPE: Floppy disk
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: Windows
; SOFTWARE: WordPerfect 6.1
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/08/583,447A
; FILING DATE: 05-JAN-1996
; CLASSIFICATION: 435
; PRIOR APPLICATION DATA:
; APPLICATION NUMBER: US 08/141,892
; FILING DATE: 26-OCT-1993
; CLASSIFICATION: 435
; ATTORNEY/AGENT INFORMATION:
; NAME: DeLuca, Mark
; REGISTRATION NUMBER: 33,229
; REFERENCE/DOCKET NUMBER: TJU-1702
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: 215-568-3100
; TELEFAX: 215-568-3439
; INFORMATION FOR SEQ ID NO: 56:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 16 amino acids
; TYPE: amino acid
; TOPOLOGY: linear
; MOLECULE TYPE: peptide
US-08-583-447A-56

Query Match 96.8%; Score 92; DB 2; Length 16;
Best Local Similarity 93.8%; Pred. No. 2.9e-06;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

Qy 1 NDECELCVNVACTGCL 16
||:||||||||||||
Db 1 NDDCELCVNVACTGCL 16

RESULT 3
US-08-145-940-2
; Sequence 2, Application US/08145940
; Patent No. 5489670
; GENERAL INFORMATION:
; APPLICANT: Currie, Mark G.
; APPLICANT: Kita, Toshihiro
; APPLICANT: Smith, Christine E.
; APPLICANT: Fok, Kam F.
; TITLE OF INVENTION: Human Uroguanylin
; NUMBER OF SEQUENCES: 2
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: Dennis A. Bennett, G.D. Searle & Co.,
; ADDRESSEE: Corporate Patent Dept.
; STREET: P. O. Box 5110
; CITY: Chicago
; STATE: Illinois
; COUNTRY: USA
; ZIP: 60680
; COMPUTER READABLE FORM:
; MEDIUM TYPE: Floppy disk
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: PC-DOS/MS-DOS
; SOFTWARE: PatentIn Release #1.0, Version #1.25
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/08/145,940
; FILING DATE:
; CLASSIFICATION: 530
; ATTORNEY/AGENT INFORMATION:
; NAME: Bennett, Dennis A.
; REGISTRATION NUMBER: 34,547
; REFERENCE/DOCKET NUMBER: 07-21(808)A
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: (708)470-6501
; TELEFAX: (708)470-6881
; INFORMATION FOR SEQ ID NO: 2:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 15 amino acids
; TYPE: amino acid
; TOPOLOGY: linear
; MOLECULE TYPE: peptide
US-08-145-940-2

Query Match 90.5%; Score 86; DB 1; Length 15;
Best Local Similarity 93.3%; Pred. No. 1.7e-05;
Matches 14; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

Qy 2 DECELCVNVACTGCL 16
|:|||||||||||||
Db 1 DDCELCVNVACTGCL 15

RESULT 4
US-08-583-447A-55
; Sequence 55, Application US/08583447A
; Patent No. 5879656
; GENERAL INFORMATION:
; APPLICANT: Waldman, Scott A.
; TITLE OF INVENTION: ST Receptor Binding Compounds and
; TITLE OF INVENTION: Methods of Using the Same
; NUMBER OF SEQUENCES: 56
; CORRESPONDENCE ADDRESS:
; ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz & No. 5879656ris
; STREET: One Liberty Place, 46th Floor
; CITY: Philadelphia
; STATE: Pennsylvania
; COUNTRY: USA
; ZIP: 19103
; COMPUTER READABLE FORM:
; MEDIUM TYPE: Floppy disk
; COMPUTER: IBM PC compatible
; OPERATING SYSTEM: Windows
; SOFTWARE: WordPerfect 6.1
; CURRENT APPLICATION DATA:
; APPLICATION NUMBER: US/08/583,447A
; FILING DATE: 05-JAN-1996
; CLASSIFICATION: 435
; PRIOR APPLICATION DATA:
; APPLICATION NUMBER: US 08/141,892
; FILING DATE: 26-OCT-1993
; CLASSIFICATION: 435
; ATTORNEY/AGENT INFORMATION:
; NAME: DeLuca, Mark
; REGISTRATION NUMBER: 33,229
; REFERENCE/DOCKET NUMBER: TJU-1702
; TELECOMMUNICATION INFORMATION:
; TELEPHONE: 215-568-3100
; TELEFAX: 215-568-3439
; INFORMATION FOR SEQ ID NO: 55:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 15 amino acids

FILE 'REGISTRY' ENTERED AT 12:52:53 ON 14 FEB 2005
L1 1 S NDECELCVNVACTGCL/SQSP

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN 467426-54-6 REGISTRY
CN L-Leucine, L-asparaginyl-L-α-aspartyl-L-α-glutamyl-L-cysteinyl-L-α-glutamyl-L-leucyl-L-cysteinyl-L-valyl-L-asparaginyl-L-valyl-L-alanyl-L-cysteinyl-L-threonylglycyl-L-cysteinyl-, cyclic (4→12),(7→15)-bis(disulfide) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 20: PN: WO02078683 SEQID: 20 claimed protein
SQL 16

SEQ 1 NDECELCVNV ACTGCL
========== ======
HITS AT: 1-16

REFERENCE 1: 137:304753

FILE 'CAPLUS' ENTERED AT 12:53:20 ON 14 FEB 2005
L2 1 S L1

L2 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
ED Entered STN: 11 Oct 2002
ACCESSION NUMBER: 2002:777706 CAPLUS
DOCUMENT NUMBER: 137:304753
TITLE: Guanylate cyclase receptor agonists for the treatment of tissue inflammation and carcinogenesis
INVENTOR(S): Shailubhai, Kunwar; Nikiforovich, Gregory; Jacob, Gary S.
PATENT ASSIGNEE(S): Synergy Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002078683	A1	20021010	WO 2002-US9551	20020328
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2441970	AA	20021010	CA 2002-2441970	20020328
US 2003073628	A1	20030417	US 2002-107814	20020328
EP 1379224	A1	20040114	EP 2002-721604	20020328
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004532208	T2	20041021	JP 2002-576949	20020328

Searcher : Shears 571-272-2528

PRIORITY APPLN. INFO.:

US 2001-279437P	P	20010329
US 2001-279438P	P	20010329
US 2001-300850P	P	20010627
US 2001-303806P	P	20010710
US 2001-307358P	P	20010725
US 2002-348646P	P	20020117
WO 2002-US9551	W	20020328

AB A method of treatment of inflamed, pre-cancerous or cancerous 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 mols. 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 mol., peptide, protein or other compound that inhibits the degradation of cGMP. Without requiring a particular mechanism of action, this treatment may restore a healthy balance between proliferation and apoptosis in the subject's population of epithelial cells, and also suppress carcinogenesis. Thus, the method may be used to treat, <i>inter alia<i/>, inflammation, including gastrointestinal inflammatory disorders, general organ inflammation and asthma, and carcinogenesis of the lung, gastrointestinal tract, bladder, testis, prostate and pancreas, or polyps.

IT **467426-54-6**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(guanylate cyclase receptor agonists for the treatment of tissue inflammation and carcinogenesis)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

(FILE 'MEDLINE, BIOSIS, EMBASE, CANCERLIT' ENTERED AT 12:53:39 ON 14 FEB 2005)

L3 0 S L1

FILE 'HOME' ENTERED AT 12:53:48 ON 14 FEB 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number	:	10/107,814	Confirmation No. 9117
Applicant(s)	:	Kunwar Shailubhai et al.	
Filed	:	March 28, 2002	
Tech Cntr/AU	:	1642	
Examiner	:	Stephen L. Rawlings	
Entitled	:	Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis	
Attorney Reference	:	121634-40284943	
Customer Number	:	43569	

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §1.97

Sir:

Pursuant to 37 CFR §1.97 and 1.56, the attention of the U.S. Patent and Trademark Office is hereby directed to the following disclosures made herein, which include:

REFERENCES AND RELEVANCY

☒ Applicant(s) wish(es) to make of record the documents listed on the attached Form PTO-1449. Copies of the listed documents are attached, where required, as are any readily available full or partial English translations of any non-English language documents.

☐ Applicant(s) wish(es) to make of record the documents listed on the attached Form PTO-1449. The references cited herein were cited for consideration in the parent application, and, pursuant to 37 CFR 1.98(d), copies of the cited references can be found in the file of the parent application (*U.S. Serial No. , filed).*

☐ Applicant(s) wish(es) to make of record the documents listed on the attached Form PTO-1449. The references cited herein were cited in the International Search Report issued for the corresponding International application, and copies of the International Search Report and the cited references are attached for the Examiner's consideration.

☐ Applicant(s) wish(es) to make of record the documents listed on the attached Form PTO-1449. The references cited herein were cited in a communication from a foreign or international patent office in a counterpart foreign or international application(s), and copies of both the relevant communication and the cited references, where required, are attached for the Examiner's consideration.

CERTIFICATION

The undersigned certifies that, pursuant to 37 CFR §1.97(e)(1),

☐ each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign or international patent office in a counterpart foreign or international application not more than three months prior to the filing of this Statement.

RELATED CASES

☐ Identified in the attached Appendix are related applications directed to related technical subject matter. Copies of the related applications, where required, are attached for the Examiner's consideration. *The identification of the related U.S. patent applications is not to be construed as a waiver of secrecy for those applications, now or upon issuance of the present application as a patent.*

BASIS FOR CONSIDERATION

This Information Disclosure Statement is filed:

☐ within three months of the filing date of the application and/or before the mailing date of a first Official Action on the merits, and no fee is required [37 C.F.R. §1.97(b)].

☐ with the appropriate certification, and no fee is required [37 C.F.R. §1.97(e)(1)].

☒ after the mailing date of the first Official Action on the merits, but prior to the issuance of a Notice of Allowance, and the requisite fee is authorized herein for payment [37 C.F.R. §1.97(c)].

☐ with a Request for Continued Examination (RCE), and no fee is required [37 C.F.R. §1.97(b)(4)].

FEE AUTHORIZATION

☒ Authorization is hereby given to charge any deficient fee(s) under 37 CFR §1.16 and §1.17 as necessary to ensure the consideration of this disclosure, or to credit any fee overpayments, to Deposit Account No. 503-121.

☒ Authorization is hereby given to charge the requisite fee of $180 (Fee Code 1806) for submission of this Information Disclosure Statement to Deposit Account No. 503-121.

It is respectfully requested that this information be expressly considered during the prosecution of this application, and that the reference(s) be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

The Examiner is further respectfully requested to return of a copy of the enclosed Form PTO-1449 with the Examiner's initials in the left column.

The examination and allowance of this Application is respectfully requested.

Respectfully Submitted,

MAYER BROWN ROWE & MAW LLP

By: _____

Christopher M. Beck
Registration No. 52,603
Direct No. (202) 263-3374

Paul L. Sharer
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Intellectual Property Group
1909 K Street, N.W.
Washington, D.C. 20006
(202) 263-3000 Telephone
(202) 263-3300 Facsimile

Date: March 7, 2005

Attachment(s): PTO Form 1449
Cited References

FORM PTO-1449 (modified)
U.S. Department of Commerce
U.S. Patent & Trademark Office

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Attorney Reference: 121634-40284943	
Applicant: Kunwar Shailubhai et al.	
Application Serial No. 10/107,814	
Filing Date: March 28, 2002	
Examiner: unassigned	Group Art Unit: unassigned

Date: March 7, 2005 Page 1 of 1

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR	2005/0032684 A1	2/10/2005	Cetin et al.			
	BR						
	CR						
	DR						
	ER						
	FR						
	GR						
	HR						
	IR						
	JR						
	KR						
	LR						
	MR						
	NR						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country			Translation Readily Available		English Abstract	
							Enclosed	No	Enclosed	No
	OR	WO 02/098912 A2	12/12/2002	PCT					X	
	PR	WO 02/098912 A3	12/12/2002	PCT					X	
	QR									
	RR									
	SR									
	TR									
	UR									
	VR									
	WR									
	XR									

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

	YR	
	ZR	
	AAR	
	BBR	
	CCR	
	DDR	

Examiner	Date Considered:

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
12. Dezember 2002 (12.12.2002)

PCT

(10) Internationale Veröffentlichungsnummer
WO 02/098912 A3

(51) Internationale Patentklassifikation[7]: C07K 14/47, A61P 11/00, A61K 38/17, G01N 33/68, A61M 15/00

(21) Internationales Aktenzeichen: PCT/DE02/02040

(22) Internationales Anmeldedatum: 5. Juni 2002 (05.06.2002)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
101 27 119.0 5. Juni 2001 (05.06.2001) DE

(71) Anmelder und
(72) Erfinder: CETIN, Yalcin [DE/DE]; Boschhof 2, 30655 Hannover (DE). SAVAS, Yüksel [DE/DE]; Salzgitterstrasse 23, 38268 Lengede (DE).

(74) Anwalt: LÄUFER, Martina; Gramm, Lins & Partner GbR, Freundallee 13, 30173 Hannover (DE).

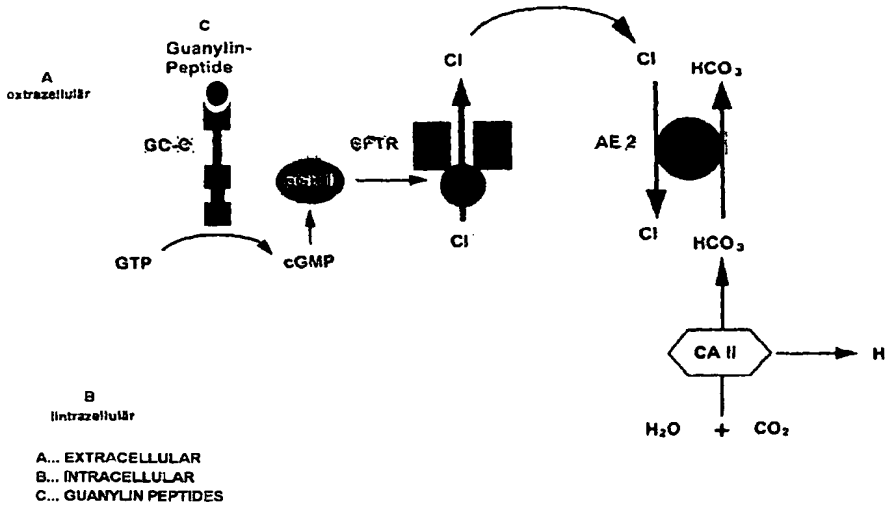
(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),

[Fortsetzung auf der nächsten Seite]

(54) Title: GUANYLATE-CYCLASE C LIGAND, ADMINISTERED VIA THE AIRWAYS, FOR THE TREATMENT OF RESPIRATORY AIRWAY PROBLEMS

(54) Bezeichnung: LUFTSEITIG VERABREICHTE GUANYLAT CYCLASE C LIGANDEN FÜR ATEMWEGSERKRANKUNGEN



(57) Abstract: The invention relates to the use of a guanylate cyclase C activated peptide for the treatment of respiratory airway problems and problems associated with ventilation disorder and/or mucous secretion disorders via the airways, in addition to a medicament which is fed via the airways. The invention also relates to an inhalation device which contains the medicament and a method for diagnosing the illnesses associated with inhalation disorders and mucous secretion disorders in the airways, by detecting a guanylate cyclase C activated peptide. The peptides which are used are guanylin, uroguanylin and lymphoguanylin or a heat resistant enterotoxin.

[Fortsetzung auf der nächsten Seite]

WO 02/098912 A3

eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Erklärungen gemäß Regel 4.17:

— *hinsichtlich der Berechtigung des Anmelders, ein Patent zu beantragen und zu erhalten (Regel 4.17 Ziffer ii) für die folgenden Bestimmungsstaaten AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *Erfindererklärung (Regel 4.17 Ziffer iv) nur für US*

Veröffentlicht:

— *mit internationalem Recherchenbericht*

(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 31. Juli 2003

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(57) Zusammenfassung: Es wird die Verwendung eines Guanylat Cyclase C aktivierenden Peptids für die Behandlung von Atemwegserkrankungen und Erkrankungen, die mit Ventilationsstörungen und/oder Störungen der Schleimhautsekretion einhergehen, über die Luftwege vorgeschlagen, sowie eines Arzneimittels, das über die Luftwege zugeführt wird. Des weiteren wird eine Inhalationsvorrichtung, die das Arzneimittel enthält, angegeben und ein Verfahren zur Diagnose von Erkrankungen, die mit Ventilationsstörungen und Störungen der Schleimhaut in den Atemwegen einhergehen, durch Nachweis eines Gualylat Cyclase C aktivierenden Peptids. Als Peptide werden Guanylin, Uroguanylin und Lymphoguanylin oder ein hitzebeständiges Enterotoxin eingesetzt.

INTERNATIONAL SEARCH REPORT

Int[illegible]nal Application No
PCT/DE 02/02040

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/47 A61P11/00 A61K38/17 G01N33/68 A61M15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, MEDLINE, EMBASE, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OHBAYASHI HIROYUKI ET AL: "Both inhalant and intravenous uroguanylin inhibit leukotriene C4-induced airway changes." PEPTIDES (NEW YORK), vol. 21, no. 10, October 2000 (2000-10), pages 1467-1472, XP002230927 ISSN: 0196-9781 abstract page 1467, left-hand column -page 1468, left-hand column, paragraph 2 page 1468, right-hand column, paragraph 2 page 1468, right-hand column, last paragraph page 1469, right-hand column, last paragraph -page 1470, left-hand column, line 6 page 1470, right-hand column, paragraph 1 - paragraph 2 figures 1,2 -/--	1-3,5-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2003	04/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Hars, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DE 195 43 628 A (FORSSMANN WOLF GEORG) 28 May 1997 (1997-05-28) claims 1,2,10,17,19	4,12-15
A	OHBAYASHI HIROYUKI ET AL: "Effects of uroguanylin and guanylin against antigen-induced bronchoconstriction and airway microvascular leakage in sensitized guinea-pigs." LIFE SCIENCES, vol. 62, no. 20, 10 April 1998 (1998-04-10), pages 1833-1844, XP002230928 ISSN: 0024-3205 abstract page 1834, paragraph 1 - paragraph 2 page 1841, paragraph 2 -page 1842, paragraph 4	1-15
A	HOENSCHEID M ET AL: "Guanylin activates chloride currents in H441 lung epithelial cells." PFLUEGERS ARCHIV EUROPEAN JOURNAL OF PHYSIOLOGY, vol. 441, no. 6 Supplement, 2001, page R270 XP009005486 Joint Congress of the Scandinavian and the German Physiological Societies;Berlin, Germany; March 10-13, 2001 ISSN: 0031-6768 the whole document	1-15
A	CETIN YALCIN ET AL: "Bronchiolar nonciliated secretory (Clara) cells: Source of guanylin in the mammalian lung." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 92, no. 13, 1995, pages 5925-5929, XP002230929 1995 ISSN: 0027-8424 abstract page 5925, left-hand column, last paragraph -right-hand column, paragraph 1 page 5928, left-hand column, line 18 -right-hand column, line 7 page 5929, left-hand column	1-15

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	ZHANG ZHI HAO ET AL: "The airway-epithelium: A novel site of action by guanylin." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 244, no. 1, 6 March 1998 (1998-03-06), pages 50-56, XP002230930 ISSN: 0006-291X abstract page 50, right-hand column, paragraph 2 page 55, left-hand column, last paragraph -right-hand column ---	1-15
A	ABDEL-RAZEL T ET AL: "Smooth muscle relaxation by guanylin: Implications for mediator role of cyclic GMP in vascular and airway smooth muscle relaxation." FASEB JOURNAL, vol. 8, no. 4-5, 1994, page A556 XP009005528 Experimental Biology 94, Parts I and II;Anaheim, California, USA; April 24-28, 1994 ISSN: 0892-6638 the whole document ---	1-15
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; April 1999 (1999-04) FORTE LEONARD R ET AL: "Lymphoguanylin: Cloning and characterization of a unique member of the guanylin peptide family." Database accession no. PREV199900204569 XP002230932 cited in the application abstract & ENDOCRINOLOGY, vol. 140, no. 4, April 1999 (1999-04), pages 1800-1806, ISSN: 0013-7227 ---	1-15
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; July 2000 (2000-07) CHEN YAHONG ET AL: "The changes of guanylin in plasma and lung tissue from asthmatic guinea pigs." Database accession no. PREV200000544836 XP002230933 abstract & ZHONGHUA JIEHE HE HUXI ZAZHI, vol. 23, no. 7, July 2000 (2000-07), pages 410-412, ISSN: 1001-0939 --- -/—	1-15

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	KULAKSIZ HASAN ET AL: "Clara cell impact in air-side activation of CFTR in small pulmonary airways." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 99, no. 10, 14 May 2002 (2002-05-14), pages 6796-6801, XP002230931 http://www.pnas.org May 14, 2002 ISSN: 0027-8424 cited in the application abstract page 6801, right-hand column, last paragraph	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DE 02/02040

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

See supplemental sheet FURTHER INFORMATION PCT/ISA/210

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See supplemental sheet FURTHER INFORMATION PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION

Continuation of I.1

Although Claims 12-15 relate to a diagnostic method practiced on the human or animal body, the search was carried out on the basis of the alleged properties of the compound or composition.

Continuation of I.1

PCT Rule 39.1(iv) – diagnostic methods practiced on the human or animal body.

Continuation of I.2

The current Claims 1, 2, 4-6, 8-12, 14, 15 relate to peptides characterized in each case by a desirable characteristic or property, namely the activation of guanylate cyclase C, or relate to compounds similar to the peptides guanylin, uroguanylin, lymphoguanylin or heat-resistant enterotoxin, also characterized by the activation of guanylate cyclase C.
The claims therefore encompass all products, etc., that have this characteristic or property, but the application provides support by the description (PCT Article 5) for only a limited number of such products, etc. In the present case the claims lack the proper support and the application lacks the requisite disclosure to such an extent that it appears impossible to carry out a meaningful search covering the entire range of protection sought. Moreover, the claims also lack the requisite clarity (PCT Article 6) since they attempt to define the product in terms of the desired result. This lack of clarity too is such that it is impossible to carry out a meaningful search covering the entire scope of protection sought. Therefore, the search was directed to the parts of the claims that appear to be clear, supported or disclosed in the above sense, that is the parts concerning the peptides guanylin, uroguanylin, lymphoguanylin and heat-resistant enterotoxin (according to Claims 3, 7 and 13 and SEQ ID 1-7).

The applicant is advised that claims or parts of claims relating to inventions in respect of which no international search report has been established normally cannot be the subject of an international preliminary examination (PCT Rule 66.1(e)). In its capacity as International Preliminary Examining Authority the EPO generally will not carry out a preliminary examination for subjects that have not been searched. This also applies to cases where the claims were amended after receipt of the international search report (PCT Article 19) or where the applicant submits new claims in the course of the procedure under PCT Chapter II.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]tional Application No
PCT/DE 02/02040

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19543628 A	28-05-1997	DE 19543628 A1	28-05-1997
		AU 1031397 A	19-06-1997
		WO 9720049 A1	05-06-1997

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONALER RECHERCHENBERICHT

Internales Aktenzeichen
PCT/DE 02/02040

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES
IPK 7 C07K14/47 A61P11/00 A61K38/17 G01N33/68 A61M15/00

Nach der internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)
IPK 7 C07K A61M

Recherchierte aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)
BIOSIS, MEDLINE, EMBASE, EPO-Internal, WPI Data, PAJ

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	OHBAYASHI HIROYUKI ET AL: "Both inhalant and intravenous uroguanylin inhibit leukotriene C4-induced airway changes." PEPTIDES (NEW YORK), Bd. 21, Nr. 10, Oktober 2000 (2000-10), Seiten 1467-1472, XP002230927 ISSN: 0196-9781 Zusammenfassung Seite 1467, linke Spalte -Seite 1468, linke Spalte, Absatz 2 Seite 1468, rechte Spalte, Absatz 2 Seite 1468, rechte Spalte, letzter Absatz Seite 1469, rechte Spalte, letzter Absatz -Seite 1470, linke Spalte, Zeile 6 Seite 1470, rechte Spalte, Absatz 1 - Absatz 2 Abbildungen 1,2 --- -/--	1-3,5-11

[X] Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen

[X] Siehe Anhang Patentfamilie

° Besondere Kategorien von angegebenen Veröffentlichungen :
"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist
"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)
"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht
"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist
"T" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist
"X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden
"Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist
"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
13. Februar 2003	04/03/2003

Name und Postanschrift der internationalen Recherchenbehörde	Bevollmächtigter Bediensteter
Europäisches Patentamt, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70, 340-3016	Hars, J

Formblatt PCT/ISA/210 (Blatt 2) (Juli 1992)

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	DE 195 43 628 A (FORSSMANN WOLF GEORG) 28. Mai 1997 (1997-05-28) Ansprüche 1,2,10,17,19 ---	4,12-15
A	OHBAYASHI HIROYUKI ET AL: "Effects of uroguanylin and guanylin against antigen-induced bronchoconstriction and airway microvascular leakage in sensitized guinea-pigs." LIFE SCIENCES, Bd. 62, Nr. 20, 10. April 1998 (1998-04-10), Seiten 1833-1844, XP002230928 ISSN: 0024-3205 Zusammenfassung Seite 1834, Absatz 1 - Absatz 2 Seite 1841, Absatz 2 -Seite 1842, Absatz 4 ---	1-15
A	HOENSCHEID M ET AL: "Guanylin activates chloride currents in H441 lung epithelial cells." PFLUEGERS ARCHIV EUROPEAN JOURNAL OF PHYSIOLOGY, Bd. 441, Nr. 6 Supplement, 2001, Seite R270 XP009005486 Joint Congress of the Scandinavian and the German Physiological Societies;Berlin, Germany; March 10-13, 2001 ISSN: 0031-6768 das ganze Dokument ---	1-15
A	CETIN YALCIN ET AL: "Bronchiolar nonciliated secretory (Clara) cells: Source of guanylin in the mammalian lung." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, Bd. 92, Nr. 13, 1995, Seiten 5925-5929, XP002230929 1995 ISSN: 0027-8424 Zusammenfassung Seite 5925, linke Spalte, letzter Absatz -rechte Spalte, Absatz 1 Seite 5928, linke Spalte, Zeile 18 -rechte Spalte, Zeile 7 Seite 5929, linke Spalte --- -/--	1-15

C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
A	ZHANG ZHI HAO ET AL: "The airway-epithelium: A novel site of action by guanylin." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, Bd. 244, Nr. 1, 6. März 1998 (1998-03-06), Seiten 50-56, XP002230930 ISSN: 0006-291X Zusammenfassung Seite 50, rechte Spalte, Absatz 2 Seite 55, linke Spalte, letzter Absatz -rechte Spalte	1-15
A	ABDEL-RAZEL T ET AL: "Smooth muscle relaxation by guanylin: Implications for mediator role of cyclic GMP in vascular and airway smooth muscle relaxation." FASEB JOURNAL, Bd. 8, Nr. 4-5, 1994, Seite A556 XP009005528 Experimental Biology 94, Parts I and II;Anaheim, California, USA; April 24-28, 1994 ISSN: 0892-6638 das ganze Dokument	1-15
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; April 1999 (1999-04) FORTE LEONARD R ET AL: "Lymphoguanylin: Cloning and characterization of a unique member of the guanylin peptide family." Database accession no. PREV199900204569 XP002230932 in der Anmeldung erwähnt Zusammenfassung & ENDOCRINOLOGY, Bd. 140, Nr. 4, April 1999 (1999-04), Seiten 1800-1806, ISSN: 0013-7227	1-15
A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; Juli 2000 (2000-07) CHEN YAHONG ET AL: "The changes of guanylin in plasma and lung tissue from asthmatic guinea pigs." Database accession no. PREV200000544836 XP002230933 Zusammenfassung & ZHONGHUA JIEHE HE HUXI ZAZHI, Bd. 23, Nr. 7, Juli 2000 (2000-07), Seiten 410-412, ISSN: 1001-0939	1-15

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C.(Fortsetzung) ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie°	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
P,A	KULAKSIZ HASAN ET AL: "Clara cell impact in air-side activation of CFTR in small pulmonary airways." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, Bd. 99, Nr. 10, 14. Mai 2002 (2002-05-14), Seiten 6796-6801, XP002230931 http://www.pnas.org May 14, 2002 ISSN: 0027-8424 in der Anmeldung erwähnt Zusammenfassung Seite 6801, rechte Spalte, letzter Absatz	1-15

INTERNATIONALER RECHERCHENBERICHT

nationales Aktenzeichen
PCT/DE 02/02040

Feld I Bemerkungen zu den Ansprüchen, die sich als nicht recherchierbar erwiesen haben (Fortsetzung von Punkt 2 auf Blatt 1)

Gemäß Artikel 17(2)a) wurde aus folgenden Gründen für bestimmte Ansprüche kein Recherchenbericht erstellt:

1. [X] Ansprüche Nr. –
weil sie sich auf Gegenstände beziehen, zu deren Recherche die Behörde nicht verpflichtet ist, nämlich

siehe Zusatzblatt WEITERE ANGABEN PCT/ISA/210

2. [X] Ansprüche Nr. –
weil sie sich auf Teile der internationalen Anmeldung beziehen, die den vorgeschriebenen Anforderungen so wenig entsprechen, daß eine sinnvolle internationale Recherche nicht durchgeführt werden kann, nämlich

siehe Zusatzblatt WEITERE ANGABEN PCT/ISA/210

3. [ ] Ansprüche Nr.
weil es sich dabei um abhängige Ansprüche handelt, die nicht entsprechend Satz 2 und 3 der Regel 6.4 a) abgefaßt sind.

Feld II Bemerkungen bei mangelnder Einheitlichkeit der Erfindung (Fortsetzung von Punkt 3 auf Blatt 1)

Die internationale Recherchenbehörde hat festgestellt, daß diese internationale Anmeldung mehrere Erfindungen enthält:

1. [ ] Da der Anmelder alle erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht auf alle recherchierbaren Ansprüche.

2. [ ] Da für alle recherchierbaren Ansprüche die Recherche ohne einen Arbeitsaufwand durchgeführt werden konnte, der eine zusätzliche Recherchengebühr gerechtfertigt hätte, hat die Behörde nicht zur Zahlung einer solchen Gebühr aufgefordert.

3. [ ] Da der Anmelder nur einige der erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht nur auf die Ansprüche, für die Gebühren entrichtet worden sind, nämlich auf die Ansprüche Nr.

4. [ ] Der Anmelder hat die erforderlichen zusätzlichen Recherchengebühren nicht rechtzeitig entrichtet. Der internationale Recherchenbericht beschränkt sich daher auf die in den Ansprüchen zuerst erwähnte Erfindung; diese ist in folgenden Ansprüchen erfaßt:

Bemerkungen hinsichtlich eines Widerspruchs

[ ] Die zusätzlichen Gebühren wurden vom Anmelder unter Widerspruch gezahlt.

[ ] Die Zahlung zusätzlicher Recherchengebühren erfolgte ohne Widerspruch.

WEITERE ANGABEN PCT/ISA/ 210

Fortsetzung von Feld I.1

Obwohl die Ansprüche 12-15 sich auf ein Diagnostizierverfahren, das am menschlichen/tierischen Körper vorgenommen wird, beziehen, wurde die Recherche durchgeführt und gründete sich auf die angeführten Wirkungen der Verbindung/Zusammensetzung.

Fortsetzung von Feld I.1

Regel 39.1(iv) PCT - Diagnostizierverfahren, die am menschlichen oder tierischen Körper vorgenommen werden

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Fortsetzung von Feld I.2

Die geltenden Patentansprüche 1,2,4-6,8-12,14,15 beziehen sich auf Peptide, jeweils charakterisiert durch eine erstrebenswerte Eigenheit oder Eigenschaft, nämlich die Aktivierung von Guanylat Cyclase C beziehungsweise beziehen sich auf den Peptiden Guanylin, Uroguanylin, Lymphoguanylin oder hitzebeständigem Enterotoxin ähnlichen Verbindungen, ebenfalls charakterisiert durch die Aktivierung von Guanylat Cyclase C. Die Patentansprüche umfassen daher alle Produkte etc., die diese Eigenheit oder Eigenschaft aufweisen, wohingegen die Patentanmeldung Stütze durch die Beschreibung im Sinne von Art. 5 PCT nur für eine begrenzte Zahl solcher Produkte etc. liefert. Im vorliegenden Fall fehlen den Patentansprüchen die entsprechende Stütze bzw. der Patentanmeldung die nötige Offenbarung in einem solchen Maße, daß eine sinnvolle Recherche über den gesamten erstrebten Schutzbereich unmöglich erscheint. Desungeachtet fehlt den Patentansprüchen auch die in Art. 6 PCT geforderte Klarheit, nachdem in ihnen versucht wird, das Produkt über das jeweils erstrebte Ergebnis zu definieren. Auch dieser Mangel an Klarheit ist dergestalt, daß er eine sinnvolle Recherche über den gesamten erstrebten Schutzbereich unmöglich macht. Daher wurde die Recherche auf die Teile der Patentansprüche gerichtet, welche im o.a. Sinne als klar, gestützt oder offenbart erscheinen, nämlich die Teile betreffend die Peptide Guanylin, Uroguanylin, Lymphoguanylin und hitzebeständiges Enterotoxin (entsprechend der Ansprüche 3,7 und 13 und den SEQ ID 1-7).

Der Anmelder wird darauf hingewiesen, daß Patentansprüche, oder Teile von Patentansprüchen, auf Erfindungen, für die kein internationaler Recherchenbericht erstellt wurde, normalerweise nicht Gegenstand einer internationalen vorläufigen Prüfung sein können (Regel 66.1(e) PCT). In seiner Eigenschaft als mit der internationalen vorläufigen Prüfung beauftragte Behörde wird das EPA also in der Regel keine vorläufige Prüfung für Gegenstände durchführen, zu denen keine Recherche vorliegt. Dies gilt auch für den Fall, daß die Patentansprüche nach Erhalt des internationalen Recherchenberichtes geändert wurden (Art. 19 PCT), oder für den Fall, daß der Anmelder im Zuge des Verfahrens gemäß Kapitel II

WEITERE ANGABEN **PCT/ISA/ 210**

PCT neue Patentansprüche vorlegt.

INTERNATIONALER RECHERCHENBERICHT

Angaben zu Veröffentlichungen, die zur selben Patentfamilie gehören

Internationales Aktenzeichen
PCT/DE 02/02040

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
DE 19543628 A	28-05-1997	DE 19543628 A1	28-05-1997
		AU 1031397 A	19-06-1997
		WO 9720049 A1	05-06-1997

Formblatt PCT/ISA/210 (Anhang Patentfamilie)(Juli 1992)

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
12. Dezember 2002 (12.12.2002)

PCT

(10) Internationale Veröffentlichungsnummer
WO 02/098912 A2

(51) Internationale Patentklassifikation[7]: C07K 14/47, A61P 11/00, A61K 38/17, G01N 33/68, A61M 15/00

(21) Internationales Aktenzeichen: PCT/DE02/02040

(22) Internationales Anmeldedatum:
5. Juni 2002 (05.06.2002)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
101 27 119.0 5. Juni 2001 (05.06.2001) DE

(71) Anmelder und
(72) Erfinder: CETIN, Yalcin [DE/DE]; Boschhof 2, 30655 Hannover (DE). SAVAS, Yüksel [DE/DE]; Salzgitterstrasse 23, 38268 Lengede (DE).

(74) Anwalt: LÄUFER, Martina; Gramm, Lins & Partner GbR, Freundallee 13, 30173 Hannover (DE).

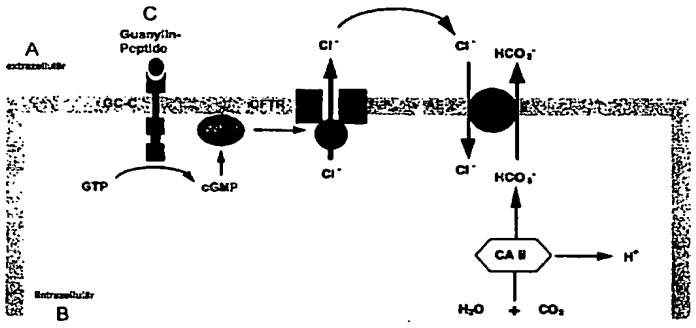
(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),

[Fortsetzung auf der nächsten Seite]

(54) Title: USE OF A PEPTIDE WHICH ACTIVATES GUANYLATE-CYCLASE C FOR THE TREATMENT OF RESPIRATORY AIRWAY PROBLEMS VIA THE AIRWAYS, MEDICAMENT, INHALATION DEVICES AND METHOD OF DIAGNOSIS

(54) Bezeichnung: VERWENDUNG EINES PEPTIDS, WELCHES GUANYLAT CYCLASE C AKTIVIERT, FÜR DIE BEHANDLUNG VON ATEMWEGSERKRANKUNGEN ÜBER DIE LUFTWEGE, ARZNEIMITTEL, INHALATIONSVORRICHTUNG UND DIAGNOSEVERFAHREN



Signaltransduktion der Guanylin-Peptide an Epithelzellen

D

A ... EXTRACELLULAR
B ... INTRACELLULAR
C ... GUANYLIN PEPTIDES
D ... SIGNAL TRANSDUCTION OF THE GUANYLIN PEPTIDES ON THE EPITHEL CELLS

(57) Abstract: The invention relates to the use of a guanylate cyclase C activated peptide for the treatment of respiratory airway problems and problems associated with ventilation disorder and/or mucous secretion disorders via the airways, in addition to a medicament which is fed via the airways. The invention also relates to an inhalation device which contains the medicament and a method for diagnosing the illnesses associated with inhalation disorders and mucous secretion disorders in the airways, by detecting a gualylate cyclase C activated peptide. The peptides which are used are guanylin, uroguanylin and lymphoguanylin or a heat resistant enterotoxin.

[Fortsetzung auf der nächsten Seite]

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Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(57) Zusammenfassung: Es wird die Verwendung eines Guanylat Cyclase C aktivierenden Peptids für die Behandlung von Atemwegserkrankungen und Erkrankungen, die mit Ventilationsstörungen und/oder Störungen der Schleimhautsekretion einhergehen, über die Luftwege vorgeschlagen, sowie eines Arzneimittels, das über die Luftwege zugeführt wird. Des weiteren wird eine Inhalationsvorrichtung, die das Arzneimittel enthält, angegeben und ein Verfahren zur Diagnose von Erkrankungen, die mit Ventilationsstörungen und Störungen der Schleimhaut in den Atemwegen einhergehen, durch Nachweis eines Gualylat Cyclase C aktivierenden Peptids. Als Peptide werden Guanylin, Uroguanylin und Lymphoguanylin oder ein hitzebeständiges Enterotoxin eingesetzt.

Verwendung eines Peptids, welches Guanylat Cyclase C aktiviert, für die Behandlung von Atemwegserkrankungen über die Luftwege, Arzneimittel, Inhalationsvorrichtung und Diagnoseverfahren

Die Erfindung betrifft die Verwendung eines Peptids, welches Guanylat Cyclase C aktiviert, für die Behandlung von Atemwegserkrankungen und Erkrankungen, die mit Ventilationsstörungen und/oder Störungen der Schleimsekretion einhergehen, ein zugehöriges Arzneimittel, eine Inhalationsvorrichtung und ein Verfahren zur Diagnose der vorgenannten Erkrankungen.

Die obstruktiven Ventilationsstörungen sind ein ernstes klinisches Problem. Sie gehen mit einer Einengung der Atemwege und damit einer Erhöhung des Strömungswiderstands, Spasmen der Bronchialmuskulatur, ödematösen Schwellungen der Bronchialwand sowie gesteigerter Sekretion (Hyperkrinie) von Schleim zäher Konsistenz einher. Die Erkrankungen, die mit Ventilationsstörungen und/oder Störungen der Schleimsekretion einhergehen, umfassen u.a. Asthma bronchiale, chronische Bronchitis und Mukoviszidose.

Es stehen zur Zeit keine Substanzen zur Verfügung, die nachhaltig und effizient wirksam sind und zur wesentlichen Verbesserung der Symptome führen.

Als Sekretolytika oder Mukolytika - die auch unter Expektorantien zusammengefasst werden - sind u.a. Bromhexin, Ambroxol, Acetylcystein und Carbocistein im Einsatz. Der therapeutische Wert dieser Substanzen ist jedoch laut Mutschler, "Arzneimittelwirkungen", -Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 1996, zweifelhaft.

Der Erfindung liegt die Aufgabe zugrunde, ein neues effektives Mittel zur Behandlung von Atemwegserkrankungen und allgemein von Erkrankungen, die mit Ventilationsstörungen und/oder Störungen der Schleimsekretion einhergehen, bereitzustellen, wobei dieses Mittel die Verflüssigung und den besseren Abtransport insbesondere von Bronchialschleim ermöglichen soll.

Die Aufgabe wird gelöst durch die Verwendung eines Peptids, welches Guanylat Cyclase C aktiviert, für die Herstellung eines Arzneimittels zur Behandlung von Atemwegserkrankungen und Erkrankungen, die mit Ventilationsstörungen und/oder Störungen der Schleimsekretion einhergehen, über die Luftwege, wobei das Arzneimittel

so formuliert ist, dass die Zuführung des Peptids auf der Luftseite der Atemwege, nämlich zur apikalen Membran der Schleimhaut-Epithelzellen gerichtet, erfolgt.

Mehrere dieser Peptide können auch gemeinsam oder in Folge verabreicht werden. Äquivalent zur Verwendung dieser Peptide selbst ist die Verwendung homologer, im wesentlichen funktionsgleicher Peptide, insbesondere solcher Peptidvarianten mit durch Deletion, Insertion oder Austausch einzelner und/oder mehrerer Aminosäuren, sequenzverlängerndes Anfügen von einzelnen und/oder mehreren Aminosäuren und/oder chemischer Derivatisierung (insbesondere der terminalen Aminosäuren) verbundener Sequenz-Modifikation.

Pharmakologisch verträgliche Derivate sind vorzugsweise amidierte, acetylierte, phosphorylierte und glycosylierte Formen der Peptide und andere posttranslationale Derivatisierungen, einschließlich Salze dieser Peptide und Peptidderivate.

Es können natürliche, beispielsweise aus Blut, Lymphe, Urin oder humanen oder tierischen Geweben isolierte Peptide oder Peptidgemische, die aufgereinigt seien sollten, oder synthetische oder gentechnisch gewonnene (rekombinante) Peptide eingesetzt werden.

Bei dem Peptid handelt es sich insbesondere um wenigstens eines der als Guanylin, Uroguanylin und Lymphoguanylin bezeichneten Peptide oder um ein hitzebeständiges Enterotoxin. Diese Peptide sind als solche bekannt. Es kann auch ein zu den genannten Peptiden homologes Peptid mit im wesentlichen gleicher Funktion verwendet werden. Unter den Homologen werden hier solche Peptide verstanden, die weitgehend mit den nachfolgend noch beschriebenen Sequenzen übereinstimmen und vom Fachmann aufgrund ihrer Funktion und Sequenzhomologie noch den Guanylin-Peptiden zugerechnet werden. Dem Fachmann ist bekannt, dass z.B. Punktmutationen, Deletionen und Insertionen die Funktion eines Peptids nicht beeinträchtigen müssen. Derartig veränderte Peptide würden daher zu den Homologen gerechnet.

Bevorzugt wird derzeit ein Guanylin-Peptid mit 15 Aminosäuren in folgender Sequenz:

Seq. ID 1 (Guanylin, 15 AS): PGTCEICAYAACTGC
Pro-Gly-Thr-Cys-Glu-Ile-Cys-Ala-Thr-Ala-Ala-Cys-Thr-Gly-Cys

Ein 115 Aminosäuren langes Vorläufermolekül, das die vorstehende Sequenz enthält, wird häufig ebenfalls als "Guanylin" bezeichnet. Beide Peptide sind im Sinne der Erfindung geeignet, bevorzugt ist das Peptid mit Seq. ID 1, das sich als relativ kleines Peptid gut über die Inhalation zuführen lässt.

Ein 15-AS-Peptid mit der Sequenz **PGTCEICAYAACTGC** wurde zunächst aus Darmextrakten der Ratte isoliert und als "Guanylin" bezeichnet. Nach der Klonierung und Charakterisierung der cDNA für das menschliche Guanylin war es offensichtlich, dass das Guanylin als Vorläufer-Molekül mit 115 AS (Seq. ID 4: MNAFLLFALC LLGAWAALAG GVTVQDGNFS FSLESVKKLK DLQEPQEPRV GKLRNFAPIP GEPVVPILCS NPNFPEELKP LCKEPNAQEI LQRLEEIAED **PGTCEICAYAACTGC)** synthetisiert wird. Inzwischen ist bekannt, dass nicht das Vorläufer-Molekül als bioaktives Protein im Blut zirkuliert, sondern das Guanylin mit 94 AS (Proguanylin 22-115: VTVQDGNFS.....**PGTCEICAYA ACTGC)**. Der in der Literatur etablierte Begriff "Guanylin" umschreibt sowohl das 15-AS-Peptid als auch das längere 94-AS-Peptid.

Humanes Uroguanylin ist ein Peptid, dem folgende Aminosäuresequenzen zugeordnet wurde:

Seq. ID 2 (Uroguanylin, 16 AS): NDDCELCVNVACTGCL
Asn-Asp-Asp-Cys-Glu-Leu-Cys-Val-Asn-Val-Ala-Cys-Thr-Gly-Cys-Leu

und wurde ursprünglich aus menschlichem Urin isoliert, worauf die Namensgebung beruht. Die US 5 489 670 beschreibt die Isolierung und Synthese von humanem Uroguanylin und sieht eine Verwendung als Laxans gegen Obstipationen vor.

Das Uroguanylin wurde zunächst als ein 16-AS-Peptid (**NDDC ELCVNVACTG CL**) aus dem Harn isoliert. Die Klonierung und Charakterisierung der cDNA für menschliches Uroguanylin ergab ein Uroguanylin Vorläufer-Molekül mit 112 AS (Seq. ID 5: MGCRAASGLL PGVAVVLLLL LQSTQSVYIQ YQGFRVQLES MKKLSDLEAQ WAPSPRLQAQSLLPAVCHHP ALPQDLQPVC ASQEASSI FKTLRTIA **NDDC ELCVNVACTG CL)**. Nach Abspaltung des Signalpeptids entsteht ein 86 AS-Uroguanylin (unterstrichene Sequenz). Das 16-AS- und das 86-AS-Peptid werden als Uroguanylin bezeichnet.

Lymphoguanylin ist ein in Lymphgeweben exprimiertes Guanylin-Peptid, das von Forte et al. gefunden wurde (Forte et al. Endocrinology 1999, 140, 1800-1806). Es handelt sich um ein 15 Aminosäuren langes Peptid mit folgender Aminosäuresequenz:

Seq. ID 3 (Lymphoguanylin, 15 AS): QEECELCINMACTGY
Gln-Glu-Glu-Cys-Glu-Leu-Cys-Ile-Asn-Met-Ala-Cys-Thr-Gly-Tyr

Das Vorläufer-Molekül für Lymphoguanylin umfasst 109 Aminosäuren (Seq. ID 6: MKVLALPMAV TAMLLIL AQN TQSVYIQYEG FQVNLDSVKK LDKLLEQLRG FHHQMGDQRD PSILCSDPALPSDLQPVCEN SQAVNIFRAL RYIN **QEECELCINMACTGY**).

Die für Lymphoguanylin angegebenen Sequenzen stammen aus dem Opossum. Die menschliche Sequenz ist bisher nicht bekannt. Das 15-Aminosäuren-Lymphoguanylin aktiviert ebenso die menschliche Guanylat Cyclase C.

Von den vorgenannten Peptiden ist seit längerer Zeit bekannt, dass sie Guanylat-Cyclase stimulieren oder aktivieren, einen G-Protein-gekoppelten Rezeptor, der die Bildung von zyklischem Guanosinmonophosphat (cGMP) aus Guanosintriphosphat (GTP) katalysiert. Es wurden nacheinander mehrere Guanylat-Cyclase aktivierende Peptide entdeckt, die als endogene Liganden für die Guanylat Cyclase C betrachtet werden. Das erste dieser Peptide wurde Guanylin genannt (Currie, H.G. et al. Proc. Natl. Acad. Sci. USA 1992, 89, 947-951).

Im Darm rufen hitzstabile Enterotoxine - kleine Peptide, die u.a. von pathogenen Escherichia coli Stämmen produziert werden - sekretorische Diarrhöen hervor. Auch diese Toxine entfalten ihre Wirkung durch Stimulation der Guanylat Cyclase C, die von Darmepithellzellen exprimiert wird. Wie die hitzestabilen Enterotoxine führen die Guanylin-Peptide zu einer erhöhten Elektrolyt/Wasser-Sekretion an der Darmschleimhaut. Damit fungiert die Guanylat Cyclase C nicht nur als Rezeptor für die hitzestabilen Enterotoxine, sondern sie stellt den genuinen Rezeptor der endogenen Guanylin-Peptide dar.

Eine im Rahmen der Erfindung geeignete Sequenz eines hitzestabilen Enterotoxins ist:
Seq. ID 7 (hitzestabiles Enterotoxin): N S S N Y C C E L C C N P A C T G C Y (19 AS) aus enteropathogenen E. coli.

Gemeinsamer Wirkmechanismus der hitzestabilen Enterotoxine, Guanylin, Uroguanylin und Lymphoguanylin an der Darmschleimhaut.

In der Darmschleimhaut führen diese oben aufgelisteten Guanylin-Peptide und die hitzestabilen Enterotoxine über die Aktivierung des gemeinsamen Rezeptors zu einem Anstieg von cGMP in den Enterozyten. Durch den erhöhten cGMP-Spiegel wird in den Enterozyten die cGMP-abhängige Proteinkinase II (cGKII) aktiviert. Diese aktivierte Proteinkinase phosphoryliert und öffnet dadurch den CFTR-Chloridkanal in der apikalen Membran der Enterozyten. Dadurch kommt es zu einer Sekretion von Chlorid-Ionen und Wasser in das Lumen des Darms. Der CFTR-Chloridkanal gilt heute als der finale Effektor der Signaltransduktionskette der Guanylin-Peptide. Damit stellen diese Peptide einen direkten Regulator des CFTR-Chlorid-Kanals dar.

Besonderes Augenmerk gilt der Sekretion von Bikarbonat, die auch durch die Guanylin-Peptide vermittelt wird. Nach den bisherigen Erkenntnissen erfolgt die Bikarbonat-Sekretion über einen spezifischen Cl^-/HCO_3^- - Austauscher (AE-2). Aufgrund bisheriger Befunde kann gefolgert werden, dass das über CFTR luminal sezernierte Cl^- wieder in die jeweiligen Zellen aufgenommen und durch HCO_3^- ausgetauscht wird. Damit kann festgehalten werden, dass die Guanylin-Peptide in den genannten Enterozyten eine zentrale Rolle in der Regulation von Cl^- und HCO_3^- spielen. Der Wirkmechanismus der Guanylin-Peptide ist in Abbildung 1 dargestellt.

Die genannten Peptide zirkulieren als endogene Aktivatoren im Blut. Sie können auch aus Blut bzw. Haemofiltrat gewonnen werden. So wird in der DE 195 28 544 ein Guanylin-Peptid beschrieben, das aus menschlichem Blut gewonnen wurde und für die diagnostische, medizinische und gewerbliche Verwendung als Arzneimittel vorgesehen ist. Dieses Peptid wurde als GCAP-II bezeichnet. Auf Grund der bekannten Wirkung der Guanylin-Peptide auf Guanylat Cylase C (s.o.) wurde GCAP-II speziell für die Behandlung von Erkrankungen, die mit Störungen des Elektrolyttransportes in den Zellen einhergehen vorgesehen. Die Anwendung soll vorzugsweise per Injektion erfolgen.

Der endogene Aktivator Guanylin wird an verschiedenen Orten im Körper gefunden. Nachgewiesen wurde Guanylin z. B. in der menschlichen Bauchspeicheldrüse (Kulaksiz et al, Histochem Cell Biol. (2001) 115, 131-145), in der Niere (Forte et al, Annu Rev. Physiol 2000, 62, 673-695) , im Intestinaltrakt (Quian et al, Endocrinology 2000, 141, 3210-24) und in der Lunge (Cetin et al, Proc. Natl. Acad. Sci. USA, 92, 5925 - 5929, 1995).

Durch die Anmelder konnte nun gefunden werden, dass der gemeinsame Rezeptor für hitzestabile Enterotoxine und Guanylin-Peptide, die Guanylat Cyclase C, in der Schleimhaut der Luftwege lokalisiert ist und dort in hohem Maße auf der apikalen Membran (Luftseite) der jeweiligen Epithelzellen exprimiert wird, nicht jedoch auf der basolateralen Membran (Blutseite). Der in der Lunge lokalisierte Rezeptor kann daher nicht über die Blutbahn, sondern ausschließlich über die Luftwege stimuliert werden.

Der Wirkungsmechanismus auf zellulärer und molekularer Ebene wird in der Figur 1 dargestellt, die schematisch die Signaltransduktion der Guanylin-Peptide an Epithelzellen zeigt.

Guanlyat Cyclase (GC-C) ist ein Enzym-Rezeptor-Komplex, der als Membranprotein ausschließlich in der apikalen, zur Atemwege-Lichtung hin gerichteten Zelldomäne lokalisiert ist. Er fehlt an der basolateralen Membran der Zellen (Blutseite), die bekanntlich in Kontakt mit dem zirkulierenden Blut steht.

Guanylin-Peptide, die über die Lichtung der Atemwege an den Rezeptor (GC-C) binden, setzen einen spezifischen intrazellulären Mechanismus in Gang, der verschiedene Proteinmodule enthält. Die durch die Guanylin-Peptide von außen aktivierte GC-C bildet intrazellulär in hohen Mengen cGMP aus GTP. Dieser second messenger (cGMP) aktiviert eine membranassoziierte cGMP-abhängige Proteinkinase Typ II (cKGII), die die Phosphorylierung und damit Aktivierung des CFTR-Proteins an seiner regulatorischen (R-) Domäne vornimmt. CFTR ist ein Membranprotein in der apikalen Membran der Epithelzellen und ist ein wichtiger Chlorid-Kanal, der nach Aktivierung Chlorid-Ionen aus der Zelle in Richtung Lichtung der Atemwege sezerniert. Aufgrund des so entstandenen ionischen Gradienten folgt das Wasser den sezernierten Chlordi-Ionen und fließt in die Lichtung der Atemwege. Das Wasser stammt aus den Epithelzellen und aus den Zwischenräumen zwischen den Zellen (parazellulär). Ein Teil der in die Lichtung sezernierten Chlorid-Ionen wird erneut in die Zellen aufgenommen; dafür werden Bikarbonat-Ionen aus den Zellen sezerniert. Dieser Austauch von Ionen wird durch den Anionen-Austauscher Typ II (AE2) bewerkstelligt. Auch das AE2-Protein ist in der apikalen Membran der Epithelzellen lokalisiert. Intrazellulär werden die Bikarbonat-Ionen durch das Enzym Carboanhydrase Typ II (CAII) aus Wasser und Kohlendioxid hergestellt.

Damit ist die luftseitige Membran der Epithelzellen der Schleimhaut die entscheidende Stelle der Signal-Rezeption, regulatorischen Aktivität und Elektrolyt/Wasser-sezernierenden Kapazität in den Atemwegen.

Insgesamt werden aufgrund dieses Wirkmechanismus der Guanylin-Peptide Ionen und Flüssigkeit in die Lichtung der Atemwege sezerniert, die die Qualität und Fließeigenschaften des Bronchialschleims maßgeblich beeinflussen und bestimmen.

In der Figur werden folgende Abkürzungen verwendet: GC-C = Guanylat Cyclase C; cGKII = cGMP-abhängige Proteinkinase Typ II; CFTR = cystic fibrosis transmembrane conductance regulator; AE-2 = Anionenaustauscher Typ 2; CAII = Carboanhydrase Typ II.

Die Aufklärung des der Erfindung zugrundeliegenden Wirkmechanismus wurde veröffentlicht in "Kulaksiz, H., Schmid, A., Hönscheid, M., Ramaswamy, A., Cetin, Y., PNAS, May 2002, Vol. 99, Seiten 6796-6801", "Kulaksiz et al., Histochem Cell Biol. (2001 115,131-145",

Eine zentrale Erkenntnis des erfindungsgemäßen Konzepts ist, dass die Aktivierung des Rezeptors durch Applikation der endogenen Liganden gezielt über die Luftwege zu erfolgen hat. Der Fachmann muss daher die Zuführung des Peptids oder des Arzneimittels, das das Peptid enthält, so einstellen, dass das Peptid - möglichst ausschließlich - auf der Luftseite zur apikalen Membran der Atemwege zugeführt wird und nicht etwa in größerem Ausmaß in die Blutbahn gelangt. Gerade hierdurch wird die gezielte lokale therapeutische Anwendung im Atemtrakt ermöglicht, zumal der Rezeptor in den Atemwegen ausschließlich luftseitig lokalisiert ist.

Bei der Zuführung der erfindungsgemäßen Peptide, nämlich der Guanylat Cyclase C-Liganden über die Luftwege handelt es sich um eine gerichtete und unmittelbare Zuführung zu dem luftseitig gelegenen Rezeptor. Eine Erhöhung der Blutkonzentration des Peptids durch Aufnahme über die Lunge, wie bei der Inhalation andere Peptide (die systemisch wirden, z.B. Insulin) angestrebt, soll hier gerade strikt vermieden werden.

Dem Fachmann stehen hierfür die geeigneten Mittel zur Verfügung. Er kann die gerichtete Zuführung zur Luftseite über die Einstellung der Peptidkonzentration in der Arzneimittelformulierung, die Dosierung und die Einstellung der Partikel/Tröpfchengröße innerhalb der Formulierung oder des Inhalationsmittels so beeinflussen, dass praktisch kein Peptid zur Blutseite der Atemwege (zur basolateralen Membran) und damit in die Blutbahn durchtritt. Die optimalen Bedingungen können für jedes gewählte Peptid in gezielten Vorversuchen ermittelt werden.

Die Erfindung ermöglicht eine Therapie mit Dosen, die sehr viel geringer sind als solche, die für die Erhöhung der Blutkonzentration erforderlich wären, unter Minimierung bis Ausschaltung der systemischen Nebenwirkungen der jeweiligen Peptide.

Nur bei einer Applikation über die Luft führen die hitzestabilen Enterotoxine und die genannten Guanylin-Peptide zu einer ausreichenden Aktivierung des Rezeptors Guanylat Cyclase C und dadurch zu einer erhöhten Flüssigkeitssekretion in den Atemwegen. Bei einer systemischen Applikation wäre außerdem mit unerwünschten Nebenreaktionen zu rechnen, beispielsweise führt das Enterotoxin zu sehr unangenehmen sekretorischen Durchfallerkrankungen.

Weiterhin wirken die erfindungsgemäßen Peptide als Stimulantien im Sinne einer Sekretolyse durch Auflösen des in den Luftwegen vorliegenden zähen Schleims, wobei die Ionen-Zusammensetzung und der pH-Wert der Flüssigkeit unmittelbar auf den Epithelzellen ("Mikroklima") so eingestellt werden, dass der zähe Schleim sich zunehmend "verflüssigt".

Der Abtransport von Schleim und Mikropartikeln aus den Atemwegen wird durch Epithelzellen ermöglicht, die auf ihrer apikalen Seite (Luftseite) Flimmerhärchen (Zilien) tragen. Die "reinigende" Funktion wird durch Schlagen (rachenwärts) der Zilien erreicht.

Da die Guanylin-Peptide nebst ihrer Funktion, die Elektrolyt- und Wasser-Sekretion zu erhöhen, insbesondere auch die Zilien-tragenden Epithelzellen aktivieren, kommt es an diesen Zellen zu einer erhöhten Schlagfrequenz der Zilien. Damit wird im Sinne einer konzertierten Aktion das Sekret und kleinste Partikel auf der Schleimhaut der Atemwege wesentlich effizienter abtransportiert, was die physiologische und therapeutische Bedeutung der Guanylin-Peptide unterstreicht.

Weiterhin ist anzuführen, dass die genannten Substanzen relaxierend auf die glatte Muskulatur in der Wand der Bronchien und Bronchioli wirken. Dies führt insgesamt zu einer wesentlich verbesserten Atmung.

Die vorgenannten neugefundenen Eigenschaften der erfindungsgemäßen Peptide wirken synergistisch im Sinne der Erfindung zusammen und führen zu der sehr guten Wirkung der durch die Luftwegen zugeführten Peptide zur Behandlung der eingangs genannten Störung und Erkrankungen.

Die erfindungsgemäßen Peptide können auf Basis dieser Erkenntnisse zusätzlich für die Herstellung von Diagnostika für Atemwegserkrankungen und Erkrankungen, die mit Ventilationsstörungen und/oder Störungen der Schleimsekretion einhergehen, verwendet werden.

Zunächst sind hierfür die Peptide selbst als Referenzsubstanzen für die Diagnostik geeignet. Ein Fehlen/Mangel oder ein Überschuss dieser Peptide beispielsweise in Bronchialschleim, Exsudat oder Lavage kann das Vorhandensein behandlungsbedürftiger Störungen anzeigen. Der Nachweis der Peptide kann mit den üblichen und bekannten Mitteln, wie spektrokopisch, chromatographisch oder chemisch geschehen.

Weiterhin können für diesen Nachweis vom Fachmann mit Hilfe dafür üblicher Verfahren und Mittel Antikörper gegen die erfindungsgemäßen Peptide hergestellt werden, die dann innerhalb molekularbiologischer bzw. enzymatischer Assays eingesetzt werden können.

Zur Lösung der Aufgabe der Erfindung trägt daher auch ein Verfahren zur Diagnose der genannten Erkrankungen bei, bei welchem wenigstens eines der Peptide, das Guanylat Cyclase C aktiviert, nachgewiesen wird, und zwar vorzugsweise im Bronchialschleim, Exsudat, Lavage, Nasensekret oder Speichel.

Der Nachweis kann durch Nachweis einer der Sequenzen zu Seq. ID 1 bis ID 6

Seq. ID 1 (Guanylin): **PGTCEICAYA ACTGC**
Seq. ID 4 (Guanylin-Vorläufer-Molekül): MNAFLLFALC LLGAWAALAG GVTVQDGNFS FSLESVKKLK DLQEPQEPRV GKLRNFAPIP GEPVVPILCS NPNFPEELKPLCKEPNAQEI LQRLEEIAED **PGTCEICAYA ACTGC**

Seq. ID 2 (Uroguanylin): **NDDC ELCVNVACTGCL**
Seq. ID 5 (Uroguanylin-Vorläufer-Molekül): MGCRAASGLLPGVAVVLLLL LQSTQSVYIQ YQGFRVQLES MKKLSDLEAQ WAPSPRLQAQ SLLPAVCHHPALPQDLQPVC ASQEASSIFK TLRTIAN **DDC ELCVNVACTG CL**

Seq. ID 3 (Lymphoguanylin): **QEECELCINMACTGY**
Seq. ID 6 (Lymphoguanylin-Vorläufer-Molekül): MKVLALPMAVTAMLLILAQN TQSVYIQYEG FQVNLDSVKK LDKLLEQLRG FHHQMGDQRD PSILCSDPALPSDLQPVCEN SQAVNIFRAL RYIN **QEECELCINMACTGY**

Seq. ID 7 (hitzestabiles Enterotoxin): N S S N Y C C E L C C N P A C T G C Y (19 AS) aus enteropathogenen E. coli.

erfolgen. Als positives Testergebnis für den Nachweis einer Störung wird gewertet, wenn eine von Vergleichsproben gesunder Probanden abweichende Konzentration wenigstens eines der Peptide, die Guanylat Cyclase C aktivieren, gefunden wird.

Die erfindungsgemäße Verwendung der Peptide besteht weiter darin, dass ein Arzneimittel formuliert wird. welches über die Luftwege zugeführt wird und wenigstens ein Peptid enthält, das Guanylat Cyclase C aktiviert. Diese Peptide wurden oben bereits ausführlich beschrieben.

Neben dem Peptid oder dem Peptidgemisch kann wenigstens ein weiterer Wirkstoff sowie gegebenenfalls Hilfs- und Zusatzstoffe in dem Arnzeimittel enthalten sein. Als weitere Wirkstoffe kommen hier beispielsweise muskelrelaxierende Mitteln, Lokalantibiotika, vorwiegend für die Behandlung gleichzeitig aufgepfropfter bakterieller Infektionen, oder auch zusätzliche Mukolytika, Sekretolytike, Antitussiva oder bronchodilatierende Substanzen in Betracht. Die Auswahl wird der Fachmann auf Basis der jeweiligen Bedürfnisse bei der Behandlung der eingangs genannten Erkrankungen treffen.

Das Arzneimittel kann in fester oder flüssiger Form zubereitet werden und wird vom Benutzer in geeigneter Weise über die Luftwege zugeführt. Hierfür kann es mit einem handelsüblichen Zerstäuber oder Inhalationsgerät verabreicht werden.

In bevorzugter Ausführungsform liegt das Arzneimittel als Inhalationsmittel vor und enthält wenigstens ein Treibmittel. Als Treibmittel eignen sich besonders Fluorchlorkohlenwasserstoffe. Geeignete Treibmittel sind dem Fachmann auf diesem Gebiet bekannt. Allgemein können alle geeigneten Aerosolbildner oder auch Rauchbildner verwendet werden. Je nach Hilfsstoff wird ein Aerosol oder ein Rauch inhaliert, wobei ein Aerosol bevorzugt ist.

Zur Lösung der Aufgabe ist schließlich eine Inhalationsvorrichtung vorgesehen, die das Arzneimittel enthält, d.h. dass das Arzneimittel in der Inhalationsvorrichtung fertig konfektioniert vorliegt. Eine solche Inhalationsvorrichtung kann aus einer Sprühvorrichtung, insbesondere einer Dosier-Sprühvorrichtung oder einem Dosier-Inhalator (englisch: MDI, metered dose inhaler) bestehen. Geeignete Inhalatoren sind dem Fachmann bekannt und beispielsweise beschrieben in US 3 915 165, EP 166476 und US 6 099 517. Geeignet sind auch Ultraschallvernebler.

Die erfindungsgemäßen Peptide sollten für die Verabreichung zunächst in eine feindisperse Form überführt werden. Hierfür können sie zunächst in Lösung oder Suspension gebracht und gegebenenfalls mit pharmazeutischen verträglichen Zusätzen in dieser Form stabilisiert werden. Zur Stabilisierung können verträgliche Tenside, z.B. Tween ®. verwendet werden. Geeignet sind je nach Inhalationsverfahren auch handelsübliche als Lebensmittel zugelassene Emulgatoren, z.B. Lecithin. Als weitere Zusatzstoffe können Salze, Puffer, Zucker, Sorbitol, Aminosäuren u.a.m. vorhanden sein. Die Gesamtzubereitung sollte isotonisch sein. Zur Stabilisierung der Feinverteilung kann ebenfalls eine Mikroverkapselung der betreffenden Peptide oder eine Verkapselung in Liposome vorgesehen sein.

Die zu verabreichenden Peptide können auch im festen Zustand pulverisiert, beispielsweise aus Lösung gefriergetrocknet, sprühgetrocknet oder kristallisiert, vorliegen und werden dann bevorzugt mit trockenen Fluorchlorkohlenwasserstoffen als Treibmittel und Aerosolbildner gemischt. Bei pulverförmiger Verabreichung können feste Zusätze, insbesondere Stabilisatoren, beispielsweise Zucker oder zuckerartige Stoffe, Lactose und dergleichen, zugesetzt sein.

Es sind auch Inhalationsvorrichtungen bekannt, in denen die Aerosolbildner oder Treibmittel einerseits und die eigentliche Arzneimittelzubereitung andererseits in verschiedenen Kammern aufbewahrt und gemeinsam in vorgegebener Dosierung abgegeben werden. Dies vermeidet ungenaue Dosierung durch Entmischung bei Lagerung.

Die Größe der zu inhalierenden Partikel ist weniger kritisch als bei vielen anderen Anwendungen, da die erfindungsgemäßen Peptide nicht transmembran ins Blut transportiert werden sollen, sondern lediglich den in der Lunge apikal lokalisierten Rezeptor Guanylat Cyclase C erreichen müssen. Teilchengrößen zwischen 0,5 und 10 µm erscheinen geeignet.

Im folgenden wird die Erfindung anhand eines Beispiels erläutert:

Die Anwendung der Peptide soll am Beispiel der "obstruktiven und restriktiven Ventilationsstörungen" erläutert werden. Diese Atemwegserkrankungen sind gekennzeichnet durch eine endobronchiale Obstruktion mit Bronchospasmus, Schleimhautödem und durch eine Hypersekretion eines zähen Schleims (Dyskrinie). Diese Erscheinungen führen dazu, dass der betroffene Patient durch vermehrte und insuffiziente Atemarbeit regelrecht erschöpft. Als restriktive Komponente wird der Gasaus-

tausch durch das Schleimhautödem wesentlich verschlechtert, die Sauerstoffaufnahme der Lungen deutlich vermindert.

Die Anwendung der Peptide zielt auf eine diesen Pathomechanismen entgegenstehende Wirkung ab. Die inhalative Applikation führt zu einer Relaxierung der glatten Atemwegs-Muskulatur, so dass der bronchiale Widerstand und damit die Atemarbeit des Patienten abnimmt. Mit der Erleichterung der Atemarbeit wird eine Erschöpfung des Patienten gemindert bzw. verhindert.

Aufgrund von Elektrolyt/Wasser-sezernierenden Wirkungen dieser Peptide wird eine vermehrte Wasserausschwemmung aus der Schleimhaut der Atemwege induziert, die im Sinne einer Abnahme des Schleimhautödems (Abschwellung) wirkt und damit zu einer verbesserten Atmung führt. Durch den vermehrten Wasseraustritt aus der Schleimhaut wird die Dyskrinie vermindert, der zähe Schleim verflüssigt und der Abtransport des Sekretes durch erhöhten Zilienschlag verbessert.

Somit üben die Peptide unterschiedliche Funktionen aus, die in ihrer Kombination und Synergie zu einer deutlichen Verbesserung der Atmung führen.

Patentansprüche:

1. Verwendung eines Peptids, welches Guanylat Cyclase C aktiviert, für die Herstellung eines Arzneimittels zur Behandlung von Atemwegserkrankungen und Erkrankungen, die mit Ventilationsstörungen und/oder Störungen der Schleimsekretion einhergehen, über die Luftwege, wobei das Arzneimittel so formuliert ist, dass die Zuführung des Peptids auf der Luftseite der Atemwege, nämlich zur apikalen Membran der Schleimhaut-Epithelzellen gerichtet, erfolgt.

2. Verwendung nach Anspruch 1, dadurch gekennzeichnet, dass das Peptid ein natürliches oder rekombinantes Guanylin, Uroguanylin, Lymphoguanylin oder hitzebeständiges Enterotoxin ist, oder ein zu diesen homologes, im wesentlichen funktionsgleiches Peptid, insbesondere eine solche Peptidvariante mit durch Deletion, Insertion oder Austausch einzelner und/oder mehrerer Aminosäuren, sequenzverlängerndes Anfügen von einzelnen und/oder mehreren Aminosäuren und/oder chemischer Derivatisierung insbesondere der terminalen Aminosäuren verbundener Sequenz-Modifikation.

3. Verwendung nach Anspruch 1 oder 2, dadurch gekennzeichnet, dass das Peptid eine der Sequenzen zu Seq. ID 1 bis Seq. ID 7 umfasst.

4. Verwendung eines Peptids, wie in einem der Ansprüche 1 bis 3 angegeben, für die Herstellung eines Diagnostikums für Atemwegserkrankungen und Erkrankungen, die mit Ventilationsstörungen und/oder Störungen der Schleimsekretion einhergehen.

5. Arzneimittel in einer Zubereitung, welche über die Luftwege an der apikalen Membran zugeführt wird, dadurch gekennzeichnet, dass es wenigstens ein Peptid enthält, das Guanylat Cyclase C aktiviert.

6. Arzneimittel nach Anspruch 5, dadurch gekennzeichnet, dass das Peptid Guanylin, Uroguanylin, Lymphoguanylin oder ein hitzebeständiges Enterotoxin ist, oder ein zu diesen homologes, im wesentlichen funktionsgleiches Peptid, insbesondere ein solcher Peptidvarianten mit durch Deletion, Insertion oder Austausch einzelner und/oder mehrerer Aminosäuren, sequenzverlängerndes Anfügen von einzelnen und/oder

mehreren Aminosäuren und/oder chemischer Derivatisierung insbesondere der terminalen Aminosäuren verbundener Sequenz-Modifikation,
oder ein wenigstens eines dieser Peptide enthaltendes Peptidgemisch.

7. Arzneimittel nach Anspruch 5 oder 6, dadurch gekennzeichnet, dass wenigstens eines der Peptide eine der Sequenzen zu Seq. ID 1 bis Seq. ID 7 umfasst.

8. Arzneimittel nach einem der Ansprüche 5 bis 7, dadurch gekennzeichnet, dass das Arzneimittel neben dem wenigstens einen Peptid als Wirkstoff wenigstens einen weiteren Wirkstoff enthält, sowie gegebenenfalls Hilfs- und Zusatzstoffe.

9. Arzneimittel nach einem der Ansprüche 5 bis 8, dadurch gekennzeichnet, dass das Arzneimittel in Form eines Inhalationsmittels vorliegt und wenigstens ein Treibmittel, wenigstens einen Aerosolbildner oder wenigstens einen Rauchbildner enthält.

10. Inhalationsvorrichtung, enthaltend das Arzneimittel nach einem der Ansprüche 5 bis 9.

11. Inhalationsvorrichtung nach Anspruch 10, dadurch gekennzeichnet, dass sie eine Sprühvorrichtung, insbesondere eine Dosier-Sprühvorrichtung oder einen Dosier-Inhalator umfasst.

12. Verfahren zur Diagnose von Erkrankungen, die mit Ventilationsstörungen und Störungen der Schleimsekretion in den Atemwegen einhergehen, durch Nachweis wenigstens eines Peptids, das Guanylat Cyclase C aktiviert.

13. Verfahren nach Anspruch 12, dadurch gekennzeichnet, dass der Nachweis auf wenigstens eine der Sequenzen zu Seq. ID 1 bis Seq. ID 7 gerichtet ist.

14. Verfahren nach Anspruch 12 oder 13, dadurch gekennzeichnet, dass das Peptid in Exsudat, Bronchialschleim oder Lavage nachgewiesen wird.

15. Verfahren nach einem der Ansprüche 12 bis 14, dadurch gekennzeichnet, dass eine von Vergleichsproben gesunder Probanden abweichende Konzentration wenig-

stens eines der Peptide, die Guanylat Cyclase C aktivieren, als positives Testergebnis für den Nachweis einer Störung gewertet wird.

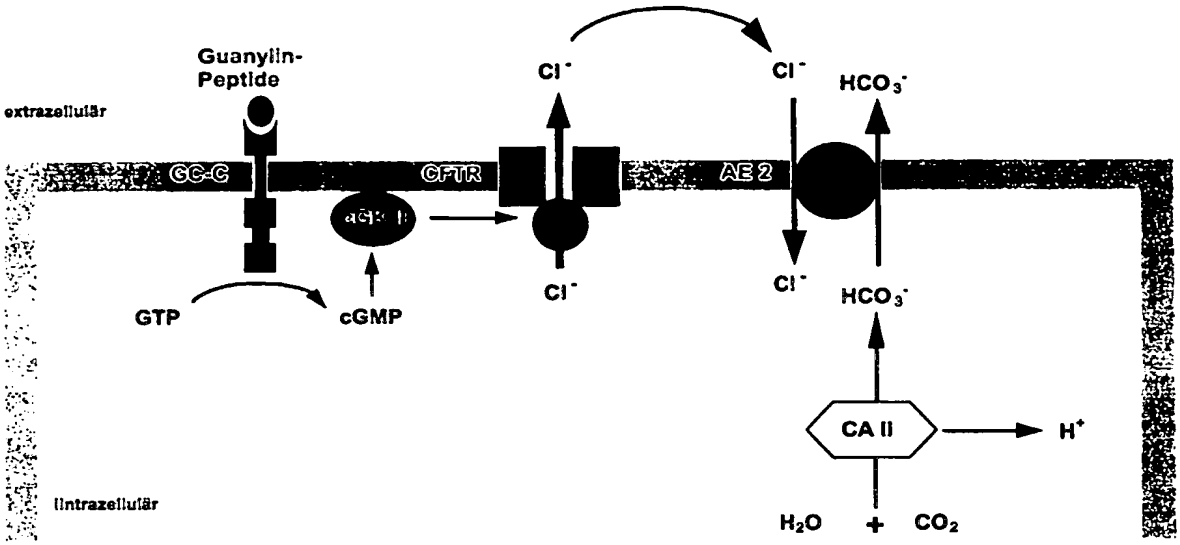

Fig. 1 Signaltransduktion der Guanylin-Peptide an Epithelzellen

Abb. 1

SEQUENCE LISTING

<110> Cetin, Y.

Savas, Y.

<120> Verwendung eines Peptids, welches Guanylat Cyclase C aktiviert, für die Behandlung von Atemwegserkrankungen über die Luftwege, Arzneimittel, Inhalationsvorrichtung und Diagnoseverfahren

<130> 3147-1 PCT-1

<150> DE10127119.0

<151> 2001-06-05

<160> 7

<170> PatentIn version 3.1

<210> 1

<211> 15

<212> PRT

<213> Ratte

<400> 1

Pro Gly Thr Cys Glu Ile Cys Ala Tyr Ala Ala Cys Thr Gly Cys
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<210> 2

<211> 16

<212> PRT

<213> Homo sapiens

<400> 2

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1 5 10 15

<210> 3

<211> 15

<212> PRT

<213> Opossum (Lymphgewebe)

<400> 3

Gln Glu Glu Cys Glu Leu Cys Ile Asn Met Ala Cys Thr Gly Tyr
1 5 10 15

<210> 4

<211> 115

<212> PRT

<213> Ratte oder Homo sapiens (Guanylin)

<400> 4

Met Asn Ala Phe Leu Leu Phe Ala Leu Cys Leu Leu Gly Ala Trp Ala
1 5 10 15

Ala Leu Ala Gly Gly Val Thr Val Gln Asp Gly Asn Phe Ser Phe Ser
20 25 30

Leu Glu Ser Val Lys Lys Leu Lys Asp Leu Gln Glu Pro Gln Glu Pro
35 40 45

Arg Val Gly Lys Leu Arg Asn Phe Ala Pro Ile Pro Gly Glu Pro Val
50 55 60

Val Pro Ile Leu Cys Ser Asn Pro Asn Phe Pro Glu Glu Leu Lys Pro
65 70 75 80

Leu Cys Lys Glu Pro Asn Ala Gln Glu Ile Leu Gln Arg Leu Glu Glu
85 90 95

Ile Ala Glu Asp Pro Gly Thr Cys Glu Ile Cys Ala Tyr Ala Ala Cys
100 105 110

Thr Gly Cys
115

<210> 5

<211> 112

<212> PRT

<213> Homo sapiens

<400> 5

Met Gly Cys Arg Ala Ala Ser Gly Leu Leu Pro Gly Val Ala Val Val
1 5 10 15

Leu Leu Leu Leu Leu Gln Ser Thr Gln Ser Val Tyr Ile Gln Tyr Gln
20 25 30

Gly Phe Arg Val Gln Leu Glu Ser Met Lys Lys Leu Ser Asp Leu Glu
35 40 45

Ala Gln Trp Ala Pro Ser Pro Arg Leu Gln Ala Gln Ser Leu Leu Pro
50 55 60

Ala Val Cys His His Pro Ala Leu Pro Gln Asp Leu Gln Pro Val Cys
65 70 75 80

Ala Ser Gln Glu Ala Ser Ser Ile Phe Lys Thr Leu Arg Thr Ile Ala
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Asn Asp Asp Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu
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<210> 6

<211> 109

<212> PRT

<213> Opossum

<400> 6

Met Lys Val Leu Ala Leu Pro Met Ala Val Thr Ala Met Leu Leu Ile
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Leu Ala Gln Asn Thr Gln Ser Val Tyr Ile Gln Tyr Glu Gly Phe Gln
20 25 30

Val Asn Leu Asp Ser Val Lys Lys Leu Asp Lys Leu Leu Glu Gln Leu
35 40 45

Arg Gly Phe His His Gln Met Gly Asp Gln Arg Asp Pro Ser Ile Leu
50 55 60

Cys Ser Asp Pro Ala Leu Pro Ser Asp Leu Gln Pro Val Cys Glu Asn
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Ser Gln Ala Val Asn Ile Phe Arg Ala Leu Arg Tyr Ile Asn Gln Glu
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Glu Cys Glu Leu Cys Ile Asn Met Ala Cys Thr Gly Tyr
100 105

<210> 7

<211> 19

<212> PRT

<213> Escherichia coli

<400> 7

Asn Ser Ser Asn Tyr Cys Cys Glu Leu Cys Cys Asn Pro Ala Cys Thr
1 5 10 15

Gly Cys Tyr

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/107,814	03/28/2002	Kunwar Shailubhai	P 0284943	9117

43569 7590 04/13/2005

MAYER, BROWN, ROWE & MAW LLP
1909 K STREET, N.W.
WASHINGTON, DC 20006

EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/107,814	SHAILUBHAI ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *4-18,24,25 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,20-23 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20020801;20050307*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The election filed January 13, 2005 is acknowledged and has been entered. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant has elected the invention of Group I, claims 1-3, 20-23, and 26, drawn to a peptide and/or a composition thereof, and a conjugate thereof further comprising polyethylene glycol attached to said peptide, wherein said peptide consists essentially of the amino acid sequence of any one of SEQ ID NOs: 2-21 or wherein the peptide is uroguanylin, guanylin, or E. coli ST peptide.

In addition, Applicant has elected the species of the invention of Group I, wherein said peptide consists essentially of SEQ ID NO: 20.

2. Claims 1-27 are pending in the application. Claims 4-19, 24, 25, and 27 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1-3, 20-23, and 26 are currently under prosecution.

Information Disclosure Statement

4. The information disclosures filed August 1, 2002 and March 7, 2005 have been considered. An initialed copy of each is enclosed.

Priority

5. Applicant's claim to the benefit of the earlier filing dates of U.S. Provisional Application Nos. 60/279,438, 60/300,850, 60/307,358, 60/279,437, 60/303,806, and 60/348,646. However, Applicant have not complied with one or more conditions for receiving the benefit of the earlier filing dates of U.S. Provisional Application Nos.

60/279,438, 60/300,850, 60/307,358, 60/279,437, and 60/303,806 under 35 U.S.C. § 119(e) as follows:

The disclosures of U.S. Provisional Application Nos. 60/279,438, 60/300,850, 60/307,358, 60/279,437, and 60/303,806 do not disclose the claimed invention in a manner that would satisfy the requirements set forth under 35 U.S.C. § 112, first paragraph. In particular, it is noted that none of these provisional applications disclose the peptide of SEQ ID NO: 20.

To receive benefit of the earlier filing date under 35 USC § 119(e), the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. § 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of this application is considered to be the date U.S. Provisional Application No. 60/348,646 was filed, namely January 17, 2002.

Specification

6. This application fails to comply with requirements of 37 C.F.R. §§ 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 121 1 OG 82 (June 23, 1998). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the Federal Register at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000).

In particular, the disclosures of amino acid sequences (e.g., page 15, lines 12-16) use symbols that are not provided for by 37 CFR § 1 .822. See MPEP § 2423.

Furthermore, it is noted that the symbols used in the specification are not the symbols used in the Sequence Listing; so the sequences in the disclosure and the Sequence Listing are discrepant.

As also noted in the attached Notice to Comply, Applicant must provide appropriate amendments to the specification, as correction of the deficiencies are required. See MPEP §§ 2420- 2426. See 37 CFR §§ 1 .821-1 .825.

7. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark is Taxol™ (page 5, line 2).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

8. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

An example of such an impermissible disclosure appears in the specification at page 23, line 31.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

Claim Objections

9. Claims 1, 3, 20-23, and 26 are objected to as being drawn in the alternative to the subject matter of non-elected species of invention.

10. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 1 is drawn to a peptide consisting essentially of the amino acid sequence of SEQ ID NO: 20 (in this instance, "consisting essentially of" is interpreted to mean "comprising", such that the claim is drawn to a peptide having the amino acid sequence set forth as SEQ ID NO: 20). SEQ ID NO: 20 is disclosed in the Sequence Listing as an artificial (4,12; 7,15) bicyclic amino acid sequence in which the amino acids at positions 4 and 12 and 7 and 15 are bridged by disulfide bonds. Claim 2 is drawn to the peptide of claim 1, wherein said peptide is a (4,12; 7,15) bicycle having the sequence of SEQ ID NO: 20. Because a peptide consisting essentially of SEQ ID NO: 20 is a peptide having the (4,12; 7,15) bicyclic amino acid sequence set forth as SEQ ID NO: 20, claim 2 fails to further limit the subject matter of claim 1.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1, 2, 20-23, and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Claim 1 is directed to a genus of peptides consisting essentially of the amino acid sequence set forth as SEQ ID NO: 20.

The Office ordinarily interprets "consisting essentially of" as "comprising". However, it is noted that the term "consisting essentially of" is defined in the specification. At page 4 (lines 10-15), the specification reads (emphasis added):

> 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%.

Notably, therefore, the recitation of the term "consisting essentially of" in the claims does not exclude peptides that are *not* identical to identical to a recited sequence identification number and other sequences that do not differ substantially in terms of either structure or function, since the term is meant only to include such peptides that are. Moreover, the term is defined to include peptides that do not vary substantially in terms of either structure or function, not both.

Accordingly, the broadest reasonable interpretation of claim 1, which is consistent with the supporting disclosure, is that the invention includes a genus of peptides that are not necessarily identical to a recited sequence identification number or other sequences that do not differ substantially in terms of either their structure or their function, but not

necessarily both (i.e., the peptides encompassed the claims vary substantially in structure and function).

Claims 2 and 26 are directed to a genus of peptides having the amino acid sequence set forth as SEQ ID NO: 20; whereas claims 20-23 are directed to a genus of "guanylate cyclase receptor agonist peptides" having the amino acid sequence set forth as SEQ ID NO: 20.

A peptide that has the amino acid sequence of SEQ ID NO: 20 necessarily comprise the amino acid sequence but may also comprise additional amino acid sequences.

The specification defines the terms "guanylate cyclase receptor" and "guanylate cyclase receptor agonist". At page 9, lines 13-15, the term "guanylate cyclase receptor" is defined as referring to "the class of guanylate cyclase receptors on any cell type to which the inventive agonist peptides or natural agonists described herein bind". Then at page 9, lines 17-25, the specification reads (emphasis added):

> As used herein, the term "guanylate cyclase receptor-agonist" refers to peptides and/or other compounds that bind to a guanylate cyclase receptor and stimulate cGMP production. The term also **includes** all peptides that have amino acid sequences substantially equivalent to **at least a portion** of the binding domain comprising amino acid residues 3-15 of SEQ ID NO:1. This term also **covers** fragments and pro-peptides that bind to guanylate cyclase receptor and stimulate cGMP production. The term "substantially equivalent" refers to a peptide that has an amino acid sequence equivalent to that of the binding domain where certain residues may be deleted or replaced with other amino acids without imparing the peptide's ability to bind to a guanylate cyclase receptor and stimulate cGMP production.

Notably, therefore, the recitation of the term "guanylate cyclase receptor-agonist peptide" in the claims does not exclude peptides that do not bind a guanylate cyclase receptor and stimulate cGMP production, since the term is expressly defined to include peptides that have amino acid sequences substantially equivalent to at least a portion of the binding domain comprising amino acid residues 3-15 of SEQ ID NO: 1. Substituting the definition of the term "substantially equivalent" into the definition of the term "guanylate cyclase receptor-agonist" yields a definition reading, in essence, "peptides

that have amino acid sequences equivalent to that of **at least a portion** of the binding domain comprising amino acid residues 3-15 of SEQ ID NO: 1, where certain residues may be deleted or replaced with other amino acids without imparing the peptide's ability to bind to a guanylate cyclase receptor and stimulate cGMP production. A peptide that has *only a portion of* a binding domain or a substantial equivalent thereof does not bind the receptor, since given its plain meaning, "a binding domain" comprises the amino acids necessary for binding and a portion thereof would lack at least some of the necessary amino acids.

Accordingly, despite the fact that the peptides of claims 2, 20-23, and 26 necessarily comprise the amino acid sequence of SEQ ID NO: 20, the broadest reasonable interpretation of claims 2, 20-23, and 26, which is consistent with the supporting disclosure, is that the invention includes a genus of peptides that commonly comprise at least only a portion of a binding domain comprising amino acids 3-15 or a substantial equivalent thereof (i.e., the amino acid sequence of SEQ ID NO: 20), but which do not necessarily bind a guanylate cyclase receptor and thereby stimulate cGMP production (i.e., the peptides encompassed the claims vary substantially in structure and function).

The specification describes an artificial peptide consisting of the (4,12; 7,15) bicyclic amino acid sequence of SEQ ID NO: 20 in which the amino acids at positions 4 and 12 and 7 and 15 are bridged by disulfide bonds. The specification teaches that this peptide binds to a guanylate cyclase receptor and thereby stimulates the production of cGMP.

However, the peptide consisting of SEQ ID NO: 20 is not representative of the genus as a whole, since, as explained above, the genus includes peptides that comprise amino acid sequences that either bear no requisite degree of similarity to the amino acid sequence set forth as SEQ ID NO: 20, or which comprise the amino acid sequence of SEQ ID NO: 2 but do not necessarily have any particular function that is attributable to this structural feature. Moreover, the peptide consisting of SEQ ID NO: 20 is not representative of the genus as a whole, since the genus includes peptides that comprise

additional amino acid sequences, and so vary in structure, despite having a common amino acid sequence, and also vary in function.

For example, the members of the claimed genus include polypeptides that are the "pre-pro-" and "pro-forms" of peptides, such as uroquanylin and guaynlin, which comprise a bioactive amino acid sequence and additional amino acid sequences. Forte (*Regul. Pept.* 1999 May 31; **81** (1-3): 25-39), for example, teaches these forms of peptides, such as uroguanylin and guanylin, are not bioactive (i.e., lack the ability to bind to guanylate cyclase receptor and stimulate production of cGMP); see, e.g., page 26, column 2. Thus, despite comprising the amino acid sequence of bioactive guanylin or uroguanylin (i.e., the 15 or 16 carboxy (C)-terminal amino acids of the peptides), they are lack the activity of their bioactive forms. Because the amino acid sequence of which the claimed peptides are comprised (i.e., SEQ ID NO: 20) is a variant of the amino acid sequence, the presence of additional amino acid sequences in the peptides is expected to affect their function, such that the claimed peptides vary in function.

In addition, Hikada et al. (*J. Biol. Chem.* 2000 Aug 18; **275** (33): 25155-25162) teaches a peptide comprising the amino acid sequence of uroguanylin; see entire document. This peptide is a "circulating plasma form of uroguanylin", which consists of 24 amino acids. While the full-length peptide is bioactive, a mutant peptide in which the first two amino (N)-terminal amino acids have been deleted nearly completely lacked the ability to form the correct disulfide pairing to form the bioactive bicyclic peptide (page 25158, column 1). The correct disulfide pairing of peptide is an absolute requirement for its biological activity; see, e.g., Hikada et al. (*Biochemistry*. 1998; **37**: 8498-8507, e.g., the abstract). Thus, despite sharing the amino acid sequence of bioactive uroguanylin (i.e., the 16 carboxy (C)-terminal amino acids of the naturally occurring peptide), the mutant peptide is inactive.

The peptide consisting of SEQ ID NO: 20 is not representative of the genus as a whole, since the members of the claimed genus include peptides comprising amino acid sequences, in whole or in part, that are variants of SEQ ID NO: 20. For example, the specification describes a peptide consisting of the (4,12; 7,15) bicyclic amino acid sequence of SEQ ID NO: 14 in which the amino acids at positions 4 and 12 and 7 and 15

are bridged by disulfide bonds. SEQ ID NO: 14 represents a genus of (4,12; 7,15) bicyclic amino acid sequence peptide sequences; the peptides having this sequence vary at positions 1, 5, 6, 8, 10, 11, 13, 14, and 16 and any amino acid can occur at any of these positions. However, the specification discloses that peptides consisting of the (4,12; 7,15) bicyclic amino acid sequence of SEQ ID NO: 14 are inactive, despite the formation of the appropriate disulfide bridging, since such peptides failed to stimulate the production of cGMP; see, e.g., page 21, lines 7 and 8; and Table 4. This disclosure indicates that while formation of the correct disulfide bonds is essential to the bioactivity of the peptides, it is not the sole requirement. Thus, the structural features of SEQ ID NO: 20 are not particularly representative of the claimed genus of peptides.

Because the members of the claimed genus of peptides are both structurally and functionally disparate, there is no disclosed correlation between any one particularly identifying structural feature of the peptides and any one particularly identifying functional feature that is also shared by at least a substantial number of the members of the claimed genus.

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (*supra*) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

As explained above, the claims are directed to a genus of polypeptides, which includes members that vary markedly in both structure and function. Because the claims encompass a genus of variant species, an adequate written description of the claimed

invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. Furthermore, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

13. Claims 1, 2, 20-23, and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a peptide consisting of a (4,12; 7,15) bicyclic peptide of the amino acid sequence set forth as SEQ ID NO: 20, wherein said cysteine residues at positions 4 and 12 form a disulfide bond and said cysteine residues at positions 7 and 15 form a disulfide bond, a composition thereof, and a conjugate of said peptide and polyethylene glycol, **does not reasonably provide enablement for making and using** a peptide consisting of, consisting essentially of, or having the amino acid sequence set forth as SEQ ID NO: 20, a pharmaceutical composition thereof, or a conjugate of said peptide and polyethylene glycol. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The amount of guidance, direction, and exemplification set forth in the specification would not sufficient to enable the skilled artisan to make and use the claimed invention without undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the

predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The prior art teaches various members of the "guanylin" family of peptides, which bind to a guanylate cyclase receptor and thereby, stimulate the production of cGMP; see, e.g., Forte (*supra*). The family includes uroguanylin.

As explained above, the specification teaches a variant of uroguanuylin consisting of the amino acid sequence set forth as SEQ ID NO: 20, which retains the activity of uroguanylin; see, e.g., page 21, Table 4.

The claims, however, are not limited to a peptide consisting of SEQ ID NO: 20; rather as explained above in section 12 the claims encompass members of a genus of peptides that vary substantially both in terms of their structures and their functions.

A peptide that is encompassed by the claims, which does not retain the activity of uroguanylin and its functionally related peptides, could not be used without the need to first discover how such a peptide can be used, which would require the skilled artisan to perform undue experimentation before using the claimed invention.

Provided that the peptides retain the specific biological activity of uroguanylin, the amount of guidance, direction, and exemplification provided by the supporting disclosure would not be sufficient to enable the skilled artisan to make the claimed invention.

As explained above in section 12, the claims encompass peptides that comprise SEQ ID NO: 20, or unrelated sequences, and additional amino acid sequences. The amount of guidance, direction, and exemplification disclosed would not enable the skilled artisan to make peptides that retain the activity of uroguanylin but lack structural similarity to uroguanylin or other members of the family of guanylin-like peptides; but moreover, the disclosure would not enable the skilled artisan to make peptides, which despite sharing the structural features of SEQ ID NO: 20, are bioactive.

In addition to those references cited above, which show the unpredictable nature of the art, Klodt et al. (*J. Pept. Res.* 1997 Sep; **50** (3): 222-230) teaches that amino acid substitutions among different members of the family of guanylin-like peptides have unexpected effects; see entire document (e.g., the abstract).

Further regarding the lack of predictability in peptides comprising the amino acid sequences of bioactive peptides, Garcia et al. (*J. Biol. Chem.* 1993 Oct 25; **268** (30): 22397-22401) teaches a peptide comprising the 22 or 32 C-terminal amino acids of proguanylin are bioactive but a peptide comprising the 63 C-terminal amino acids is not; see entire document (e.g., the abstract). Garcia et al. disclose that very little is known about the structure of prohormones (page 22401, column 1) and admit that certain discrepancies between the activities of these different peptides is not yet understood (page 22400, column 2).

As noted above, the specification teaches similar levels of unpredictability, since even peptides that form the characteristic bicyclic structure that is essential to the bioactivity of uroguanylin and guanylin fail to exhibit such activity. The specification also shows that the peptides of SEQ ID NO: 4, for example, in which the cysteine residues at positions 4, 7, 12, and 15 are substituted by β,β-dimethylcysteines (penicillamine), are inactive, despite having the potential to form the essential bicyclic structure of uroguanylin and its bioactive variant set forth as SEQ ID NO: 20; see, e.g., page 21, lines 9-11; and page 21, Table 4.

Upon the basis of this factual evidence, it is apparent that the skilled artisan cannot reliably and accurately predict whether any given peptide comprising the amino acid sequence of SEQ ID NO: 20 or a variant thereof will retain the bioactivity of uroguanylin and other guanlyin-like peptides. Therefore, the activity of even structurally related peptides can only be determined empirically. The need to empirically determine how to make such peptides comprising the amino acid sequence of SEQ ID NO: 20 or a variant thereof that retain the bioactivity of uroguanylin and other guanlyin-like peptides falls into the realm of undue experimentation.

Echoing these facts, Takada et al. (*Mol. Endocrinol.* 2000; **14** (5): 733-740) teaches that the lack of predictability in the art remains, despite technological advances and a better understanding of the structure-function relationship; see entire document (e.g., the abstract). Takada et al. teaches their work illustrates that a single amino acid change may be sufficient to cause the acquisition of a new ligand binding specificity as well as to suppress recognition of a previous ligand, extending observations by others

who showed that changes in one or several amino acids can result in marked alterations in activity and function of nuclear receptors (page 738, column 1). Notably, Takada et al. teaches that the functional consequence of amino acid substitution may be rather subtle, since the variants of the receptors were still able to bind to the promoter of the reporter construct and activate transcription in the presence of some ligands but not others; see, e.g., page 739, Figure 5. Takada et al. teaches the difference in ligand binding specificity caused by the amino acid changes results in the variants having the activity of different member of the family of proteins; see, e.g., the abstract. Thus, Takada et al. discloses that seemingly subtle differences resulting from amino acid differences, such as changes in ligand binding specificity, may cause variants of a protein to have a function that differs markedly from that of the protein. Accordingly, depending upon the assay used to assess the activity of the proteins and its variants, the effects of amino acid sequence variation may not be immediately recognized or appreciated, since the variants may appear to function normally otherwise, but in actuality have substantially different functions. In this instance, a peptide may bind a guanylate cyclase receptor but not stimulate the production of cGMP, or as Takada et al. found, the peptide may bind to a functionally distinct receptor to cause even more unexpected results.

With particular regard to claims 20-23, drawn to pharmaceutical compositions comprising such peptides, the specification discloses that the claimed invention is used to reduce, alleviate, or prevent the symptoms of disease, or even to prevent the disease; see, e.g., page 18, lines 22 and 23. The diseases the invention is used to treat or prevent notably include a wide variety of cancers; see, e.g., page 19, lines 5-30. However, the disclosure does not include exemplification of the use of the invention to treat or prevent any disease.

Baxter (*Basic Res. Cardiol.* 2004 Mar; 99 (2): 71-75), for example, teaches that the relevance of the "natriuretic peptides", such as uroguanylin, to human physiology and pathology remain uncertain; see entire document (e.g., the abstract). Therefore, despite the advances made in the prior art toward understanding the roles of these peptides in disease, there is still no consensus as to whether or not, and how these peptides might be used therapeutically or prophylactically.

One cannot extrapolate the teachings of the specification to the enablement of the invention, particularly in the absence of exemplification that is commensurate in scope with the claims, because it is well known that the art of drug discovery for is highly unpredictable. With regard to anticancer drug discovery, for example, Gura (*Science.* 1997; **278**: 1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Moreover, because of the lack of predictability in the art, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, indicating that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2).

Although the teachings of Bergers, et al (*Current Opinion in Genetics and Development.* 2000; **10**: 120-127) are drawn to specific antitumor agents, namely matrix metalloproteinase inhibitors, the great extent of unpredictability in the art is underscored by the disclosures of Berger, et al. Bergers, et al teach, "a body of data over the past few years indicate [...] that proteinases and proteinase inhibitors may, under special circumstance, either favor or block tumor progression. For example, ectopic expression of TIMP-1 [a natural inhibitor of metalloproteinases] allows for some tumors to grow, while inhibiting others" (page 125, column 2). In fact, Bergers, et al, disclose that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers, et al comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, columns 1-2). Bergers, et al also teaches that the absence of a metalloproteinase activity in mice actually predisposes the mice to *de novo* squamous carcinomas. Thus, it is relatively clear that one skilled in the art cannot predict the effect of administering a pharmaceutical composition or a combination

of such compositions purported to have a desired pharmacological effect to a subject. Always the efficacy of any unproven drug regimen must be determined empirically. Therefore, in such an unpredictable art as this, the disclosure of such empirical determinations (i.e., working exemplification) must be commensurate in scope with its expected and indicated uses if the specification is to be considered enabling; otherwise, in the absence of sufficient exemplification, the skilled artisan would have to perform undue experimentation to use the claimed invention to treat or prevent a disease, such as cancer.

Unpredictability aside, the art of preventing cancer is for the most part intractable. In this regard, it is noted that Shailubhai et al. (*Cancer Res.* 2000 Sep 15; **60**: 5151-5157) (of record) teaches that uroguanylin treatment suppressed polyp formation in a mouse model but did not prevent their formation, nor their progression to adenocarcinoma; see entire document (e.g., the abstract). In as much as uroguanylin therapy cannot prevent colorectal cancer in mice, it is unlikely that the claimed invention will prove capable of doing so in any animal, including a human.

Summarizing, as the claims are drawn to variants of uroquanylin having structures (and functions) that vary significantly, the amount of guidance, direction and exemplification disclosed is not reasonably commensurate in scope with the claims. Yet, in order to satisfy the enablement provision set forth under 35 U.S.C. § 112, first paragraph, reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

"Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify a peptide having a useful bioactivity, such as the

bioactivity of uroguanylin; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification contained in the supporting disclosure would not be sufficient to enable the skilled artisan to use the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claim 1 rejected under 35 U.S.C. 102(b) as being anticipated by Hikada et al. (*Biochemistry*. 1998; **37**: 8498-8507).

Claim 1 is drawn to a peptide consisting essentially of the amino acid sequence of SEQ ID NO: 20.

As explained above in section 12 above, in light of the supporting disclosure, and particularly the definition of the term "consisting essentially of", the broadest reasonable interpretation of claim 1 is that the invention includes the members of a genus of peptides that are not necessarily identical to the recited sequence identification number (i.e., SEQ ID NO: 20), or not necessarily identical to other sequences that do not differ substantially in terms of either their structure or their function (i.e., the peptides encompassed the claim vary substantially in structure and function and are not limited to a peptide comprising the amino acid sequence of SEQ ID NO: 20).

Hikada et al. teaches several peptides, including uroguanylin; see entire document (e.g., page 8499, Figure 1).

Conclusion

16. Claims 1-3, 20-23, and 26 are free of the prior art of record, as the prior art of record does not teach or fairly suggest a peptide comprising the amino acid sequence set forth as SEQ ID NO: 20. More particularly, while the prior art teaches uroguanylin, the prior art does not teach or suggest a variant of uroguanylin having a glutamate residue at position 3, rather than the naturally occurring aspartate residue.

17. No claim is allowed.

18. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Shailubhai et al. (*Clinical Cancer Res.* (Proc. 1999 AACR NCI EORTC International Conference) 1999; **5** (Suppl.); Abstract #0734) teaches oral administration of uroguanylin inhibits polyps in mice. Pitari et al. (*Proc. Natl. Acad. Sci. USA.* 2001; **98**: 7846-7851) suggests the combination of uroguanylin-like peptides and zaprinast or other inhibitors of cGMP-dependent phosphodiesterases. Nathan et al. (*Bioconjug. Chem.* 1993 Jan-Feb; **4** (1): 54-62), Caliceti et al. (*Biochimica et Biophysica Acta.* 2001; **1528**: 177-186), and Hinds K, et al. (*Bioconjug. Chem.* 2000; **11**: 195-201) teach conjugates of polyethylene glycol. U.S. Patent Application Publication No. 2002/ teaches C-Type natriuretic polypeptide (CNP) as a monotherapy or in combination with phosphodiesterase inhibitors.

Shailubhai K. (Curr. Opin. Drug Discov. Devel. 2002 Mar; 5 (2): 261-268) reviews the potential of therapeutic application of guanylate cyclase-C receptor agonists.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is

(571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
April 7, 2005

Notice to Comply	Application No.	Applicant(s)	
	10/107,814	SHAILUBHAI ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: See the Office action for a complete explanation of the reasons the application is not compliant; if necessary to correct the deficiency, Applicant must submit a substitute sequence listing and a statement, as indicated below.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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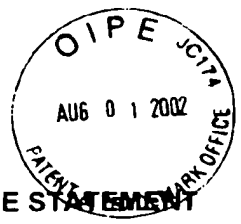

Atty. Dkt. No.	M#	Client Ref.
	0284943	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Applicant: Shailubhai et al.

Application Serial No. 10/107,814

Filing Date: March 28, 2002

Date: August 1, 2002 Page 1 of 1

Examiner: unassigned Group Art Unit: unassigned

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
SR	AR	5,489,670	Feb 1996	Currie et al.			
	BR	5,518,888	May 1996	Waldman			
	CR	5,601,990	Feb 1997	Waldman			
	DR	5,731,159	Mar 1998	Waldman			
	ER	5,879,656	Mar 1999	Waldman			
	FR	5,928,873	Jul 1999	Waldman			
	GR	5,969,097	Oct 1999	Wiegand et al.			
	HR						
	IR						
	JR						
	KR						
	LR						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country	Inventor Name		English Abstract		Translation Readily Available	
							Enclosed	No	Enclosed	No
	MR									
	NR									
	OR									
	PR									
	QR									
	RR									
	SR									

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

SR	TR	Shailubhai et al., "Uroguanylin Treatment Suppresses Polyp Formation in the Apc Min/+ Mouse and Induces Apoptosis in Human Colon Adenocarcinoma Cells via Cyclic GMP" *Cancer Research* 60 (September 15, 2000) 5151-5157.
	UR	Carrithers et al., "Guanylyl cyclase C is a selective marker for metastatic colorectal tumors in human extraintestinal tissues" *Proc. Natl. Acad. Sci. USA* 93 (December 1996) 14827-14832.
	VR	Hill et al., "Analysis of the human guanylin gene and the processing and cellular localization of the peptide" *Proc. Natl. Acad. Sci. USA* 92 (March 1995) 2046-2050.
	WR	Hamra et al., "Uroguanylin: Structure and activity of a second endogenous peptide that stimulates intestinal guanylate cyclase" *Proc. Natl. Acad. Sci. USA* 90 (November 1993) 10464-10468.
	XR	De Sauvage et al., "Precursor structure, expression and tissue distribution of human guanylin" *Proc. Natl. Acad. Sci. USA* 89 (October 1992) 9089-9093.
	YR	Currie et al., "Guanylin: An endogenous activator of intestinal guanylate cyclase" *Proc. Natl. Acad. Sci. USA* 89 (February 1992) 947-951.

Examiner [signature] Date Considered: 3/22/05

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

PAT-1449 12/98

FORM PTO-1449 (modified)
U.S. Department of Commerce
U.S. Patent & Trademark Office

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Attorney Reference: 121634-40284943	
Applicant: Kunwar Shailubhai et al.	
Application Serial No. 10/107,814	
Filing Date: March 28, 2002	
Examiner: unassigned	Group Art Unit: unassigned

Date: March 7, 2005 Page 1 of 1

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
SR	AR	2005/0032684 A1	2/10/2005	Cetin et al.			
	BR						
	CR						
	DR						
	ER						
	FR						
	GR						
	HR						
	IR						
	JR						
	KR						
	LR						
	MR						
	NR						

FOREIGN PATENT DOCUMENTS

		Document Number	Date MM/YYYY	Country			Translation Readily Available		English Abstract	
							Enclosed	No	Enclosed	No
SR	OR	WO 02/098912 A2	12/12/2002	PCT					X	
SR	PR	WO 02/098912 A3	12/12/2002	PCT					X	
	QR									
	RR									
	SR									
	TR									
	UR									
	VR									
	WR									
	XR									

OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

	YR	
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	AAR	
	BBR	
	CCR	
	DDR	

Examiner [signature] Date Considered: 3/22/05

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Notice of References Cited	Application/Control No. 10/107,814	Applicant(s)/Patent Under Reexamination SHAILUBHAI ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	Page 1 of 4

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2002/0128176	09-2002	Forssmann et al.	514/2
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Shailubhai K, et al. Clinical Cancer Res. (Proc. 1999 AACR NCI EORTC International Conference) 1999; 5 (Suppl.); Abstract #0734.
	V	Pitari GM, et al. Proc. Natl. Acad. Sci. USA. 2001 Jul 3; 98 (14): 7846-51.
	W	Nathan A, et al. Bioconjug Chem. 1993 Jan-Feb; 4 (1): 54-62
	X	Caliceti P, et al. Biochimica et Biophysica Acta. 2001; 1528: 177-86.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 10/107,814	Applicant(s)/Patent Under Reexamination SHAILUBHAI ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	Page 2 of 4

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
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FOREIGN PATENT DOCUMENTS

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	N					
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	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Hinds K, et al. Bioconjug. Chem. 2000; 11: 195-201.
	V	Forte LR. Regul. Pept. 1999 May 31; 81 (1-3): 25-39.
	W	Hikada Y, et al. Biochemistry. 1998; 37: 8498-507.
	X	Hikada Y, et al. J. Biol. Chem. 2000 Aug 18; 275 (33): 25155-62.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 10/107,814	Applicant(s)/Patent Under Reexamination SHAILUBHAI ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	Page 3 of 4

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
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	C	US-			
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FOREIGN PATENT DOCUMENTS

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	N					
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	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Klodt J, et al. J. Pept. Res. 1997 Sep; 50 (3): 222-30.
	V	Garcia KC, et al. J. Biol. Chem. 1993 Oct 25; 268 (30): 22397-401.
	W	Baxter GF. Basic Res. Cardiol. 2004 Mar; 99 (2): 71-5.
	X	Takada I, et al. Mol. Endocrinol. 2000; 14 (5): 733-40.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Notice of References Cited	Application/Control No. 10/107,814	Applicant(s)/Patent Under Reexamination SHAILUBHAI ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	Page 4 of 4

U.S. PATENT DOCUMENTS

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	N					
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	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Bergers G, et al. Current Opinion in Genetics and Development. 2000; 10: 120-7.
	V	Gura T. Science. 1997; 278: 1041-2
	W	Shailubhai K. Curr. Opin. Drug Discov. Devel. 2002 Mar; 5 (2): 261-8.
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims

Application/Control No.	Applicant(s)/Patent under Reexamination
10/107,814	SHAILUBHAI ET AL.
Examiner	**Art Unit**
Stephen L. Rawlings, Ph.D.	1642

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	+	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	4/5/05
	1	√
	2	√
	3	√
	4	N
	5	N
	6	N
	7	N
	8	N
	9	N
	10	N
	11	N
	12	N
	13	N
	14	N
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	18	N
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Claim		Date
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Bib Data Sheet

CONFIRMATION NO. 9117

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/107,814	03/28/2002 RULE	514	1642	P 0284943

APPLICANTS

Kunwar Shailubhai, Blue Bell, PA;

Gregory Nikiforovich, St. Louis, MO;
Gary S. Jacob, Creve Coeur, MO;

** CONTINUING DATA **********

This appln claims benefit of 60/279,438 03/29/2001
and claims benefit of 60/300,850 06/27/2001
and claims benefit of 60/307,358 07/25/2001
and claims benefit of 60/279,437 03/29/2001
and claims benefit of 60/303,806 07/10/2001
and claims benefit of 60/348,646 01/17/2002

SR

** FOREIGN APPLICATIONS **********

SR

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 05/02/2002

Foreign Priority claimed	STATE OR	SHEETS	TOTAL	INDEPENDENT
☐ yes ☒ no	COUNTRY	DRAWING	CLAIMS	CLAIMS
35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance	PA	0	27	12
Verified and Acknowledged Examiner's Signature Initials SR				

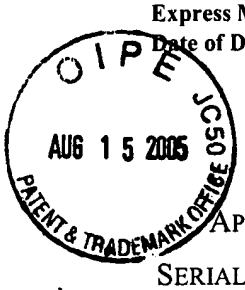
ADDRESS
43569
MAYER, BROWN, ROWE & MAW LLP
1909 K STREET, N.W.
WASHINGTON , DC
20006

TITLE
Guanylate cyclase receptor agonists for the treatment of tissue inflammation and carcinogenesis

☐ All Fees

Express Mail Label No.: EV463107857US
Date of Deposit: August 15, 2005

Attorney Docket No: 33357-503



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Shailubhai *et al.*
SERIAL NUMBER: 10/107,814 EXAMINER : Stephen L. Rawlings
FILING DATE: March 28, 2002 ART UNIT 1642
FOR: Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE

This paper is in response to the Office Action of April 13, 2005, in the above-identified patent application. A petition for a one-month extension of time and the required fee are filed herewith. With the extension of time, this response is due on Monday, August 15, 2005 (August 13, 2005 being a Saturday). The Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 23357-500.

Please amend the above-identified application as follows:

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims that begins on page 5 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Amendments to the Specification:

Please amend the paragraph beginning on page 1, line 4 as follows:

-- The present application claims the benefit of U.S. provisional application ~~No. 60/279,438, filed on March29, 2001; No. 60/279,437, filed on March29, 2001; No. 60/300,850, filed on Jun. 27, 2001; No. 60/303,806, filed on Jul. 10, 2001; No. 60/307,358, filed on Jul. 25, 2001; and~~ No. 60/348,646, filed on Jan. 17, 2002.--

Please amend the paragraph beginning on page 4, line 30 as follows:

-- 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, antimetabolites, vinca alkaloids, anthracycline antibiotics, nitrogen mustard agents, and the like. Particular anti-neoplastic agents may include tamoxifen, TAXOL™ ~~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.--

Please amend Table 2 beginning on page 15 as follows:

Table 2

1. **Parent compound, uroguanylin**

SEQ ID NO:1

Asn[1]-Asp[2]-Asp[3]-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Val[10]-Ala[11]-Cys[12]-Thr[13]-Gly[14]-Cys[15]-Leu[16]

2. **Compounds without modifications of cysteines:**

Common sequence (SEQ ID NO:2):

Asn[1]-Xaa[2]~~**Aaa**[2]~~-Xaa[3]~~**Bbb**[3]~~-Cys[4]-Glu[5]-Leu[6]-Cys[7]-Val[8]-Asn[9]-Xaa[10]~~**Xxx**[10]~~-Xaa[11]~~**Yyy**[11]~~-Cys[12]-Thr[13]-Xaa[14]~~**Zzz**[14]~~-Cys[15]-Leu[16]

where ~~Aaa~~Xaa[2]=Asp, Glu; Xaa[3]~~Bbb~~=Asp, Glu

with the exception that Xaa^2 ~~Ass~~ and Xaa^3 ~~Bbb~~ are not both Asp in same molecule
And where Xaa^{10}~~Xxx~~=Val, Pro; Xaa^{11}~~Yyy~~=Ala, Aib; Xaa^{14}~~Zzz~~=Gly, Ala

3. **Compounds with mercaptoproline (Mpt) substituted for cysteine in position 7:**

Common sequence (SEQ ID NO:3):

Asn^1-Xaa^2~~Aaa~~^{2}-Xaa^3 ~~Bbb~~^{3}-Cys^4-Glu^5-Leu^6-Xaa^7~~Mpt~~^{7}-Val^8-Asn^9-Xaa^{10}~~Xxx~~^{10}-
Xaa^{11}~~Yyy~~^{11}-Cys^{12}-Thr^{13}-Xaa^{14}~~Zzz~~^{14}-Cys^{15}-Leu^{16}

where Xaa^2~~Aaa~~=Asp, Glu; Xaa^3~~Bbb~~=Asp, Glu
where Xaa^{10}~~Xxx~~=Val, Pro; Xaa^{11}~~Yyy~~=Ala, Aib; Xaa^{14} ~~Zzz~~=Gly, Ala

4. **Compounds with penicillamines (ß, ß-dimethylcysteines, Pen) substituted for cysteines:**

Common sequence (SEQ ID NO:4):

Asn^1-Xaa^2~~Aaa~~^{2}-Xaa^3~~Bbb~~^{3}-Xaa^4~~Kkk~~^{4}-Glu^5-Leu^6-Xaa^7~~Lll~~^{7}-Val^8-Asn^9-Xaa^{10}~~Xxx~~^{10}-
Xaa^{11}~~Yyy~~^{11}-Xaa1^2~~Mmm~~^{12}-Thr^{13}-Xaa^{14}~~Zzz~~^{14}-Xaa^{15}~~Nnn~~^{15}-Leu^{16}

where Xaa^2~~Aaa~~=Asp, Glu; Xaa^3~~Bbb~~=Asp, Glu
where Xaa^{10}~~Xxx~~=Val, Pro; Xaa^{11}~~Yyy~~=Ala, Aib; Xaa^{14}~~Zzz~~=Gly, Ala
and Xaa^4~~Kkk~~, Xaa^7~~Lll~~, Xaa^{12} ~~Mmm~~, Xaa^{15} ~~Nnn~~ are either Cys or Pen (except not all are Cys in the same conformer)

5. **Compounds with lactam bridges substituted for disulfide bridges:**

Common sequence (SEQ ID NO:5):

Asn^1-Xaa^2~~Aaa~~^{2}-Xaa^3~~Bbb~~^{3}-Xaa^4~~Kkk~~^{4}-Glu^5-Leu^6-Xaa^7~~Lll~~^{7}-Val^8-Asn^9-Xaa^{10}~~Xxx~~^{10}-
Xaa^{11}~~Yyy~~^{11}-Xaa^{12}~~Mmm~~^{12}-Thr^{13}-Xaa^{14}~~Zzz~~^{14}-Xaa^{15}~~Nnn~~^{15}-Leu^{16}

where Xaa^2~~Aaa~~=Asp, Glu; Xaa^3~~Bbb~~=Asp, Glu
where Xaa^{10}~~Xxx~~=Val, Pro; Xaa^{11}~~Yyy~~=Ala, Aib; Xaa^{14}~~Zzz~~=Gly, Ala

and all combinations of the following (Dpr is diaminopropionic acid):

Xaa^4~~Kkk~~ is either Asp or Glu, and Xaa^{12}~~Mmm~~ is Dpr;
Xaa^7~~Lll~~ is either Cys or Pen;
Xaa^{15}~~Nnn~~ is either Cys or Pen;
or:
Xaa^7~~Lll~~ is Dpr and Xaa^{15}~~Nnn~~ is either Asp or Glu;
Xaa^7~~Lll~~ is either Asp or Glu, and Xaa^{15}~~Nnn~~ is Dpr;

Xaa^{4}~~Kkk~~ is either Cys or Pen;
Xaa^{12}~~Mmm~~ is either Cys or Pen;

Please amend the paragraph beginning on page 23, line 30 as follows:

--12. Basoglu, et al., in: Proceedings of the Second FEPS Congress, June 29-Jul. 4, 1999, Prague, Czech Republic., http://~~www.~~1f2.cuni.cz/ physiolres/feps/basoglu.htm.--

Listing of Claims:

The following list of claims shall replace all previous versions.

1. (Currently amended). A peptide consisting of ~~consisting essentially of~~ the amino acid sequence of SEQ ID NO: 20 ~~any one of SEQ ID NO:2- SEQ ID NO:21~~.

2-19. (Canceled).

20. (Currently amended). A pharmaceutical composition in unit dose comprising a guanylate cyclase receptor agonist peptide consisting of ~~having~~ the amino acid sequence of SEQ ID NO: 20 ~~any one of SEQ ID NOs:2-21~~ present in a therapeutically effective amount.

21. (Currently amended). A pharmaceutical composition in unit dose form comprising:

a) a guanylate cyclase receptor agonist peptide consisting of ~~having~~ the amino acid sequence of SEQ ID NO: 20 ~~any one of: SEQ ID NOs:2-21; uroguanylin; guanylin; or E. coli ST peptide~~; and

b) at least one compound selected from the group consisting of: a cGMP-dependent phosphodiesterase inhibitor, an anti-inflammatory agent, an antiviral agent and an anticancer agent; wherein said guanylate cyclase receptor agonist and said compound are each present in a therapeutically effective amount.

22. (original) The pharmaceutical composition of either claim 20 or 21, wherein the unit dose form is selected from the group consisting of a tablet, a capsule, a solution or inhalation formulation.

23. (original) The pharmaceutical composition of either claim 20 nor 21, further comprising one or more excipients.

24-25. (Canceled).

26. (Currently amended). A peptide conjugate comprising polyethylene glycol (PEG) attached to a peptide consisting of ~~having~~ the amino acid sequence of SEQ ID NO: 20 ~~any of: SEQ ID NO:2 - SEQ ID NO:21; uroguanylin; guanylin; or *E. coli* ST peptide~~.

27. (Canceled).

REMARKS

Amendments to the Claims

Upon entry of the present amendments, claims 1, 20-23, and 26 are pending. Claims 2-19, 24-25 and 27 have been canceled herein without prejudice or disclaimer as directed to non-elected inventions. Claims 1, 20, 21 and 26 have been amended herein. Support for the amendment to claim 1 can be found in the originally filed specification at, *e.g.*, page 9, lines 17-25; and page 17, line 32. The specification has been amended to meet the requirements of 37 CFR §§ 1.821-1.825 in regard to amino acid sequences, to properly label trademarks, and remove hyperlinks. No new matter is added.

Information Disclosure Statements

Applicants note that the Examiner has considered the information disclosure statements filed August 1, 2002 and March 7, 2005. Applicants file herewith a Supplemental IDS along with the required fee of $180.00 as set forth in 37 C.F.R. §1.17(p).

Priority

The Examiner has indicated that Applicants are entitled to the priority date of U.S. Provisional Application 60/348,646, filed January 17, 2002 but not entitled to priority under 35 U.S.C. § 119(e) for US Provisional Application numbers 60/279,438; 60/300,850; 60/307,358; 60/279,437; and 60/303,806, stating that these provisional applications do not disclose the claimed invention in a manner satisfying 35 U.S.C. § 112, first paragraph, because none of these provisional applications disclose the peptide of SEQ ID NO: 20. Applicants have amended the priority section of the specification to indicate that the present application claims priority only to provisional application No. 60/348,646. This objection should be withdrawn.

Specification

The Examiner has indicated that the application fails to comply with the sequence listing requirements of 37 CFR §§ 1.821-1.825, stating that the disclosure of amino acid sequences uses symbols not provided for by 37 CFR § 1.822, and that the symbols used in the specification are not identical to the symbols used in the sequence listing. Applicants have amended Table 2 of the specification to meet the requirements of 37 CFR § 1.821-1.825.

The Examiner has also objected to the specification because of improperly demarcated trademarks, including Taxol™. Applicants have amended the specification herein to properly demarcate trademarks. This objection can be withdrawn.

The Examiner has also objected to the specification because of the presence of embedded hyperlinks. Applicants have amended the specification herein to remove embedded hyperlinks. This objection can be withdrawn.

Claim Objections

The Examiner has indicated that claims 1, 3, 20-23 and 26 are objected to as being drawn in the alternative to non-elected species of the invention. Applicants have canceled claim 3 and amended claims 1 and 20-21 herein to delete the phrase, "any one of SEQ ID NO:2- SEQ ID NO:21," and Applicants have amended claim 26 herein to delete the phrase, "any of: SEQ ID NO:2 - SEQ ID NO:21; uroguanylin; guanylin; or *E. coli* ST peptide." Claims 22-23 depend from claims 20 and 21. Thus, Applicants assert that pending claims 1, 20-23 and 26, as amended herein, are not drawn to non-elected species of the invention.

The Examiner has also indicated that claim 2 is objected to under 37 CFR § 1.75(c) for failing to further limit the subject matter of claim 1. Applicants have canceled claim 2 herein. Thus this objection is moot.

For the above-stated reasons, these objections have been overcome and can be withdrawn.

Claim Rejections – 35 U.S.C. § 112, first paragraph

Written description

The Examiner has indicated that claims 1, 2, 20-23 and 26 are rejected under 35 U.S.C. § 112, first paragraph for lack of written description. Applicants have canceled claim 2 herein. Thus this objection is moot in regard to claim 2. The Examiner states that the broadest interpretation of claim 1 that is consistent with the supporting disclosure is that the invention includes a genus of peptides that are not necessarily identical to a recited sequence identification number or other sequences that do not differ substantially in terms of either their structure or their function, but not necessarily both (*i.e.*, the peptides encompassed by the claims vary substantially in structure and function). (See, Office action, paragraph bridging pages 6 and 7).

Applicants respectfully disagree with the Examiner's interpretation of claim 1. Claim 1 has been amended herein to require a peptide consisting of the amino acid sequence of SEQ ID NO: 20. The peptide of SEQ ID NO: 20 is explicitly disclosed at, *e.g.*, page 17, line 32. Therefore, Applicants assert that one skilled in the art would recognize that the Applicants were in possession of the peptide of claim 1 when the application was filed.

In regard to claims 20-23 and 26, the Examiner indicates that the broadest reasonable interpretation of claims 20-23 and 26 consistent with the supporting disclosure is a genus of peptides that commonly comprise only a portion of amino acids 3-15 of SEQ ID NO: 20 or a substantial equivalent thereof, which do not necessarily bind a guanylate cyclase receptor and thereby stimulate cGMP production.

This rejection has been mooted, as the pending claims have been limited to peptides consisting of SEQ ID NO: 20. Claims 20 and 21, as amended herein, specifically require a guanylate cyclase receptor agonist peptide consisting of the amino acid sequence of SEQ ID NO: 20 present in a therapeutically effective amount. Similarly, claim 26 requires a peptide conjugate comprising polyethylene glycol (PEG) attached to a peptide consisting of the amino acid sequence of SEQ ID NO: 20. Therefore, these claims also cannot include only a portion of amino acids 3-15 of SEQ ID NO: 20. Claims 22 and 23 depend from claims 20 and 21 and necessarily contain all the limitations of these claims. The originally filed application discloses the peptide of SEQ ID NO: 20 at, *e.g.*, page 17, line 32. Thus, Applicants assert that one of skill in the art would recognize that Applicants were in possession of the subject matter of claims 20-23 and 26 when the application was filed.

This rejection has been overcome and should be withdrawn.

Enablement

The Examiner has indicated that claims 1, 2, 20-23 and 26 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. Claim 2 has been canceled herein. Thus, this rejection is moot in regard to claim 2. The Examiner acknowledges that the specification is enabled for making and using a peptide consisting of a (4,12; 7,15) bicycle peptide of the amino acid sequence set forth as SEQ ID NO: 20. The pending claims have been limited to the peptide of SEQ ID NO: 20. Thus, one of ordinary skill in the art would be able to use the claimed invention without undue experimentation.

For all these reasons, Applicants believe that the pending claims are fully enabled by the originally filed application. Thus, this rejection can be withdrawn.

Claim Rejections – 35 U.S.C. § 102

The Examiner has indicated that claim 1 is rejected under 35 U.S.C. § 102(b) as anticipated by Hikada *et al.*, ("Hikada") Biochemistry 37:8498-8507 (1998). Claim 1, as amended herein, is drawn to a peptide consisting of the amino acid sequence of SEQ ID NO: 20, which has a glutamic acid at position 3. Hikada teaches a peptide sequence of uroguanylin 15 amino acids in length where the residue at position 3 is an aspartic acid, but does not teach the peptide sequence of SEQ ID NO: 20. Since Hikada does not teach all the elements of claim 1, it cannot anticipate this claim. Thus, this rejection has been overcome and should be withdrawn.

CONCLUSION

Applicant respectfully requests that a timely notice of Allowance be issued in this case. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Ivor R. Elrifi, Reg. No. 39,529
Gregory J. Sieczkiewicz, Reg. No. 48,223
Attorneys for Applicant
c/o MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C.
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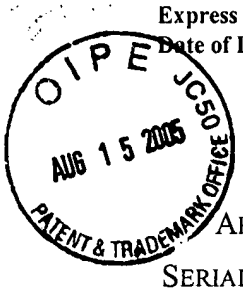
Dated: August 15, 2005

TRA 2056585v2

Express Mail Label No.: EV463107857US
Date of Deposit: August 15, 2005

Attorney Docket No: 33357-503



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Shailubhai *et al.*
SERIAL NUMBER: 10/107,814 EXAMINER : Stephen L. Rawlings
FILING DATE: March 28, 2002 ART UNIT 1642
FOR: Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. § 1.136(a), Applicant hereby petitions for a one-month extension of time to respond to the April 13, 2005 Office Action in the above-identified application. With the extension, this Response is due on or before Monday, August 15, 2005 (August 13, 2005 being a Saturday). A check in the amount of $120.00, in payment of the fee required by 37 C.F.R. § 1.17(a)(1), is enclosed herewith.

The Commissioner is hereby authorized to charge payment of any fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311, (Reference No. 33357-503).

Respectfully submitted,

Ivor R. Elrifi, Reg. No. 39,529
Gregory J. Sieczkiewicz, Reg. No. 48,223
Attorneys for Applicant
c/o MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C.
Customer No. 30623
Tel: (617) 542-6000
Fax: (617) 542-2241

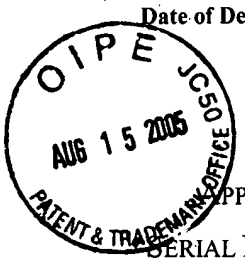
08/17/2005 EFLORES 00000142 10107814
01 FC:1251 120.00 OP

Dated: August 15, 2005

TRA 2064015v1

Express Mail Label No.: EV463107857US
Date of Deposit: August 15, 2005

Attorney Docket No: 33357-503



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Shailubhai *et al.*

SERIAL NUMBER: 10/107,814 EXAMINER : Stephen L. Rawlings

FILING DATE: March 28, 2002 ART UNIT 1642

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

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Pursuant to the duty of disclosure under 37 C.F.R. §§§1.56, 1.97 and 1.98, Applicants hereby make of record the documents listed on the attached modified Form PTO-1449, as well as copies of the listed documents.

This Information Disclosure Statement is being filed after the mailing date of the first Office Action, but before the mailing date of either a final action under 37 C.F.R. §1.113 or a Notice of Allowance under 37 C.F.R. §1.311. The fee of $180.00 as set forth in 37 C.F.R. §1.17(p) is enclosed.

It is respectfully requested that the Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims, and sign the enclosed form PTO-1449 to evidence that the cited information has been fully considered by the Patent and Trademark Office during the examination of this application.

By submitting this Information Disclosure Statement, the Applicants make no representation that: (1) a search has been performed, of the extent of any search performed, or that more relevant information does not exist; (2) the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. §1.56(b); and (3) the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. §102.

08/17/2005 EFLORES 00000142 10107814
02 FC:1806 180.00 OP

Notwithstanding any statements by the Applicants, the Examiner is urged to form his/her own conclusion regarding the relevance of the cited information. An early and favorable action is hereby requested.

Please charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 33357-503.

Respectfully submitted,

Ivor R. Elrifi, Reg. No. 39,529
Gregory J. Sieczkiewicz, Reg. No. 48,223
Attorneys for Applicant
c/o MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C.
Customer No. 30623
Tel: (617) 542-6000
Fax: (617) 542-2241

Dated: August 15, 2005

TRA 2064006v1

Please type a plus sign (+) in this box [+]

PTO/SB (12-97)
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Modified Form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Application Number	10/107,814
Filing Date	March 28, 2002
First Named Inventor	Shailubhai
Group Art Unit	1642
Examiner Name	Stephen L. Rawlings
Attorney Docket Number	33357-503

U.S. PATENT DOCUMENTS

Exam Initials	Cite No.	U.S. Patent Document No.	Issue Date	Name of Patentee(s) or Applicant(s)	Class	Sub Class	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS

Exam Initials	Cite No.	Foreign Patent Document Office	Number	Name of Patentee(s) or Applicant(s)	Date of Publication	Translation Yes	No

OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS

Exam Initials	Cite No.	Name of Author, Title (when appropriate), Publication, Volume, Page(s), Date, Etc.
	ZR	Sindice, et al., Journal of Biological Chemistry, 277:17758-17764 (2002).

Examiner Signature		Date Considered	

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

TRA 2064031v1

08-16-05 1642

Express Mail Label No.: EV463107857US
Date of Deposit: August 15, 2005

Attorney Docket No: 33357-503

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Shailubhai *et al.*
SERIAL NUMBER: 10/107,814 EXAMINER : Stephen L. Rawlings
FILING DATE: March 28, 2002 ART UNIT 1642
FOR: Guanylate Cyclase Receptor Agonists for the Treatment of Tissue Inflammation and Carcinogenesis

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Enclosed herewith for filing in the above-identified application please find the following documents:

1. Amendment and Response (10 pages);
2. Petition for Extension of Time (1 page);
3. Check No. 20992 in the amount of $120.00 to cover the Extension fee;
4. Information Disclosure Statement (2 pages)
5. Reference ZR (7 pages) and Form 1449 (1 page);
6. Check No. 20993 in the amount of $180.00; and
7. Return Postcard

The Commissioner is hereby authorized to charge payment of any fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311, (Reference No. 33357-503).

Respectfully submitted,

Ivor R. Elrifi, Reg. No. 39,529
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Tel: (617) 542-6000
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Dated: August 15, 2005

TRA 2064024v1

GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: August 26, 2005, 18:54:31 ; Search time 39 Seconds
(without alignments)
39.474 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 283416 seqs, 96216763 residues

Total number of hits satisfying chosen parameters: 283416

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : PIR_79:*
1: pir1:*
2: pir2:*
3: pir3:*
4: pir4:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	92	96.8	112	2	JC4651	uroguanylin precur
2	73	76.8	116	2	JC7620	guanylin precursor
3	63	66.3	72	1	QHEC4	heat-stable entero
4	63	66.3	72	1	QHECIB	heat-stable entero
5	60	63.2	17	2	A54534	heat-stable entero
6	60	63.2	78	1	QHVC1	heat-stable entero
7	58	61.1	18	2	A60103	heat-stable entero
8	58	61.1	72	1	QHEC1	heat-stable entero
9	56	58.9	53	2	S68705	heat-stable entero
10	56	58.9	115	1	A46279	guanylin precursor
11	56	58.9	115	1	JN0318	guanylin precursor
12	56	58.9	116	1	B46279	guanylin precursor
13	55	57.9	66	2	S31652	enterotoxin - Yers
14	54	56.8	71	2	S25659	heat-stable entero
15	51	53.7	106	2	S74084	follitropin beta c
16	50	52.6	18	1	QHEC2	heat-stable entero
17	45	47.4	240	2	T27629	hypothetical prote
18	44.5	46.8	892	2	T40040	GTPase-activator p
19	44	46.3	1016	2	T00375	hypothetical prote
20	43.5	45.8	334	2	G75344	probable polyferre
21	43.5	45.8	1548	2	S34583	serine proteinase
22	43	45.3	65	2	S34671	heat-stable entero
23	43	45.3	153	2	S52605	probable membrane
24	43	45.3	282	1	YPDOD1	prestalk D11 prote
25	42.5	44.7	1052	2	T14343	zinc finger RNA bi
26	42	44.2	84	2	B69014	ferredoxin 2[4Fe-4
27	42	44.2	128	2	S74085	lutropin beta chai
28	42	44.2	159	2	I51373	luteinizing hormon
29	42	44.2	201	2	A48827	zinc finger protei
30	42	44.2	268	2	T04787	hypothetical prote
31	42	44.2	275	2	T21933	hypothetical prote
32	42	44.2	342	2	T27785	hypothetical prote
33	42	44.2	495	2	G82371	FixG-related prote
34	42	44.2	618	2	G72281	glutamate synthase
35	42	44.2	698	2	T23469	hypothetical prote
36	42	44.2	937	2	A45082	neurotrophic recep
37	42	44.2	1253	2	T45787	disease resistance
38	42	44.2	1664	2	F84485	probable retroelem
39	41.5	43.7	187	2	F88124	protein T12C9.5 [i
40	41.5	43.7	410	2	T24020	hypothetical prote
41	41.5	43.7	1274	2	T42017	cysteine rich prot
42	41	43.2	129	1	FTHUB	follitropin beta c
43	41	43.2	129	1	FTPGB	follitropin beta c
44	41	43.2	129	1	FTSHB	follitropin beta c
45	41	43.2	130	2	JC4526	follitropin beta c

ALIGNMENTS

RESULT 1
JC4651
uroguanylin precursor - human
N;Alternate names: guanylyl cyclase activating peptide II
C;Species: Homo sapiens (man)
C;Date: 10-May-1996 #sequence_revision 19-Jul-1996 #text_change 09-Jul-2004
C;Accession: JC4651; S63702; S68052
R;Miyazato, M.; Nakazato, M.; Yamaguchi, H.; Date, Y.; Kojima, M.; Kangawa, K.; Matsuo,
Biochem. Biophys. Res. Commun. 219, 644-648, 1996
A;Title: Cloning and characterization of a cDNA encoding a precursor for human uroguany
A;Reference number: JC4651; MUID:96193705; PMID:8605041
A;Accession: JC4651
A;Molecule type: mRNA
A;Residues: 1-112 <MIY>
A;Cross-references: UNIPROT:Q16661; GB:U34279; NID:g1236798; PIDN:AAC50416.1; PID:g1236
R;Hill, O.; Cetin, Y.; Cieslak, A.; Maegert, H.J.; Forssmann, W.G.
Biochim. Biophys. Acta 1253, 146-149, 1995
A;Title: A new human guanylate cyclase-activating peptide (GCAP-II, uroguanylin): precu
A;Reference number: S63702; MUID:96106424; PMID:8519795
A;Accession: S63702
A;Molecule type: mRNA
A;Residues: 1-112 <HIL>
A;Cross-references: EMBL:Z50753; NID:g974823; PIDN:CAA90629.1; PID:g974824
A;Experimental source: tissue colon
R;Hess, R.; Kuhn, M.; Schulz-Knappe, P.; Raida, M.; Fuchs, M.; Klodt, J.; Adermann, K.;
FEBS Lett. 374, 34-38, 1995
A;Title: GCAP-II: isolation and characterization of the circulating form of human urogu
A;Reference number: S68052; MUID:96049550; PMID:7589507
A;Accession: S68052
A;Molecule type: protein
A;Residues: 89-99,'X',101-102,'X',104-107,'X',109-110,'X',112 <HES>
C;Comment: This protein, a member of the guanylin peptide family, is an endogenous acti
.
C;Superfamily: guanylin
C;Keywords: intestine
F;1-26/Domain: signal sequence #status predicted <SIG>
F;27-112/Product: uroguanylin #status predicted <MAT>

Query Match 96.8%; Score 92; DB 2; Length 112;
Best Local Similarity 93.8%; Pred. No. 9.6e-06;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db         97 NDDCELCVNVACTGCL 112
```

RESULT 2
JC7620
guanylin precursor, long form - European eel
C;Species: Anguilla anguilla (European eel)
C;Date: 30-Jun-2001 #sequence_revision 30-Jun-2001 #text_change 03-Aug-2001

```
C;Accession: JC7620
R;Comrie, M.M.; Cutler, C.P.; Cramb, G.
Biochem. Biophys. Res. Commun. 281, 1078-1085, 2001
A;Title: Cloning and expression of guanylin from the European eel (Anguilla anguilla).
A;Reference number: JC7620; MUID:21139737; PMID:11243845
A;Accession: JC7620
A;Molecule type: mRNA
A;Residues: 1-116 <COM>
A;Cross-references: GB:AJ301673
C;Comment: This protein, a member of a family of heat-stable peptides, is a potent extra
 axis. This peptide signalling system plays a role in osmoregulation in euryhaline teleo
C;Superfamily: guanylin
C;Keywords: heat-stable protein; osmoregulation
F;1-28/Domain: signal sequence #status predicted <SIG>
F;29-116/Product: guanylin precursor, long form #status predicted <MAT>
F;33-39/Region: homologous #status predicted
F;69-114/Region: highly conserved #status predicted

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Qy          2 DECELCVNVACTGCL 16
              | ||:| | ||||||
Db        102 DPCEICANAACTGCL 116


RESULT 3
QHEC4
heat-stable enterotoxin STA4 precursor - Escherichia coli
C;Species: Escherichia coli
C;Date: 31-Mar-1992 #sequence_revision 31-Mar-1992 #text_change 09-Jul-2004
C;Accession: JT0373; A35978
R;Stieglitz, H.; Cervantes, L.; Robledo, R.; Fonseca, R.; Covarrubias, L.; Bolivar, F.;
Plasmid 20, 42-53, 1988
A;Title: Cloning, sequencing, and expression in ficoll-generated minicells of an Escheri
A;Reference number: JT0373; MUID:89202548; PMID:3071819
A;Accession: JT0373
A;Molecule type: DNA
A;Residues: 1-72 <STI>
A;Cross-references: UNIPROT:P07965; GB:J03311; NID:g147875; PIDN:AAA24652.1; PID:g147876
R;Zhou, X.; Shen, L.P.; Chi, C.W.
Toxicon 28, 453-456, 1990
A;Title: Isolation and nucleotide sequence determination of a gene encoding a heat-stabl
A;Reference number: A35978; MUID:90273381; PMID:2190361
A;Accession: A35978
A;Molecule type: DNA
A;Residues: 1-72 <ZHO>
C;Genetics:
A;Gene: estA4
C;Superfamily: heat-stable enterotoxin ST
C;Keywords: enterotoxin; heat-stable protein
F;1-19/Domain: signal sequence #status predicted <SIG>
F;20-53/Domain: propeptide #status predicted <PRO>
F;54-72/Product: heat-stable enterotoxin #status predicted <MAT>
F;59-64,60-68,63-71/Disulfide bonds: #status predicted

  Query Match             66.3%;  Score 63;  DB 1;  Length 72;
  Best Local Similarity   83.3%;  Pred. No. 0.057;
  Matches   10;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db         60 CELCCNPACTGC 71


RESULT 4
QHECIB
heat-stable enterotoxin ST-Ib precursor - Escherichia coli
N;Alternate names: heat-stable enterotoxin ST-A2
C;Species: Escherichia coli
C;Date: 30-Jun-1991 #sequence_revision 30-Jun-1991 #text_change 09-Jul-2004
C;Accession: JS0292; A33068; A33067; A30567
R;Moseley, S.L.; Hardy, J.W.; Huq, M.I.; Echeverria, P.; Falkow, S.
Infect. Immun. 39, 1167-1174, 1983
A;Title: Isolation and nucleotide determination of a gene encoding a heat-stable entero
A;Reference number: JS0292; MUID:83184648; PMID:6341230
A;Accession: JS0292
A;Molecule type: DNA
A;Residues: 1-72 <MOS>
A;Cross-references: UNIPROT:Q47185; UNIPROT:P07965; GB:M34916; NID:g146407; PIDN:AAA239
R;Dwarakanath, P.; Visweswariah, S.S.; Subrahmanyam, Y.V.B.K.; Shanthi, G.; Jagannatha,
Gene 81, 219-226, 1989
A;Title: Cloning and hyperexpression of a gene encoding the heat-stable toxin of Escher
A;Reference number: A33068; MUID:90034194; PMID:2680769
A;Accession: A33068
A;Molecule type: DNA
A;Residues: 1-18,'A',20-72 <DWA>
A;Cross-references: GB:M29255; NID:g148029; PIDN:AAA24686.1; PID:g148030
A;Note: the authors translated the codon AAG for residue 2 as Val and CTA for residue 3
R;Aimoto, S.; Takao, T.; Shimonishi, Y.; Hara, S.; Takeda, T.; Takeda, Y.; Miwatani, T.
Eur. J. Biochem. 129, 257-263, 1982
A;Title: Amino acid sequence of heat-stable enterotoxin produced by human enterotoxigen
A;Reference number: A33067; MUID:83105138; PMID:6759126
A;Accession: A33067
A;Molecule type: protein
A;Residues: 54-72 <AIM>
R;Guzman-Verduzco, L.M.; Kupersztoch, Y.M.
Infect. Immun. 57, 645-648, 1989
A;Title: Rectification of two Escherichia coli heat-stable enterotoxin allele sequences
A;Reference number: A30567; MUID:89108616; PMID:2643580
A;Accession: A30567
A;Molecule type: DNA
A;Residues: 1-18,'A',20-24,'AG',27-41,'V',43-44,'N',46,'E',48,'S',50-72 <GUZ>
A;Cross-references: GB:M18345; NID:g145862; PIDN:AAA23729.1; PID:g145863
C;Comment: This is one of the type I heat-stable enterotoxins that are methanol-soluble
C;Genetics:
A;Gene: st
C;Superfamily: heat-stable enterotoxin ST
C;Keywords: enterotoxin; heat-stable protein
F;1-53/Domain: signal sequence and propeptide #status predicted <SIG>
F;54-72/Product: heat-stable enterotoxin ST-Ib #status experimental <MAT>
F;59-64,60-68,63-71/Disulfide bonds: #status experimental

  Query Match             66.3%;  Score 63;  DB 1;  Length 72;
  Best Local Similarity   83.3%;  Pred. No. 0.057;
  Matches   10;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db         60 CELCCNPACTGC 71


RESULT 5
A54534
heat-stable enterotoxin - Vibrio mimicus (fragment)
C;Species: Vibrio mimicus
C;Date: 06-Jan-1995 #sequence_revision 06-Jan-1995 #text_change 03-May-1996
C;Accession: A54534
R;Arita, M.; Honda, T.; Miwatani, T.; Takeda, T.; Takao, T.; Shimonishi, Y.
FEMS Microbiol. Lett. 79, 105-110, 1991
A;Title: Purification and characterization of a heat-stable enterotoxin of Vibrio mimic
A;Reference number: A54534
A;Accession: A54534
A;Status: preliminary
A;Molecule type: protein
A;Residues: 1-17 <ARI>
C;Superfamily: heat-stable enterotoxin ST

  Query Match             63.2%;  Score 60;  DB 2;  Length 17;
  Best Local Similarity   66.7%;  Pred. No. 0.048;
  Matches   10;  Conservative    1;  Mismatches    4;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGCL 16
              | ||:| | || |||
Db          2 DCCEICCNPACFGCL 16
```

RESULT 6
QHVC1
heat-stable enterotoxin ST precursor - Vibrio cholerae
C;Species: Vibrio cholerae
C;Date: 17-Mar-1987 #sequence_revision 30-Jun-1992 #text_change 09-Jul-2004
C;Accession: A41469; A01824; S34464; S34466; S34465; S34463
R;Ogawa, A.; Kato, J.I.; Watanabe, H.; Nair, B.G.; Takeda, T.
Infect. Immun. 58, 3325-3329, 1990
A;Title: Cloning and nucleotide sequence of a heat-stable enterotoxin gene from Vibrio c
A;Reference number: A41469; MUID:90382953; PMID:2205577
A;Accession: A41469
A;Molecule type: DNA
A;Residues: 1-78 <OGA>
A;Cross-references: UNIPROT:P04429; GB:M85198; GB:M36061; NID:g155237; PIDN:AAA64889.1;
R;Takao, T.; Shimonishi, Y.; Kobayashi, M.; Nishimura, O.; Arita, M.; Takeda, T.; Honda,
FEBS Lett. 193, 250-254, 1985
A;Title: Amino acid sequence of heat-stable enterotoxin produced by Vibrio cholerae non-
A;Reference number: A01824; MUID:86056320; PMID:4065341
A;Accession: A01824
A;Molecule type: protein
A;Residues: 62-78 <TAK>
A;Experimental source: non-O:1 serovar
R;Yoshino, K.; Miyachi, M.; Takao, T.; Bag, P.K.; Xiaozhe, H.; Nair, G.B.; Takeda, T.; S
FEBS Lett. 326, 83-86, 1993
A;Title: Purification and sequence determination of heat-stable enterotoxin elaborated b
A;Reference number: S34463; MUID:93314823; PMID:8325391
A;Accession: S34464
A;Status: preliminary
A;Molecule type: protein
A;Residues: 61-78 <YO3>
A;Accession: S34466
A;Status: preliminary
A;Molecule type: protein
A;Residues: 51-78 <YOS>
A;Accession: S34465
A;Status: preliminary
A;Molecule type: protein
A;Residues: 60-78 <YO2>
A;Accession: S34463
A;Status: preliminary
A;Molecule type: protein
A;Residues: 62-78 <YO4>
C;Superfamily: heat-stable enterotoxin ST
C;Keywords: enterotoxin; heat-stable protein
F;1-18/Domain: signal sequence #status predicted <SIG>
F;19-61/Domain: propeptide #status predicted <PRO>
F;62-78/Product: heat-stable enterotoxin ST #status experimental <MAT>
F;64-69,65-73,68-76/Disulfide bonds: #status predicted

Query Match 63.2%; Score 60; DB 1; Length 78;
Best Local Similarity 66.7%; Pred. No. 0.15;
Matches 10; Conservative 1; Mismatches 4; Indels 0; Gaps 0;

Qy 2 DECELCVNVACTGCL 16
| ||:| | || |||
Db 63 DCCEICCNPACFGCL 77

RESULT 7
A60103
heat-stable enterotoxin ST-Ia - Citrobacter freundii
C;Species: Citrobacter freundii
C;Date: 10-Nov-1992 #sequence_revision 10-Nov-1992 #text_change 09-Jul-2004
C;Accession: A60103
R;Guarino, A.; Giannella, R.; Thompson, M.R.
Infect. Immun. 57, 649-652, 1989
A;Title: Citrobacter freundii produces an 18-amino-acid heat-stable enterotoxin identica
A;Reference number: A60103; MUID:89108617; PMID:2912902
A;Accession: A60103
A;Molecule type: protein
A;Residues: 1-18 <GUA>
A;Cross-references: UNIPROT:Q7M0U3
C;Superfamily: heat-stable enterotoxin ST

Query Match 61.1%; Score 58; DB 2; Length 18;
Best Local Similarity 75.0%; Pred. No. 0.093;
Matches 9; Conservative 0; Mismatches 3; Indels 0; Gaps 0;

Qy 4 CELCVNVACTGC 15
|||| | || ||
Db 6 CELCCNPACAGC 17

RESULT 8
QHEC1
heat-stable enterotoxin ST-I precursor - Escherichia coli
N;Alternate names: heat-stable enterotoxin estA1
C;Species: Escherichia coli
C;Date: 31-Aug-1980 #sequence_revision 31-Aug-1980 #text_change 09-Jul-2004
C;Accession: A01822; A30985; A36732; JT0374; I51932
R;So, M.; McCarthy, B.J.
Proc. Natl. Acad. Sci. U.S.A. 77, 4011-4015, 1980
A;Title: Nucleotide sequence of the bacterial transposon Tn1681 encoding a heat-stale (s
A;Reference number: A01822; MUID:81054703; PMID:6254008
A;Accession: A01822
A;Molecule type: DNA
A;Residues: 1-72 <LAZ>
A;Cross-references: UNIPROT:P01559; GB:V00612; GB:J01831; NID:g43704; PIDN:CAA23883.1; I
R;Lazure, C.; Seidah, N.G.; Chretien, M.; Lallier, R.; St-Pierre, S.
Can. J. Biochem. Cell Biol. 61, 287-292, 1983
A;Title: Primary structure determination of Escherichia coli heat-stable enterotoxin of
A;Reference number: A30985; MUID:83284515; PMID:6349752
A;Accession: A30985
A;Molecule type: protein
A;Residues: 55-72 <LAZ2>
A;Experimental source: strain F11
R;Dallas, W.S.
J. Bacteriol. 172, 5490-5493, 1990
A;Title: The heat-stable toxin I gene from Escherichia coli 18D.
A;Reference number: A36732; MUID:90368614; PMID:2203756
A;Accession: A36732
A;Molecule type: DNA
A;Residues: 1-72 <DAL>
A;Cross-references: GB:M58746; NID:g145860; PIDN:AAA62776.1; PID:g145861
A;Experimental source: strain 18D
R;Stieglitz, H.; Cervantes, L.; Robledo, R.; Fonseca, R.; Covarrubias, L.; Bolivar, F.;
Plasmid 20, 42-53, 1988
A;Title: Cloning, sequencing, and expression in ficoll-generated minicells of an Escher:
A;Reference number: JT0373; MUID:89202548; PMID:3071819
A;Accession: JT0374
A;Molecule type: DNA
A;Residues: 1-72 <STI>
R;Sekizaki, T.; Akashi, H.; Terakado, N.
Am. J. Vet. Res. 46, 909-912, 1985
A;Title: Nucleotide sequences of the genes for Escherichia coli heat-stable enterotoxin
A;Reference number: I51932; MUID:85249571; PMID:2990268
A;Accession: I51932
A;Status: translated from GB/EMBL/DDBJ
A;Molecule type: DNA
A;Residues: 1-69,'P',71-72 <RES>
A;Cross-references: GB:M25607; NID:g147877; PIDN:AAA24653.1; PID:g147878
C;Comment: Both heat-stable and heat-labile enterotoxins are produced by pathogenic str
ular sizes.
C;Superfamily: heat-stable enterotoxin ST
C;Keywords: enterotoxin; heat-stable protein
F;1-19/Domain: signal sequence #status predicted <SIG>
F;20-54/Domain: propeptide #status predicted <PRO>
F;55-72/Product: heat-stable enterotoxin ST-I #status experimental <MAT>
F;59-64,60-68,63-71/Disulfide bonds: #status predicted

Query Match 61.1%; Score 58; DB 1; Length 72;
Best Local Similarity 75.0%; Pred. No. 0.27;
Matches 9; Conservative 0; Mismatches 3; Indels 0; Gaps 0;

```
Qy          4 CELCVNVACTGC 15
              |||| | || ||
Db         60 CELCCNPACAGC 71
```

RESULT 9
S68705
heat-stable enterotoxin Y-STc - Yersinia enterocolitica
C;Species: Yersinia enterocolitica
C;Date: 25-Feb-1998 #sequence_revision 13-Mar-1998 #text_change 13-Mar-1998
C;Accession: S68705
R;Yoshino, K.; Takao, T.; Huang, X.; Murata, H.; Nakao, H.; Takeda, T.; Shimonishi, Y.
FEBS Lett. 362, 319-322, 1995
A;Title: Characterization of a highly toxic, large molecular size heat-stable enterotoxi
A;Reference number: S68705; MUID:95246844; PMID:7729521
A;Accession: S68705
A;Molecule type: protein
A;Residues: 1-53 <YOS>
A;Experimental source: strain 86-11
C;Superfamily: heat-stable enterotoxin ST
C;Keywords: enterotoxin; heat-stable protein
F;41-46,42-50,45-53/Disulfide bonds: #status predicted

```
  Query Match             58.9%;  Score 56;  DB 2;  Length 53;
  Best Local Similarity   75.0%;  Pred. No. 0.4;
  Matches    9;  Conservative    0;  Mismatches    3;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              |||| | || ||
Db         42 CELCCNPACFGC 53
```

RESULT 10
A46279
guanylin precursor [validated] - human
C;Species: Homo sapiens (man)
C;Date: 21-Sep-1993 #sequence_revision 26-May-1995 #text_change 09-Jul-2004
C;Accession: A46279; S29228; S29807
R;de Sauvage, F.J.; Keshav, S.; Kuang, W.J.; Gillett, N.; Henzel, W.; Goeddel, D.V.
Proc. Natl. Acad. Sci. U.S.A. 89, 9089-9093, 1992
A;Title: Precursor structure, expression, and tissue distribution of human guanylin.
A;Reference number: A46279; MUID:93028409; PMID:1409606
A;Accession: A46279
A;Molecule type: mRNA
A;Residues: 1-115 <DE1>
A;Cross-references: UNIPROT:Q02747; GB:M95174; NID:g306823; PIDN:AAA58625.1; PID:g306824
A;Note: sequence extracted from NCBI backbone (NCBIN:115377, NCBIP:115378)
R;Wiegand, R.C.; Kato, J.; Huang, M.D.; Fok, K.F.; Kachur, J.F.; Currie, M.G.
FEBS Lett. 311, 150-154, 1992
A;Title: Human guanylin: cDNA isolation, structure, and activity.
A;Reference number: S29228; MUID:93011964; PMID:1327879
A;Accession: S29228
A;Molecule type: mRNA
A;Residues: 1-115 <WIE>
A;Cross-references: GB:M97496; NID:g183414; PIDN:AAA35915.1; PID:g183415
R;Kuhn, M.; Raida, M.; Adermann, K.; Schulz-Knappe, P.; Gerzer, R.; Heim, J.M.; Forssman
FEBS Lett. 318, 205-209, 1993
A;Title: The circulating bioactive form of human guanylin is a high molecular weight pep
A;Reference number: S29807; MUID:93178628; PMID:8095028
A;Accession: S29807
A;Molecule type: protein
A;Residues: 22-68 <KUH>
A;Experimental source: plasma
A;Note: amino-terminal sequencing of mature form and molecular weight of mature form by
C;Comment: Guanylin is an endogenous ligand for an intestine-specific receptor guanylyl
n of the same receptor.
C;Genetics:
A;Gene: GDB:GUCA2
A;Cross-references: GDB:136460; OMIM:139392
A;Map position: 1p35-1p34
C;Superfamily: guanylin
C;Keywords: hormone; intestine
F;1-21/Domain: signal sequence #status predicted <SIG>
F;22-115/Product: guanylin #status experimental <MAT>

```
  Query Match             58.9%;  Score 56;  DB 1;  Length 115;
  Best Local Similarity   66.7%;  Pred. No. 0.72;
  Matches    8;  Conservative    1;  Mismatches    3;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              ||:|   |||||
Db        104 CEICAYAACTGC 115
```

RESULT 11
JN0318
guanylin precursor - rat
C;Species: Rattus norvegicus (Norway rat)
C;Date: 04-Dec-1992 #sequence_revision 26-May-1995 #text_change 09-Jul-2004
C;Accession: JN0318; A43345; A38184; S25489
R;Wiegand, R.C.; Kato, J.; Currie, M.G.
Biochem. Biophys. Res. Commun. 185, 812-817, 1992
A;Title: Rat guanylin cDNA: characterization of the precursor of an endogenous activato
A;Reference number: JN0318; MUID:92328783; PMID:1378267
A;Accession: JN0318
A;Molecule type: mRNA
A;Residues: 1-115 <WIE>
A;Cross-references: UNIPROT:P28902; GB:M93005; NID:g204540; PIDN:AAA41300.1; PID:g20454
R;Schulz, S.; Chrisman, T.D.; Garbers, D.L.
J. Biol. Chem. 267, 16019-16021, 1992
A;Title: Cloning and expression of guanylin. Its existence in various mammalian tissues
A;Reference number: A43345; MUID:92355545; PMID:1379587
A;Accession: A43345
A;Molecule type: mRNA
A;Residues: 1-115 <SCH>
A;Cross-references: GB:M95493; NID:g204542; PIDN:AAA41302.1; PID:g204543
A;Experimental source: intestine
A;Note: sequence extracted from NCBI backbone (NCBIN:110474, NCBIP:110476)
R;Currie, M.G.; Fok, K.F.; Kato, J.; Moore, R.J.; Hamra, F.K.; Duffin, K.L.; Smith, C.E
Proc. Natl. Acad. Sci. U.S.A. 89, 947-951, 1992
A;Title: Guanylin: an endogenous activator of intestinal guanylate cyclase.
A;Reference number: A38184; MUID:92141235; PMID:1346555
A;Accession: A38184
A;Molecule type: protein
A;Residues: 101-115 <CUR>
A;Experimental source: jejunum
A;Note: sequence extracted from NCBI backbone (NCBIP:79480)
A;Note: purification included boiling in acetic acid; peptide has activity but may repr
R;Maegert, H.J.; Khun, M.; Kruhoffer, M.; Forssmann, W.G.
submitted to the EMBL Data Library, August 1992
A;Reference number: S25489
A;Accession: S25489
A;Molecule type: mRNA
A;Residues: 101-115 <MAE>
A;Cross-references: EMBL:X67669; NID:g56343; PIDN:CAA47901.1; PID:g56344
C;Comment: Guanylin is an endogenous ligand for an intestine-specific receptor guanylyl
n of the same receptor.
C;Superfamily: guanylin
C;Keywords: hormone; intestine
F;1-21/Domain: signal sequence #status predicted <SIG>
F;22-115/Product: guanylin #status predicted <MAT>

```
  Query Match             58.9%;  Score 56;  DB 1;  Length 115;
  Best Local Similarity   66.7%;  Pred. No. 0.72;
  Matches    8;  Conservative    1;  Mismatches    3;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              ||:|   |||||
Db        104 CEICAYAACTGC 115
```

RESULT 12
B46279
guanylin precursor - mouse
C;Species: Mus musculus (house mouse)
C;Date: 22-Sep-1993 #sequence_revision 26-May-1995 #text_change 09-Jul-2004

C;Accession: A55643; B46279
R;Sciaky, D.; Kosiba, J.L.; Cohen, M.B.
Genomics 24, 583-587, 1994
A;Title: Genomic sequence of the murine guanylin gene.
A;Reference number: A55643; MUID:95229161; PMID:7713512
A;Accession: A55643
A;Molecule type: DNA
A;Residues: 1-116 <SCI>
A;Cross-references: UNIPROT:P33680; GB:U60528; GB:U09741; NID:g1480667; PIDN:AAB05758.1;
R;de Sauvage, F.J.; Keshav, S.; Kuang, W.J.; Gillett, N.; Henzel, W.; Goeddel, D.V.
Proc. Natl. Acad. Sci. U.S.A. 89, 9089-9093, 1992
A;Title: Precursor structure, expression, and tissue distribution of human guanylin.
A;Reference number: A46279; MUID:93028409; PMID:1409606
A;Accession: B46279
A;Status: nucleic acid sequence not shown
A;Molecule type: mRNA
A;Residues: 1-116 <DE1>
A;Cross-references: GB:M95175; NID:g309282; PIDN:AAA37758.1; PID:g309283
A;Note: sequence extracted from NCBI backbone (NCBIP:115379)
C;Comment: Guanylin is an endogenous ligand for an intestine-specific receptor guanylyl
n of the same receptor.
C;Genetics:
A;Introns: 25/3; 96/1
C;Superfamily: guanylin
C;Keywords: hormone; intestine
F;1-21/Domain: signal sequence #status predicted <SIG>
F;22-116/Product: guanylin #status predicted <MAT>

Query Match 58.9%; Score 56; DB 1; Length 116;
Best Local Similarity 66.7%; Pred. No. 0.72;
Matches 8; Conservative 1; Mismatches 3; Indels 0; Gaps 0;

```
Qy          4 CELCVNVACTGC 15
              ||:|   |||||
Db        105 CEICAYAACTGC 116
```

RESULT 13
S31652
enterotoxin - Yersinia kristensenii
C;Species: Yersinia kristensenii
C;Date: 13-Jan-1995 #sequence_revision 13-Jan-1995 #text_change 09-Jul-2004
C;Accession: S31652
R;Ibrahim, A.; Liesack, W.; Stackebrandt, E.
submitted to the EMBL Data Library, November 1992
A;Reference number: S31652
A;Accession: S31652
A;Status: preliminary
A;Molecule type: DNA
A;Residues: 1-66 <IBR>
A;Cross-references: UNIPROT:P31518; EMBL:X69218; NID:g48617; PIDN:CAA49152.1; PID:g48618
C;Superfamily: heat-stable enterotoxin ST

Query Match 57.9%; Score 55; DB 2; Length 66;
Best Local Similarity 66.7%; Pred. No. 0.64;
Matches 8; Conservative 1; Mismatches 3; Indels 0; Gaps 0;

```
Qy          4 CELCVNVACTGC 15
              ||:| | || ||
Db         55 CEVCCNPACAGC 66
```

RESULT 14
S25659
heat-stable enterotoxin yst precursor - Yersinia enterocolitica
C;Species: Yersinia enterocolitica
C;Date: 22-Nov-1993 #sequence_revision 26-May-1995 #text_change 09-Jul-2004
C;Accession: S25659; A41474; A23114; S65849
R;Ibrahim, A.; Liesack, W.; Pike, S.; Stackebrandt, E.
FEMS Microbiol. Lett. 97, 63-66, 1992
A;Title: The polymerase chain reaction: an epidemiological tool to differentiate betwee
A;Reference number: S25659
A;Accession: S25659
A;Status: preliminary; translation not shown
A;Molecule type: DNA
A;Residues: 1-71 <IBR>
A;Cross-references: UNIPROT:P07593; EMBL:X65999; NID:g48611; PIDN:CAA46801.1; PID:g4861
R;Delor, I.; Kaeckenbeeck, A.; Wauters, G.; Cornelis, G.R.
Infect. Immun. 58, 2983-2988, 1990
A;Title: Nucleotide sequence of yst, the Yersinia enterocolitica gene encoding the heat-
A;Reference number: A41474; MUID:90354067; PMID:2201642
A;Accession: A41474
A;Status: preliminary; not compared with conceptual translation
A;Molecule type: DNA
A;Residues: 1-47,'S',49-71 <DEL>
A;Cross-references: GB:U09235; NID:g487394; PIDN:AAA18472.1; PID:g487395
R;Takao, T.; Tominaga, N.; Yoshimura, S.; Shimonishi, Y.; Hara, S.; Inoue, T.; Miyama, A
Eur. J. Biochem. 152, 199-206, 1985
A;Title: Isolation, primary structure and synthesis of heat-stable enterotoxin produced
A;Reference number: A23114; MUID:86004705; PMID:4043080
A;Accession: A23114
A;Molecule type: protein
A;Residues: 54-71 <TAK>
R;Mikulskis, A.V.; Delor, I.; Ha Thi, V.; Cornelis, G.R.
Mol. Microbiol. 14, 905-915, 1994
A;Title: Regulation of the Yersinia enterocolitica enterotoxin Yst gene. Influence of gr
A;Reference number: S65849; MUID:95231297; PMID:7715452
A;Accession: S65849
A;Status: preliminary; translation not shown
A;Molecule type: DNA
A;Residues: 1-43 <MIK>
A;Cross-references: EMBL:U09235
C;Genetics:
A;Gene: yst
C;Superfamily: heat-stable enterotoxin ST
F;1-19/Domain: signal sequence #status predicted <SIG>
F;20-41/Domain: propeptide #status predicted <PRO>
F;42-71/Product: heat-stable enterotoxin yst #status predicted <MAT>

Query Match 56.8%; Score 54; DB 2; Length 71;
Best Local Similarity 57.1%; Pred. No. 0.92;
Matches 8; Conservative 2; Mismatches 4; Indels 0; Gaps 0;

```
Qy          2 DECELCVNVACTGC 15
              | |::| | || ||
Db         58 DCCDVCCNPACAGC 71
```

RESULT 15
S74084
follitropin beta chain - ostrich
C;Species: Struthio camelus (ostrich)
C;Date: 11-Mar-1998 #sequence_revision 17-Apr-1998 #text_change 09-Jul-2004
C;Accession: S74084
R;Koide, Y.; Papkoff, H.; Kawauchi, H.
Eur. J. Biochem. 240, 262-267, 1996
A;Title: Complete amino acid sequences of follitropin and lutropin in the ostrich, Strut
A;Reference number: S74084; MUID:97025333; PMID:8925835
A;Accession: S74084
A;Molecule type: protein
A;Residues: 1-106 <KOI>
A;Cross-references: UNIPROT:P80663
A;Experimental source: pituitary glands
C;Superfamily: pituitary glycoprotein hormone beta chain
C;Keywords: glycoprotein; heterodimer; hormone; pituitary
F;1-49,15-64,18-102,26-80,30-82,85-92/Disulfide bonds: #status predicted
F;5,22/Binding site: carbohydrate (Asn) (covalent) #status predicted

Query Match 53.7%; Score 51; DB 2; Length 106;
Best Local Similarity 57.1%; Pred. No. 3.2;
Matches 8; Conservative 2; Mismatches 4; Indels 0; Gaps 0;

```
Qy          2 DECELCVNVACTGC 15
              :|||||: |  | |
Db         13 EECELCITVNATWC 26
```

Search completed: August 26, 2005, 19:04:34
Job time : 42 secs

GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: August 26, 2005, 18:50:55 ; Search time 163 Seconds
(without alignments)
37.964 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 2105692 seqs, 386760381 residues

Total number of hits satisfying chosen parameters: 2105692

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : A_Geneseq_16Dec04:*
1: geneseqp1980s:*
2: geneseqp1990s:*
3: geneseqp2000s:*
4: geneseqp2001s:*
5: geneseqp2002s:*
6: geneseqp2003as:*
7: geneseqp2003bs:*
8: geneseqp2004s:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	95	100.0	16	6	AAO16201	Aao16201 Guanylate
2	92	96.8	16	2	AAR90204	Aar90204 Uroguanyl
3	92	96.8	16	2	AAY02390	Aay02390 Heat stab
4	92	96.8	16	2	AAY29612	Aay29612 Uroguanyl
5	92	96.8	16	2	AAY06976	Aay06976 Heat stab
6	92	96.8	16	2	AAY02402	Aay02402 Heat stab
7	92	96.8	16	4	AAB92073	Aab92073 Guanylin
8	92	96.8	16	4	AAB83214	Aab83214 Human uro
9	92	96.8	16	6	AAO16182	Aao16182 Human uro
10	92	96.8	16	6	ABG74820	Abg74820 Human uro
11	92	96.8	16	8	ADN03414	Adn03414 Exemplary
12	92	96.8	16	8	ADR42249	Adr42249 Uroguanyl
13	92	96.8	19	2	AAW18470	Aaw18470 Human GCA
14	92	96.8	19	2	AAW18483	Aaw18483 Human GCA
15	92	96.8	19	2	AAW23224	Aaw23224 GCAP-II C
16	92	96.8	22	2	AAW18482	Aaw18482 Human GCA
17	92	96.8	22	2	AAW18473	Aaw18473 Human GCA
18	92	96.8	22	2	AAW23227	Aaw23227 GCAP-II C
19	92	96.8	23	2	AAW18487	Aaw18487 Human GCA
20	92	96.8	23	2	AAW23235	Aaw23235 GCAP-II C
21	92	96.8	24	2	AAW18465	Aaw18465 Human GCA
22	92	96.8	24	5	AAM47256	Aam47256 Guanylate
23	92	96.8	28	2	AAW18494	Aaw18494 Human GCA
24	92	96.8	28	2	AAW23241	Aaw23241 GCAP-II C
25	92	96.8	37	2	AAW18493	Aaw18493 Human GCA
26	92	96.8	37	2	AAW23240	Aaw23240 GCAP-II C
27	92	96.8	38	2	AAW18475	Aaw18475 Human GCA
28	92	96.8	38	2	AAW23229	Aaw23229 GCAP-II C
29	92	96.8	43	2	AAW18489	Aaw18489 Human GCA
30	92	96.8	43	2	AAW23236	Aaw23236 GCAP-II C
31	92	96.8	56	2	AAW18469	Aaw18469 Human GCA
32	92	96.8	56	2	AAW23223	Aaw23223 GCAP-II C
33	92	96.8	64	2	AAW18492	Aaw18492 Human GCA
34	92	96.8	64	2	AAW23239	Aaw23239 GCAP-II C
35	92	96.8	66	2	AAW18491	Aaw18491 Human GCA
36	92	96.8	66	2	AAW23238	Aaw23238 GCAP-II C
37	92	96.8	67	2	AAW18474	Aaw18474 Human GCA
38	92	96.8	67	2	AAW23228	Aaw23228 GCAP-II C
39	92	96.8	69	2	AAW18472	Aaw18472 Human GCA
40	92	96.8	69	2	AAW18481	Aaw18481 Human GCA
41	92	96.8	69	2	AAW18488	Aaw18488 Human GCA
42	92	96.8	69	2	AAW23226	Aaw23226 GCAP-II C
43	92	96.8	70	2	AAW18471	Aaw18471 Human GCA
44	92	96.8	70	2	AAW18480	Aaw18480 Human GCA
45	92	96.8	70	2	AAW23225	Aaw23225 GCAP-II C

ALIGNMENTS

RESULT 1
AAO16201
ID AAO16201 standard; peptide; 16 AA.
XX
AC AAO16201;
XX
DT 28-MAR-2003 (first entry)
XX
DE Guanylate cyclase receptor agonist peptide, SEQ ID No 20.
XX
KW Guanylate cyclase receptor agonist; apoptosis induction; cancer; polyps;
KW inflammation; asthma; nephritis; hepatitis; bronchitis; cystic fibrosis;
KW inflammatory bowel disease; pancreatitis; ulcerative colitis;
KW Crohn's disease; Kaposi's sarcoma.
XX
OS Unidentified.
XX
FH Key Location/Qualifiers
FT Disulfide-bond 4. .12
FT Disulfide-bond 7. .15
XX
PN WO200278683-A1.
XX
PD 10-OCT-2002.
XX
PF 28-MAR-2002; 2002WO-US009551.
XX
PR 29-MAR-2001; 2001US-0279437P.
PR 29-MAR-2001; 2001US-0279438P.
PR 27-JUN-2001; 2001US-0300850P.
PR 10-JUL-2001; 2001US-0303806P.
PR 25-JUL-2001; 2001US-0307358P.
PR 17-JAN-2002; 2002US-0348646P.
XX
PA (SYNE-) SYNERGY PHARM INC.
XX
PI Shailubhai K, Nikiforovich G, Jacob GS;
XX
DR WPI; 2003-148251/14.
XX
PT Novel guanylate cyclase receptor agonist peptide useful for preventing or
PT treating primary or metastatic cancer and polyps in a patient, and for
PT inducing apoptosis in the cells of a subject.
XX
PS Claim 1; Page 6; 47pp; English.
XX
CC The invention comprises guanylate cyclase receptor agonist peptides that
CC are useful for inducing apoptosis in the cells of a subject. The peptides

CC of the invention may be used to treat: cancer; polyps; inflammation;
CC asthma; nephritis; hepatitis; pancreatitis; bronchitis; cystic fibrosis;
CC inflammatory bowel disease; ulcerative colitis; Crohn's disease; and
CC Kaposi's sarcoma. The present amino acid sequence represents a guanylate
CC cyclase receptor agonist peptide of the invention
XX
SQ Sequence 16 AA;

Query Match 100.0%; Score 95; DB 6; Length 16;
Best Local Similarity 100.0%; Pred. No. 3.3e-06;
Matches 16; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 NDECELCVNVACTGCL 16
||||||||||||||||
Db 1 NDECELCVNVACTGCL 16

RESULT 2
AAR90204
ID AAR90204 standard; peptide; 16 AA.
XX
AC AAR90204;
XX
DT 01-AUG-1996 (first entry)
XX
DE Uroguanylin.
XX
KW intestinal guanylate cyclase regulator; laxative; constipation.
XX
OS Homo sapiens.
XX
FH Key Location/Qualifiers
FT Disulfide-bond 4. .12
FT /note= "this bond is absent in the non-active form of the
FT peptide"
FT Disulfide-bond 7. .15
FT /note= "this bond is absent in the non-active form of the
FT peptide"
XX
PN US5489670-A.
XX
PD 06-FEB-1996.
XX
PF 29-OCT-1993; 93US-00145940.
XX
PR 29-OCT-1993; 93US-00145940.
XX
PA (SEAR) SEARLE & CO G D.
XX
PI Smith CE, Fok KF, Currie MG, Kita T;
XX
DR WPI; 1996-115663/12.
XX
PT New isolated human uroguanylin peptide - an endogenous stimulator of
PT intestinal guanylate cyclase, used for the control of intestinal
PT absorption.
XX
PS Claim 1; Col 7; 9pp; English.
XX
CC The peptide, designated human uroguanylin, has been isolated from human
CC urine. It is an endogenous stimulator of intestinal guanylate cyclase and
CC acts to increase cyclic GMP levels, to control intestinal absorption, to
CC regulate fluid and electrolyte transport, to displace heat stable
CC enterotoxins, to elicit chloride secretion and to decrease water
CC absorption. It may thus act as a laxative and be useful in patients
CC suffering from constipation, e.g. cystic fibrosis patients who suffer
CC with severe intestinal complications from constipation
XX
SQ Sequence 16 AA;

Query Match 96.8%; Score 92; DB 2; Length 16;
Best Local Similarity 93.8%; Pred. No. 8.5e-06;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

Qy 1 NDECELCVNVACTGCL 16
||:|||||||||||||
Db 1 NDDCELCVNVACTGCL 16

RESULT 3
AAY02390
ID AAY02390 standard; peptide; 16 AA.
XX
AC AAY02390;
XX
DT 09-JUL-1999 (first entry)
XX
DE Heat stable ST enterotoxin uroguanylin peptide.
XX
KW Selection; candidate drug; cell receptor binding; affinity;
KW biological receptor; rational drug design; combinatorial drug design;
KW receptor antagonist; receptor agonist; ST enterotoxin; beta turn mimetic;
KW gamma-turn mimetic; beta sheet mimetic; disulphide bridge mimetic.
XX
OS Unidentified.
XX
PN WO9909416-A2.
XX
PD 25-FEB-1999.
XX
PF 20-AUG-1998; 98WO-GB002504.
XX
PR 20-AUG-1997; 97GB-00017652.
XX
PA (NYCO-) NYCOMED IMAGING AS.
PA (COCK/) COCKBAIN J.
XX
PI Wolfe HR;
XX
DR WPI; 1999-181156/15.
XX
PT Method of drug selection - and use of an acetamidomethyl-protected
PT polymer as a substrate in the solid state synthesis of an oligopeptide.
XX
PS Disclosure; Page 2; 38pp; English.
XX
CC The specification describes a method for selecting a candidate drug
CC compound having affinity for biological receptors. The method uses a
CC combination of rational and combinatorial drug design techniques. At
CC least 1 residue in the original cell receptor binding peptide is modified
CC to a non-natural amino acid, preferably a beta turn mimetic, a gamma-turn
CC mimetic, a beta sheet mimetic or a disulphide bridge mimetic. The method
CC is used for identification of a candidate receptor antagonist or agonist.
CC The present peptide is a cell receptor binding peptide, and can thus be
CC used as a starting point for identification of candidate drug compounds,
CC using the method of the invention
XX
SQ Sequence 16 AA;

Query Match 96.8%; Score 92; DB 2; Length 16;
Best Local Similarity 93.8%; Pred. No. 8.5e-06;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

Qy 1 NDECELCVNVACTGCL 16
||:|||||||||||||
Db 1 NDDCELCVNVACTGCL 16

RESULT 4
AAY29612
ID AAY29612 standard; peptide; 16 AA.
XX
AC AAY29612;
XX
DT 15-OCT-1999 (first entry)
XX

DE Uroguanylin heat stable ST enterotoxin peptide.
XX
KW Heat stable ST enterotoxin; immunoreagent; radiological therapy;
KW diagnosis; ST receptor binding moiety; macrocyclic complexing agent;
KW tumour; infectious diarrhoeal disease; diarrhoea.
XX
OS Unidentified.
XX
PN WO9939748-A1.
XX
PD 12-AUG-1999.
XX
PF 08-FEB-1999; 99WO-GB000396.
XX
PR 06-FEB-1998; 98US-00020233.
XX
PA (NYCO-) NYCOMED IMAGING AS.
PA (MATT/) MATTHEWS D P.
XX
PI Snow RA, Delecki DJ, Shah C, Black C, Wolfe H;
XX
DR WPI; 1999-494219/41.
XX
PT Macrocyclic complexing agents containing linked 2,6-pyridinylene nuclei
PT as components of targeting immunoreagents binding to ST receptor.
XX
PS Disclosure; Page 39; 79pp; English.
XX
CC The present invention describes targeting immunoreagents (TI's)
CC comprising a metal ion and a residue of a macrocyclic complexing agent
CC (MCA). TI's are of use in diagnostic imaging and therapy of specific
CC disease sites in a patient, using either radioactive, magnetic resonance,
CC or fluorescent means of detection or use of the metal ion; alternatively,
CC a substituent of these types may be introduced , e.g. radioactive iodine,
CC to perform the same function. Most notable is the imaging and
CC radiological therapy of tumours. In addition, a variety of bacteria,
CC including Escherichia coli, Vibrio cholerae, Citrobacter freundii, and
CC Yersinia enterocolitica, bind to ST receptors and cause infectious
CC diarrhoeal diseases, particularly in pediatrics and in developing
CC countries. These types of diarrhoea can also be treated using TI's. TI's
CC may specifically used to treat cancers and also be used as an
CC antidiarrhoeal agent. TI's are free from the various disadvantages of
CC prior art reagents, including rapid destruction and/or excretion,
CC instability in storage, and protein degradation. There is no perturbation
CC of protein reactive groups at the pyridyl chelating site. AAY29607 to
CC AAY29612 represent examples of heat stable ST enterotoxins given in the
CC exemplification of the present invention
XX
SQ Sequence 16 AA;

Query Match 96.8%; Score 92; DB 2; Length 16;
Best Local Similarity 93.8%; Pred. No. 8.5e-06;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

Qy 1 NDECELCVNVACTGCL 16
||:||||||||||||||
Db 1 NDDCELCVNVACTGCL 16

RESULT 5
AAY06976
ID AAY06976 standard; peptide; 16 AA.
XX
AC AAY06976;
XX
DT 02-JUL-1999 (first entry)
XX
DE Heat stable ST enterotoxin peptide uroguanylin.
XX
KW Targeting immunoreagent; metal ion; immunoreactive; terpyridine; tumour;
KW complexing agent; diagnostic imaging; radiological treatment; yttrium;
KW therapeutic; radiation toxicity; heat stable; ST enterotoxin.
XX
OS Unidentified.
XX
PN WO9921587-A1.
XX
PD 06-MAY-1999.
XX
PF 15-OCT-1998; 98WO-GB003102.
XX
PR 15-OCT-1997; 97US-00951144.
XX
PA (NYCO-) NYCOMED IMAGING AS.
PA (MATT/) MATTHEWS D P.
XX
PI Wolfe H, Delecki DJ, Yu S;
XX
DR WPI; 1999-302905/25.
XX
PT Targeting immunoreagent for diagnostic imaging and therapeutic
PT compositions.
XX
PS Claim 16; Page 51; 57pp; English.
XX
CC The invention provides a targeting immunoreagent that comprises a metal
CC ion and an immunoreactive group covalently bonded to a terpyridine
CC complexing agent of a specified formula. The immunoreagent is useful in
CC diagnostic imaging and therapeutic compositions. The immunoreagent is
CC used for radiological treatment of tumours. When the immunoreagent
CC contains yttrium, the radiation toxicity is lower compared with other
CC yttrium chelators. The immunoreagent is not rapidly metabolized and does
CC not disperse and efficiently forms covalent bonds with proteins and other
CC biological molecules. The immunoreagent has good emission characteristics
CC and are easily spectrophotometrically analysed. Protein conjugates can be
CC stored for metal complexing without activation steps that degrade
CC protein. The terpyridine complexing agent rapidly complex with metals and
CC the obtained chelates have good stability. Sequences AAY06971-976
CC represent examples of heat stable ST enterotoxin peptides that can be
CC used as the immunoreactive group in the immunoreagent of the invention
XX
SQ Sequence 16 AA;

Query Match 96.8%; Score 92; DB 2; Length 16;
Best Local Similarity 93.8%; Pred. No. 8.5e-06;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

Qy 1 NDECELCVNVACTGCL 16
||:||||||||||||||
Db 1 NDDCELCVNVACTGCL 16

RESULT 6
AAY02402
ID AAY02402 standard; peptide; 16 AA.
XX
AC AAY02402;
XX
DT 09-JUL-1999 (first entry)
XX
DE Heat stable ST enterotoxin uroguanylin peptide.
XX
KW Selection; candidate drug; cell receptor binding; affinity;
KW biological receptor; rational drug design; combinatorial drug design;
KW receptor antagonist; receptor agonist; ST enterotoxin; beta turn mimetic;
KW gamma-turn mimetic; beta sheet mimetic; disulphide bridge mimetic.
XX
OS Unidentified.
XX
PN WO9909417-A2.
XX
PD 25-FEB-1999.
XX
PF 20-AUG-1998; 98WO-GB002510.
XX
PR 20-AUG-1997; 97GB-00017652.

XX
PA (NYCO-) NYCOMED IMAGING AS.
PA (COCK/) COCKBAIN J.
XX
PI Wolfe HR;
XX
DR WPI; 1999-181157/15.
XX
PT Method of drug selection - using a combination of rational and
PT combinatorial drug design techniques.
XX
PS Disclosure; Page 2; 35pp; English.
XX
CC The specification describes a method for selecting a candidate drug
CC compound having affinity for biological receptors. The method uses a
CC combination of rational and combinatorial drug design techniques. At
CC least 1 residue in the original cell receptor binding peptide is modified
CC to a non-natural amino acid, preferably a beta turn mimetic, a gamma-turn
CC mimetic, a beta sheet mimetic or a disulphide bridge mimetic. The method
CC is used for identification of a candidate receptor antagonist or agonist.
CC The present peptide is a cell receptor binding peptide, and can thus be
CC used as a starting point for identification of candidate drug compounds,
CC using the method of the invention
XX
SQ Sequence 16 AA;

Query Match 96.8%; Score 92; DB 2; Length 16;
Best Local Similarity 93.8%; Pred. No. 8.5e-06;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

Qy 1 NDECELCVNVACTGCL 16
||:|||||||||||||
Db 1 NDDCELCVNVACTGCL 16

RESULT 7
AAB92073
ID AAB92073 standard; peptide; 16 AA.
XX
AC AAB92073;
XX
DT 22-JUN-2001 (first entry)
XX
DE Guanylin and uroguanylin peptide SEQ ID NO:1249.
XX
KW Protection; endogenous therapeutic peptide; peptidase; conjugation;
KW blood component; modification; succinimidyl; maleimido group; amino;
KW hydroxyl; thiol; hormone; growth factor; neurotransmitter.
XX
OS Homo sapiens.
OS Synthetic.
XX
PN WO200069900-A2.
XX
PD 23-NOV-2000.
XX
PF 17-MAY-2000; 2000WO-US013576.
XX
PR 17-MAY-1999; 99US-0134406P.
PR 10-SEP-1999; 99US-0153406P.
PR 15-OCT-1999; 99US-0159783P.
XX
PA (CONJ-) CONJUCHEM INC.
XX
PI Bridon DP, Ezrin AM, Milner PG, Holmes DL, Thibaudeau K;
XX
DR WPI; 2001-112059/12.
XX
PT Modifying and attaching therapeutic peptides to albumin prevents
PT peptidase degradation, useful for increasing length of in vivo activity.
XX
PS Disclosure; Page 603; 733pp; English.
XX
CC The present invention describes a modified therapeutic peptide (I)
CC comprising a therapeutically active amino acid region (III) and a
CC reactive group (II) (e.g. succinimidyl and maleimido groups) attached to
CC a less therapeutically active amino acid region (IV), which covalently
CC bonds with amino/hydroxyl/thiol groups on blood components to form a
CC peptidase stabilised therapeutic peptide composed of 3-50 amino acids.
CC (I) are useful for modifying therapeutic peptides e.g. hormones, growth
CC factors and neurotransmitters, to protect them from peptidase activity in
CC vivo for the treatment of various disorders. Endogenous therapeutic
CC peptides are not suitable as drug candidates as they require frequent
CC administration due to rapid degradation by peptidases in the body.
CC Modifying and attaching therapeutic peptides to albumin prevents or
CC reduces the action of peptidases to increase length of activity (half
CC life) and specificity as bonding to large molecules decreases
CC intracellular uptake and interference with physiological processes.
CC AAB90829 to AAB92441 represent peptides which can be used in the
CC exemplification of the present invention
XX
SQ Sequence 16 AA;

Query Match 96.8%; Score 92; DB 4; Length 16;
Best Local Similarity 93.8%; Pred. No. 8.5e-06;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

Qy 1 NDECELCVNVACTGCL 16
||:|||||||||||||
Db 1 NDDCELCVNVACTGCL 16

RESULT 8
AAB83214
ID AAB83214 standard; peptide; 16 AA.
XX
AC AAB83214;
XX
DT 06-JUL-2001 (first entry)
XX
DE Human uroguanylin.
XX
KW Intestinal polyp; human; colon cancer; intestinal cancer; uroguanylin;
KW apoptosis; chromosome 9p34-35.
XX
OS Homo sapiens.
XX
PN WO200125266-A1.
XX
PD 12-APR-2001.
XX
PF 04-OCT-2000; 2000WO-US021998.
XX
PR 06-OCT-1999; 99US-0157950P.
XX
PA (PHAA) PHARMACIA CORP.
XX
PI Shailubhai K, Currie MG;
XX
DR WPI; 2001-328323/34.
XX
PT Modulating or preventing formation of polyps in the intestine, or
PT treating cancer of the intestine comprises administering human
PT uroguanylin polypeptide.
XX
PS Example 3; Fig 7; 55pp; English.
XX
CC The present invention describes a method of modulating polyps in the
CC intestine, involving administering to the individual a composition
CC comprising the peptide shown in AAB83213 and a carrier. Peptides such as
CC uroguanylin, shown here, (the gene for which is found on chromosome 1p34-
CC 35, an area close to where the APC gene is found) are capable of binding
CC to a guanylate cyclase known as GC-C. This causes the induction of
CC apoptosis, and prevents polyp formation. As polyps can become cancerous,
CC it is also useful in the prevention and treatment of intestinal and colon
CC cancers

XX
SQ Sequence 16 AA;

Query Match 96.8%; Score 92; DB 4; Length 16;
Best Local Similarity 93.8%; Pred. No. 8.5e-06;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

Qy 1 NDECELCVNVACTGCL 16
||:||||||||||||||
Db 1 NDDCELCVNVACTGCL 16

RESULT 9
AAO16182
ID AAO16182 standard; peptide; 16 AA.
XX
AC AAO16182;
XX
DT 28-MAR-2003 (first entry)
XX
DE Human uroguanylin bicyclo peptide, SEQ ID No 1.
XX
KW Human; guanylate cyclase receptor agonist; apoptosis induction; cancer;
KW polyps; inflammation; asthma; nephritis; hepatitis; uroguanylin bicyclo;
KW bronchitis; cystic fibrosis; inflammatory bowel disease; pancreatitis;
KW ulcerative colitis; Crohn's disease; Kaposi's sarcoma.
XX
OS Homo sapiens.
XX
FH Key Location/Qualifiers
FT Disulfide-bond 4. .12
FT Disulfide-bond 7. .15
XX
PN WO200278683-A1.
XX
PD 10-OCT-2002.
XX
PF 28-MAR-2002; 2002WO-US009551.
XX
PR 29-MAR-2001; 2001US-0279437P.
PR 29-MAR-2001; 2001US-0279438P.
PR 27-JUN-2001; 2001US-0300850P.
PR 10-JUL-2001; 2001US-0303806P.
PR 25-JUL-2001; 2001US-0307358P.
PR 17-JAN-2002; 2002US-0348646P.
XX
PA (SYNE-) SYNERGY PHARM INC.
XX
PI Shailubhai K, Nikiforovich G, Jacob GS;
XX
DR WPI; 2003-148251/14.
XX
PT Novel guanylate cyclase receptor agonist peptide useful for preventing or
PT treating primary or metastatic cancer and polyps in a patient, and for
PT inducing apoptosis in the cells of a subject.
XX
PS Example; Page 10; 47pp; English.
XX
CC The invention comprises guanylate cyclase receptor agonist peptides that
CC are useful for inducing apoptosis in the cells of a subject. The peptides
CC of the invention may be used to treat: cancer; polyps; inflammation;
CC asthma; nephritis; hepatitis; pancreatitis; bronchitis; cystic fibrosis;
CC inflammatory bowel disease; ulcerative colitis; Crohn's disease; and
CC Kaposi's sarcoma. The present amino acid sequence represents a human
CC uroguanylin bicyclo peptide which was used in an example of the invention
XX
SQ Sequence 16 AA;

Query Match 96.8%; Score 92; DB 6; Length 16;
Best Local Similarity 93.8%; Pred. No. 8.5e-06;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

Qy 1 NDECELCVNVACTGCL 16
||:||||||||||||||
Db 1 NDDCELCVNVACTGCL 16

RESULT 10
ABG74820
ID ABG74820 standard; peptide; 16 AA.
XX
AC ABG74820;
XX
DT 12-JUN-2003 (first entry)
XX
DE Human uroguanylin derived peptide SEQ ID 2.
XX
KW Apical membrane; mucosal epithelial cell; respiratory tract;
KW guanylate cyclase C; G protein-coupled receptor; guanosine triphophate;
KW cyclic guanosine monophosphate; cGMP; chloride ion secretion; inhalation;
KW membrane-associated type II protein kinase; mucus fluidisation;
KW cystic fibrosis transmembrane conductance regulator; breathing disorder;
KW mucus secretion; antiasthmatic; antiinflammatory; bronchial asthma;
KW chronic bronchitis; cystic fibrosis; uroguanylin; human.
XX
OS Homo sapiens.
XX
PN WO200298912-A2.
XX
PD 12-DEC-2002.
XX
PF 05-JUN-2002; 2002WO-DE002040.
XX
PR 05-JUN-2001; 2001DE-01027119.
XX
PA (CETI/) CETIN Y.
PA (SAVA/) SAVAS Y.
XX
PI Cetin Y, Savas Y;
XX
DR WPI; 2003-156842/15.
XX
PT Composition useful for treating respiratory disease, comprises a peptide
PT that activates guanylate cyclase C, and is delivered to the apical
PT membrane through the respiratory tract.
XX
PS Claim 3; Page 3; 23pp; German.
XX
CC This invention describes a novel medicament in a formulation that is
CC delivered to the apical membrane of mucosal epithelial cells through the
CC respiratory tract. The medicament contains at least one peptide that
CC activates guanylate cyclase C (GCC). GCC is a G protein-coupled receptor
CC that catalyses conversion of guanosine triphophate to cyclic guanosine
CC monophosphate (cGMP) and is present on the apical (air) side of
CC respiratory epithelial cells but not on the basolateral (blood) side.
CC cGMP activates membrane-associated type II protein kinase which in turn
CC activates the regulatory domain of the cystic fibrosis transmembrane
CC conductance regulator, resulting in secretion of chloride ions and water
CC from the cells, causing fluidisation of the mucus. The products of the
CC invention are used to make an inhalation device containing the medicament
CC for diagnosing diseases that are accompanied by breathing disorders or
CC disorders of mucus secretion in the respiratory tract, by detecting at
CC least one GCC activator. The products of the invention have antiasthmatic
CC and antiinflammatory activity. The method is useful for diagnosing and
CC treating diseases accompanied by breathing disorders or disorders of
CC mucus secretion in the respiratory tract particularly bronchial asthma,
CC chronic bronchitis and cystic fibrosis. The product of the invention
CC improves fluidity and evacuation of bronchial mucus and acts locally
CC (since the medicament does not enter the bloodstream), so systemic side
CC effects are minimised. Only very small doses of the medicament are
CC required. This sequence represents a fragment of the human guanylate
CC cyclase C activator peptide, uroguanylin, described in the disclosure of
CC the invention
XX
SQ Sequence 16 AA;

```
  Query Match             96.8%;  Score 92;  DB 6;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 8.5e-06;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          1 NDDCELCVNVACTGCL 16


RESULT 11
ADN03414
ID   ADN03414 standard; peptide; 16 AA.
XX
AC   ADN03414;
XX
DT   17-JUN-2004  (first entry)
XX
DE   Exemplary peptide ligand for proteome analysis  #141.
XX
KW   Peptide ligand; proteome; capture compound; mass spectrometry;
KW   protein separation;
KW   matrix assisted laser desorption ionisation-time of flight; MALDI-TOF.
XX
OS   Unidentified.
XX
PN   US2003119021-A1.
XX
PD   26-JUN-2003.
XX
PF   16-JUL-2002; 2002US-00197954.
XX
PR   16-JUL-2001; 2001US-0306019P.
PR   21-AUG-2001; 2001US-0314123P.
PR   11-MAR-2002; 2002US-0363433P.
XX
PA   (KOST/) KOSTER H.
PA   (SIDD/) SIDDIQI S.
PA   (LITT/) LITTLE D P.
XX
PI   Koster H,  Siddiqi S,  Little DP;
XX
DR   WPI; 2004-059185/06.
XX
PT   Collection of capture compounds capable of binding to biomolecules to
PT   form complexes that are stable under mass spectrometry conditions, useful
PT   for analysis of biomolecules, especially proteins.
XX
PS   Disclosure; SEQ ID NO 141; 165pp; English.
XX
CC   The invention relates to a collection of capture compounds capable of
CC   binding to biomolecules to form complexes that are stable under mass
CC   spectrometry conditions. The formulae for the capture compounds comprises
CC   sets of compounds of formula (I)-(III) given in the specification. Also
CC   included are analysis of biomolecules (by contacting a composition
CC   comprising a biomolecule with the above collection and identifying or
CC   detecting bound biomolecules), separating protein conformers (by
CC   contacting a composition comprising a biomolecule with the above
CC   collection, separating the members of the collection and identifying
CC   bound proteins), reducing diversity of a complex mixture of biomolecules
CC   (by contacting the mixture with the above collection and separating each
CC   set of complexes of capture compounds with biomolecules from the other
CC   sets) and identifying phenotype-specific biomolecules (by sorting cells
CC   from a single subject into sets according to a phenotype, contacting
CC   mixtures of biomolecules from each set with the above collection and
CC   comparing the patterns of biomolecule binding from each set). The
CC   collection of capture compounds is useful for the analysis of
CC   biomolecules, especially proteins (e.g. analysis of a proteome), using
CC   mass spectrometry, especially matrix assisted laser desorption ionisation
CC   -time of flight (MALDI-TOF) mass spectrometry. The present sequence is an
CC   exemplary peptide ligand which may be incorporated into a capture
CC   compound of the invention.
XX
SQ   Sequence 16 AA;

  Query Match             96.8%;  Score 92;  DB 8;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 8.5e-06;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          1 NDDCELCVNVACTGCL 16


RESULT 12
ADR42249
ID   ADR42249 standard; peptide; 16 AA.
XX
AC   ADR42249;
XX
DT   21-OCT-2004  (first entry)
XX
DE   Uroguanylin related peptide ligand, SEQ ID 141.
XX
KW   Human; ligand; Uroguanylin.
XX
OS   Homo sapiens.
XX
PN   WO2004064972-A2.
XX
PD   05-AUG-2004.
XX
PF   16-JAN-2004; 2004WO-US001037.
XX
PR   16-JAN-2003; 2003US-0441398P.
XX
PA   (HKPH-) HK PHARM INC.
PA   (KOES/) KOESTER H.
XX
PI   Koester H,  Little DP,  Siddiqi SM,  Grealish MP,  Marappan S;
PI   Hassman CF,  Yip P;
XX
DR   WPI; 2004-642213/62.
XX
PT   Identifying drug non-target biomolecules in mixture of biomolecules
PT   involves interacting mixture of biomolecules with capture compounds
PT   having high binding affinity and analyzing captured biomolecules to
PT   identify drug non-targets.
XX
PS   Disclosure; SEQ ID NO 141; 368pp; English.
XX
CC   The present invention relates to a method for identifying drug non-target
CC   biomolecules in a mixture of biomolecules. The method comprises
CC   interacting mixture with capture compounds having moiety X which
CC   covalently binds to biomolecules with high affinity, moiety Y that
CC   increases selectivity of binding so that the capture compound binds to
CC   fewer biomolecules, and moiety Z for presenting X and Y, and analysing
CC   captured biomolecules to identify drug non-targets. The capture compound
CC   also optionally comprises a sorting function moiety Q and or a solubility
CC   function moiety W. The selectivity function moiety Y serves to modulate
CC   the reactivity function by reducing the number of groups to which the
CC   reactivity function moiety X bind, such as by steric hindrance and other
CC   interactions. Y is optionally a peptide ligand (ADR42112-ADR42256).
XX
SQ   Sequence 16 AA;

  Query Match             96.8%;  Score 92;  DB 8;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 8.5e-06;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          1 NDDCELCVNVACTGCL 16


RESULT 13
AAW18470
```

ID AAW18470 standard; peptide; 19 AA.
XX
AC AAW18470;
XX
DT 23-APR-1998 (first entry)
XX
DE Human GCAP-II (89-112) endoprotease Arg-C digested fragment 4.
XX
KW Guanyl cyclase C activating peptide II; GCAP-II; insulinotropic;
KW diabetes; endocrine disorder; diagnosis; treatment; human.
XX
OS Homo sapiens.
XX
PN DE19543628-A1.
XX
PD 28-MAY-1997.
XX
PF 24-NOV-1995; 95DE-01043628.
XX
PR 24-NOV-1995; 95DE-01043628.
XX
PA (FORS/) FORSSMANN W.
XX
PI Forssmann W, Kist A, Kruhoeffer M, Meyer M, Pardigol A, Heine G;
XX
DR WPI; 1997-290350/27.
XX
PT New guanyl cyclase C activating peptide fragments - have insulinotropic
PT activity, useful for treating diabetes, etc.
XX
PS Claim 3; Fig 3; 33pp; German.
XX
CC Peptides AAW18467-W18470 represent fragments of the guanyl cyclase C
CC activating peptide, GCAP-II, obtained by digestion with endoprotease Arg-
CC C. GCAP-II is involved in insulin secretion by pancreatic beta cells.
CC This peptide fragment could be used to which affects insulin secretion by
CC the beta cells treat pancreatic endocrine disorders, especially diabetes
CC mellitus type II, renal and intestinal disorders, disorders of the
CC gastrointestinal, respiratory and urogenital apparatus, disorders of the
CC cardiovascular and nervous systems, disorders of the integuments and
CC sense organs and diseases associated with GCAP II (89-112) deficiency.
CC This peptide can be used for treatment of electrolyte effects on bone
CC reconstruction (osteoporosis) or the dental apparatus. Antibodies to GCAP
CC -II (89-112) can be used to treat diseases associated with overproduction
CC of GCAP-II (89-112). Human GCAP-II (89-112) and GCAP I (99-15) cDNA are
CC useful for diagnosis and treatment of the above disorders e.g. gene
CC therapy for diabetes
XX
SQ Sequence 19 AA;

Query Match 96.8%; Score 92; DB 2; Length 19;
Best Local Similarity 93.8%; Pred. No. 1e-05;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

Qy 1 NDECELCVNVACTGCL 16
||:|||||||||||||
Db 4 NDDCELCVNVACTGCL 19

RESULT 14
AAW18483
ID AAW18483 standard; peptide; 19 AA.
XX
AC AAW18483;
XX
DT 22-APR-1998 (first entry)
XX
DE Human GCAP-II (89-112) trypsin digested fragment 6.
XX
KW Guanyl cyclase C activating peptide II; GCAP-II; insulinotropic;
KW diabetes; endocrine disorder; diagnosis; treatment; human.
XX
OS Homo sapiens.
XX
PN DE19543628-A1.
XX
PD 28-MAY-1997.
XX
PF 24-NOV-1995; 95DE-01043628.
XX
PR 24-NOV-1995; 95DE-01043628.
XX
PA (FORS/) FORSSMANN W.
XX
PI Forssmann W, Kist A, Kruhoeffer M, Meyer M, Pardigol A, Heine G;
XX
DR WPI; 1997-290350/27.
XX
PT New guanyl cyclase C activating peptide fragments - have insulinotropic
PT activity, useful for treating diabetes, etc.
XX
PS Claim 3; Fig 3; 33pp; German.
XX
CC Peptides AAW18478-W18483 represent fragments of the guanyl cyclase C
CC activating peptide, GCAP-II, obtained by digestion with trypsin. GCAP-II
CC is involved in insulin secretion by pancreatic beta cells. This peptide
CC fragment could be used to which affects insulin secretion by the beta
CC cells treat pancreatic endocrine disorders, especially diabetes mellitus
CC type II, renal and intestinal disorders, disorders of the respiratory,
CC gastrointestinal and urogenital apparatus, disorders of the
CC cardiovascular and nervous systems, disorders of the integuments and
CC sense organs and diseases associated with GCAP II (89-112) deficiency.
CC This peptide can be used for treatment of electrolyte effects on bone
CC reconstruction (osteoporosis) or the dental apparatus. Antibodies to GCAP
CC -II (89-112) can be used to treat diseases associated with overproduction
CC of GCAP-II (89-112). Human GCAP-II (89-112) and GCAP I (99-15) cDNA are
CC useful for diagnosis and treatment of the above disorders e.g. gene
CC therapy for diabetes
XX
SQ Sequence 19 AA;

Query Match 96.8%; Score 92; DB 2; Length 19;
Best Local Similarity 93.8%; Pred. No. 1e-05;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

Qy 1 NDECELCVNVACTGCL 16
||:|||||||||||||
Db 4 NDDCELCVNVACTGCL 19

RESULT 15
AAW23224
ID AAW23224 standard; peptide; 19 AA.
XX
AC AAW23224;
XX
DT 29-OCT-1997 (first entry)
XX
DE GCAP-II C-terminal fragment prepared by endoproteinase Arg-C.
XX
KW Human; guanylate cyclase; activating peptide; GCAP-II; cGMP;
KW transepithelial transport; treatment; kidney; intestinal; respiratory;
KW urogenital; circulatory; nervous system; disorder; disease; endocrine;
KW sensory; system; osteoporosis; dental; pancreas; diabetes; hypophysis;
KW gastrointestinal tract; diarrhoea; gene therapy; probe;
KW recombinant production; transgenic animal; antibody; immunoassay reagent.
XX
OS Homo sapiens.
XX
PN DE19528544-A1.
XX
PD 06-FEB-1997.
XX
PF 03-AUG-1995; 95DE-01028544.
XX
PR 03-AUG-1995; 95DE-01028544.

XX
PA (FORS/) FORSSMANN W.
XX
PI Forssmann W;
XX
DR WPI; 1997-110032/11.
XX
PT Guanylate cyclase activating peptide II - increases cGMP formation, and
PT controls transport of water and electrolytes across epithelial cells.
XX
PS Claim 3; Page 5; 15pp; German.
XX
CC The present sequence is a carboxy-terminal fragment of the human
CC guanylate cyclase activating peptide II (GCAP-II) precursor, prepared by
CC endoproteolytic cleavage with endoproteinase Arg-C. GCAP-II increases
CC cGMP formation, and is involved in the control of transepithelial water
CC and electrolyte transport. GCAP-II can be used to treat a variety of
CC kidney, intestinal, respiratory, urogenital, circulatory and nervous
CC system disorders, diseases of the endocrine and sensory systems (e.g.
CC osteoporosis, and dental disease), disorders of the pancreas (e.g.
CC diabetes, and hypophysis) or the endocrine gastrointestinal tract and for
CC the long term treatment of diarrhoea, without inducing an immune
CC response. The GCAP-II cDNA can be used to treat the same conditions,
CC clone the GCAP-II-encoding gene for use in gene therapy, as a
CC hybridisation probe and for the production of recombinant GCAP-II or
CC transgenic animal creation. Antibodies raised against GCAP-II are useful
CC as immunoassay reagents. GCAP-II, or a fragment, are administered at,
CC e.g. 100-1200 microg/day by intravenous or intramuscular injection or 300
CC -1200 microg/day subcutaneously. They may also be given orally,
CC intranasally or by inhalation, in typical unit doses of 0.3-30 mg. GCAP-
CC II was chemically synthesised, or isolated by chromatography from
CC transformed eukaryotic or prokaryotic cells, or human blood. When T84
CC cells were incubated with synthetic GCAP-II, generation of cGMP was
CC increased in a dose dependent manner. GCAP-II influences cGMP production
CC via a known receptor for heat stable enterotoxin. Other stomach,
CC intestinal, pancreatic and liver cells also responded to GCAP-II, e.g.
CC via changes in intracellular Ca2+ ion concentration
XX
SQ Sequence 19 AA;

Query Match 96.8%; Score 92; DB 2; Length 19;
Best Local Similarity 93.8%; Pred. No. 1e-05;
Matches 15; Conservative 1; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          4 NDDCELCVNVACTGCL 19
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Search completed: August 26, 2005, 19:00:52
Job time : 164 secs

GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: August 26, 2005, 18:53:51 ; Search time 168 Seconds
(without alignments)
48.769 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 1612378 seqs, 512079187 residues

Total number of hits satisfying chosen parameters: 1612378

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : UniProt_03:*
1: uniprot_sprot:*
2: uniprot_trembl:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	92	96.8	112	1	GUAU_HUMAN	Q16661 homo sapien
2	90	94.7	111	1	GUAU_CAVPO	P70107 cavia porce
3	84	88.4	106	1	GUAU_MOUSE	O09051 mus musculu
4	84	88.4	106	1	GUAU_RAT	P70668 rattus norv
5	84	88.4	106	2	Q9QUQ3	Q9quq3 mus musculu
6	84	88.4	107	2	Q8R5G8	Q8r5g8 notomys ale
7	82	86.3	113	1	GUAU_PIG	O13009 sus scrofa
8	77	81.1	109	1	GUAU_DIDMA	Q28358 didelphis m
9	73	76.8	108	2	Q98TI0	Q98ti0 anguilla an
10	73	76.8	108	2	Q7ZZS0	Q7zzs0 anguilla ja
11	73	76.8	116	2	Q98TH9	Q98th9 anguilla an
12	67	70.5	109	2	Q7ZZS2	Q7zzs2 anguilla ja
13	64	67.4	78	2	Q93G01	Q93g01 vibrio mimi
14	63	66.3	61	2	Q6VEG7	Q6veg7 escherichia
15	63	66.3	61	2	Q6VEG8	Q6veg8 escherichia
16	63	66.3	72	1	HST2_ECOLI	Q47185 escherichia
17	63	66.3	72	1	HST3_ECOLI	P07965 escherichia
18	62	65.3	110	2	Q7ZZS1	Q7zzs1 anguilla ja
19	60	63.2	17	2	Q9R581	Q9r581 vibrio chol
20	60	63.2	18	2	Q9R580	Q9r580 vibrio chol
21	60	63.2	19	2	Q9R579	Q9r579 vibrio chol
22	60	63.2	28	2	Q9R578	Q9r578 vibrio chol
23	60	63.2	78	1	HSTN_VIBCH	P04429 vibrio chol
24	60	63.2	78	1	HSTO_VIBCH	Q07425 vibrio chol
25	58	61.1	18	2	Q7M0U3	Q7m0u3 citrobacter
26	58	61.1	71	1	HSTB_YEREN	P74977 yersinia en
27	58	61.1	72	1	HST1_ECOLI	P01559 escherichia
28	56	58.9	72	1	HSTC_YEREN	O50319 yersinia en
29	56	58.9	115	1	GUAN_HUMAN	Q02747 homo sapien
30	56	58.9	115	1	GUAN_RAT	P28902 rattus norv
31	56	58.9	115	2	Q8R5G9	Q8r5g9 notomys ale
32	56	58.9	116	1	GUAN_MOUSE	P33680 mus musculu
33	55	57.9	66	1	HST_YERKR	P31518 yersinia kr
34	54	56.8	71	1	HSTA_YEREN	P07593 yersinia en
35	51	53.7	106	1	FSHB_STRCA	P80663 struthio ca
36	51	53.7	107	1	GUAN_CAVPO	P70664 cavia porce
37	51	53.7	109	1	GUAN_PIG	P79897 sus scrofa
38	51	53.7	131	2	Q8QGF8	Q8qgf8 gallus gall
39	50	52.6	15	1	GUAN_DIDMA	P55936 didelphis m
40	50	52.6	18	1	HSTB_ECOLI	P01560 escherichia
41	50	52.6	61	2	Q6VEG9	Q6veg9 escherichia
42	50	52.6	339	2	Q8NC41	Q8nc41 homo sapien
43	50	52.6	509	2	Q96SQ1	Q96sq1 homo sapien
44	50	52.6	510	2	Q6IE84	Q6ie84 mus musculu
45	50	52.6	702	2	Q96JL8	Q96jl8 homo sapien

ALIGNMENTS

RESULT 1
GUAU_HUMAN
ID GUAU_HUMAN STANDARD; PRT; 112 AA.
AC Q16661;
DT 01-NOV-1997 (Rel. 35, Created)
DT 01-NOV-1997 (Rel. 35, Last sequence update)
DT 25-OCT-2004 (Rel. 45, Last annotation update)
DE Uroguanylin precursor (UGN) (Guanylate cyclase activator 2B)
DE (Guanylate cyclase C activating peptide II) (GCAP-II).
GN Name=GUCA2B;
OS Homo sapiens (Human).
OC Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX NCBI_TaxID=9606;
RN [1]
RP SEQUENCE FROM N.A.
RC TISSUE=Colon;
RX MEDLINE=96193705; PubMed=8605041; DOI=10.1006/bbrc.1996.0287;
RA Miyazato M., Nakazato M., Yamaguchi H., Date Y., Kojima M.,
RA Kangawa K., Matsuo H., Matsukura S.;
RT "Cloning and characterization of a cDNA encoding a precursor for human
RT uroguanylin.";
RL Biochem. Biophys. Res. Commun. 219:644-648(1996).
RN [2]
RP SEQUENCE FROM N.A.
RC TISSUE=Colon;
RX MEDLINE=96106424; PubMed=8519795; DOI=10.1016/0167-4838(95)00204-4;
RA Hill O., Cetin Y., Cieslak A., Maegert H.-J., Forssmann W.-G.;
RT "A new human guanylate cyclase-activating peptide (GCAP-II,
RT uroguanylin): precursor cDNA and colonic expression.";
RL Biochim. Biophys. Acta 1253:146-149(1995).
RN [3]
RP SEQUENCE FROM N.A.
RC TISSUE=Placenta;
RA Maegert H.-J., Hill O., Forssmann W.-G.;
RL Submitted (AUG-1996) to the EMBL/GenBank/DDBJ databases.
RN [4]
RP SEQUENCE FROM N.A.
RX MEDLINE=97422613; PubMed=9268639; DOI=10.1006/geno.1997.4808;
RA Miyazato M., Nakazato M., Matsukura S., Kangawa K., Matsuo H.;
RT "Genomic structure and chromosomal localization of human
RT uroguanylin.";
RL Genomics 43:359-365(1997).
RN [5]
RP SEQUENCE OF 89-112, AND DISULFIDE BONDS.
RC TISSUE=Blood;
RX MEDLINE=96049550; PubMed=7589507; DOI=10.1016/0014-5793(95)01075-P;
RA Hess R., Kuhn M., Schulz-Knappe P., Raida M., Fuchs M., Klodt J.,
RA Adermann K., Kaever V., Cetin Y., Forssmann W.-G.;
RT "GCAP-II: isolation and characterization of the circulating form of
RT human uroguanylin.";
RL FEBS Lett. 374:34-38(1995).
RN [6]
RP SEQUENCE OF 97-112, AND DISULFIDE BONDS.

```
RX   MEDLINE=94189775; PubMed=8141334;
RA   Kita T., Smith C.E., Fok K.F., Duffin K.L., Moore W.M.,
RA   Karabatsos P.J., Kachur J.F., Hamra F.K., Pidhorodeckyj N.V.,
RA   Forte L.R., Currie M.G.;
RT   "Characterization of human uroguanylin: a member of the guanylin
RT   peptide family.";
RL   Am. J. Physiol. 266:F342-F348(1994).
RN   [7]
RP   STRUCTURE BY NMR OF 97-112.
RX   MEDLINE=98445220; PubMed=9774236;
RA   Marx U.C., Klodt J., Meyer M., Gerlach H., Roesch P., Forssmann W.-G.,
RA   Adermann K.;
RT   "One peptide, two topologies: structure and interconversion dynamics
RT   of human uroguanylin isomers.";
RL   J. Pept. Res. 52:229-240(1998).
CC   -!- FUNCTION: Endogenous activator of intestinal guanylate cyclase. It
CC       stimulates this enzyme through the same receptor binding region as
CC       the heat-stable enterotoxins. May be a potent physiological
CC       regulator of intestinal fluid and electrolyte transport. May be an
CC       autocrine/paracrine regulator of intestinal salt and water
CC       transport.
CC   -!- SUBCELLULAR LOCATION: Secreted.
CC   -!- TISSUE SPECIFICITY: Stomach and intestine.
CC   -!- SIMILARITY: Belongs to the guanylin family.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
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CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; U34279; AAC50416.1; -.
DR   EMBL; Z50753; CAA90629.1; -.
DR   EMBL; Z70295; CAA94311.1; -.
DR   EMBL; U55058; AAC51729.1; -.
DR   PIR; JC4651; JC4651.
DR   PDB; 1UYA; NMR; @=97-112.
DR   PDB; 1UYB; NMR; @=97-112.
DR   Genew; HGNC:4683; GUCA2B.
DR   MIM; 601271; -.
DR   GO; GO:0008048; F:calcium sensitive guanylate cyclase activat. . .; TAS.
DR   GO; GO:0007588; P:excretion; TAS.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PIRSF; PIRSF001849; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
KW   3D-structure; Direct protein sequencing; Signal.
FT   SIGNAL        1     26       Potential.
FT   PROPEP       27     88
FT   PEPTIDE      89    112       GCAP-II.
FT   PEPTIDE      97    112       Uroguanylin.
FT   DISULFID     67     80       Potential.
FT   DISULFID    100    108
FT   DISULFID    103    111
FT   TURN        109    110
SQ   SEQUENCE   112 AA;  12069 MW;  AA3030BC3D4EE412 CRC64;

  Query Match             96.8%;  Score 92;  DB 1;  Length 112;
  Best Local Similarity   93.8%;  Pred. No. 4.6e-06;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db         97 NDDCELCVNVACTGCL 112


RESULT 2
GUAU_CAVPO
ID   GUAU_CAVPO     STANDARD;      PRT;   111 AA.
AC   P70107;
DT   01-NOV-1997 (Rel. 35, Created)
DT   01-NOV-1997 (Rel. 35, Last sequence update)
DT   25-OCT-2004 (Rel. 45, Last annotation update)
DE   Uroguanylin precursor (UGN) (Guanylate cyclase activator 2B).
GN   Name=GUCA2B;
OS   Cavia porcellus (Guinea pig).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Rodentia; Hystricognathi; Caviidae; Cavia.
OX   NCBI_TaxID=10141;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   TISSUE=Stomach;
RA   Kruhoeffer M., Meyer M.F., Schlatter E., Kaempf U., Cetin Y.,
RA   Forssmann W.-G.;
RL   Submitted (AUG-1996) to the EMBL/GenBank/DDBJ databases.
CC   -!- FUNCTION: Endogenous activator of intestinal guanylate cyclase. It
CC       stimulates this enzyme through the same receptor binding region as
CC       the heat-stable enterotoxins. May be a potent physiological
CC       regulator of intestinal fluid and electrolyte transport. May be an
CC       autocrine/paracrine regulator of intestinal salt and water
CC       transport.
CC   -!- SUBCELLULAR LOCATION: Secreted.
CC   -!- SIMILARITY: Belongs to the guanylin family.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
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CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; Z74738; CAA98994.1; -.
DR   HSSP; Q16661; 1UYA.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PIRSF; PIRSF001849; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
KW   Signal.
FT   SIGNAL        1     26       Potential.
FT   PROPEP       27     96
FT   PEPTIDE      97    111       Uroguanylin.
FT   DISULFID     67     80       Potential.
FT   DISULFID    100    108       By similarity.
FT   DISULFID    103    111       By similarity.
SQ   SEQUENCE   111 AA;  12125 MW;  7C3366A721FE0411 CRC64;

  Query Match             94.7%;  Score 90;  DB 1;  Length 111;
  Best Local Similarity   93.3%;  Pred. No. 9e-06;
  Matches   14;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGC 15
              |||||||||:|||||
Db         97 NDECELCVNIACTGC 111


RESULT 3
GUAU_MOUSE
ID   GUAU_MOUSE     STANDARD;      PRT;   106 AA.
AC   O09051;
DT   01-NOV-1997 (Rel. 35, Created)
DT   16-OCT-2001 (Rel. 40, Last sequence update)
DT   05-JUL-2004 (Rel. 44, Last annotation update)
DE   Uroguanylin precursor (UGN) (Guanylate cyclase activator 2B).
GN   Name=Guca2b;
OS   Mus musculus (Mouse).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
OX   NCBI_TaxID=10090;
RN   [1]
RP   SEQUENCE FROM N.A.
RX   MEDLINE=97434109; PubMed=9287995;
```

```
RA   Whitaker T.L., Witte D.P., Scott M.C., Cohen M.B.;
RT   "Uroguanylin and guanylin: distinct but overlapping patterns of
RT   messenger RNA expression in mouse intestine.";
RL   Gastroenterology 113:1000-1006(1997).
RN   [2]
RP   REVISION TO 17.
RA   Sanford L.P., Cohen M.B.;
RL   Submitted (FEB-2000) to the EMBL/GenBank/DDBJ databases.
CC   -!- FUNCTION: Endogenous activator of intestinal guanylate cyclase. It
CC       stimulates this enzyme through the same receptor binding region as
CC       the heat-stable enterotoxins. May be a potent physiological
CC       regulator of intestinal fluid and electrolyte transport. May be an
CC       autocrine/paracrine regulator of intestinal salt and water
CC       transport (By similarity).
CC   -!- SUBCELLULAR LOCATION: Secreted.
CC   -!- TISSUE SPECIFICITY: Localized predominantly in intestinal villi
CC       and the corticomedullary junction of the kidney.
CC   -!- SIMILARITY: Belongs to the guanylin family.
CC   ---------------------------------------------------------------------
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CC   ---------------------------------------------------------------------
DR   EMBL; U95182; AAB82750.2; -.
DR   EMBL; U90727; AAB53314.1; -.
DR   HSSP; Q16661; 1UYA.
DR   MGD; MGI:1270851; Guca2b.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
KW   Signal.
FT   SIGNAL        1     21       Potential.
FT   PROPEP       22     91
FT   PEPTIDE      92    106       Uroguanylin.
FT   DISULFID     62     75       Potential.
FT   DISULFID     95    103       By similarity.
FT   DISULFID     98    106       By similarity.
FT   CONFLICT     17     17       Q -> R (in Ref. 1; AAB53314).
SQ   SEQUENCE   106 AA;  11627 MW;  30FF1CCE9D293DA8 CRC64;

  Query Match             88.4%;  Score 84;  DB 1;  Length 106;
  Best Local Similarity   92.9%;  Pred. No. 6.6e-05;
  Matches   13;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGC 15
              ||||||:|||||||
Db         93 DECELCINVACTGC 106


RESULT 4
GUAU_RAT
ID   GUAU_RAT       STANDARD;      PRT;   106 AA.
AC   P70668;
DT   01-NOV-1997 (Rel. 35, Created)
DT   01-NOV-1997 (Rel. 35, Last sequence update)
DT   25-OCT-2004 (Rel. 45, Last annotation update)
DE   Uroguanylin precursor (UGN) (Guanylate cyclase activator 2B).
GN   Name=Guca2b;
OS   Rattus norvegicus (Rat).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Rattus.
OX   NCBI_TaxID=10116;
RN   [1]
RP   SEQUENCE FROM N.A., AND SEQUENCE OF 92-106.
RC   STRAIN=Sprague-Dawley;
RX   MEDLINE=97248740; PubMed=9094754; DOI=10.1016/S0167-0115(96)02103-9;
RA   Li Z., Perkins A.G., Peters M.F., Campa M.J., Goy M.F.;
RT   "Purification, cDNA sequence, and tissue distribution of rat
RT   uroguanylin.";
RL   Regul. Pept. 68:45-56(1997).
RN   [2]
RP   SEQUENCE FROM N.A.
RX   MEDLINE=97131589; PubMed=8977100; DOI=10.1016/S0014-5793(96)01235-5;
RA   Miyazato M., Nakazato M., Matsukura S., Kangawa K., Matsuo H.;
RT   "Uroguanylin gene expression in the alimentary tract and extra-
RT   gastrointestinal tissues.";
RL   FEBS Lett. 398:170-174(1996).
RN   [3]
RP   SEQUENCE FROM N.A.
RC   STRAIN=Sprague-Dawley; TISSUE=Small intestine;
RX   MEDLINE=97319300; PubMed=9176203;
RA   Blanchard R.K., Cousins R.J.;
RT   "Upregulation of rat intestinal uroguanylin mRNA by dietary zinc
RT   restriction.";
RL   Am. J. Physiol. 272:G972-G978(1997).
CC   -!- FUNCTION: Endogenous activator of intestinal guanylate cyclase. It
CC       stimulates this enzyme through the same receptor binding region as
CC       the heat-stable enterotoxins. May be a potent physiological
CC       regulator of intestinal fluid and electrolyte transport. May be an
CC       autocrine/paracrine regulator of intestinal salt and water
CC       transport.
CC   -!- SUBCELLULAR LOCATION: Secreted.
CC   -!- TISSUE SPECIFICITY: Expressed not only in the gastrointestinal
CC       tract but also in the lung, pancreas and kidney.
CC   -!- SIMILARITY: Belongs to the guanylin family.
CC   ---------------------------------------------------------------------
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CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; U73898; AAB18331.1; -.
DR   EMBL; U41322; AAB18760.1; -.
DR   EMBL; U75186; AAB61209.1; -.
DR   HSSP; Q16661; 1UYA.
DR   RGD; 620044; Guca2b.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PIRSF; PIRSF001849; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
KW   Direct protein sequencing; Signal.
FT   SIGNAL        1     21       Potential.
FT   PROPEP       22     91
FT   PEPTIDE      92    106       Uroguanylin.
FT   DISULFID     62     75       Potential.
FT   DISULFID     95    103       By similarity.
FT   DISULFID     98    106       By similarity.
SQ   SEQUENCE   106 AA;  11573 MW;  9FB5F88A9B1DD077 CRC64;

  Query Match             88.4%;  Score 84;  DB 1;  Length 106;
  Best Local Similarity   92.9%;  Pred. No. 6.6e-05;
  Matches   13;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGC 15
              ||||||:|||||||
Db         93 DECELCINVACTGC 106


RESULT 5
Q9QUQ3
ID   Q9QUQ3       PRELIMINARY;      PRT;   106 AA.
AC   Q9QUQ3;
DT   01-MAY-2000 (TrEMBLrel. 13, Created)
DT   01-MAY-2000 (TrEMBLrel. 13, Last sequence update)
DT   25-OCT-2004 (TrEMBLrel. 28, Last annotation update)
DE   Uroguanylin (Guca2b protein) (Mus musculus adult male kidney cDNA,
DE   RIKEN full-length enriched library, clone:0610009B03 product:guanylate
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DE   cyclase activator 2b (retina), full insert sequence).
GN   Name=Guca2b;
OS   Mus musculus (Mouse).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Mus.
OX   NCBI_TaxID=10090;
RN   [1]
RP   SEQUENCE FROM N.A.
RA   Miyazato M.;
RL   Submitted (JUN-1997) to the EMBL/GenBank/DDBJ databases.
RN   [2]
RP   SEQUENCE FROM N.A.
RC   STRAIN=FVB/N; TISSUE=Kidney;
RX   MEDLINE=22388257; PubMed=12477932; DOI=10.1073/pnas.242603899;
RA   Strausberg R.L., Feingold E.A., Grouse L.H., Derge J.G.,
RA   Klausner R.D., Collins F.S., Wagner L., Shenmen C.M., Schuler G.D.,
RA   Altschul S.F., Zeeberg B., Buetow K.H., Schaefer C.F., Bhat N.K.,
RA   Hopkins R.F., Jordan H., Moore T., Max S.I., Wang J., Hsieh F.,
RA   Diatchenko L., Marusina K., Farmer A.A., Rubin G.M., Hong L.,
RA   Stapleton M., Soares M.B., Bonaldo M.F., Casavant T.L., Scheetz T.E.,
RA   Brownstein M.J., Usdin T.B., Toshiyuki S., Carninci P., Prange C.,
RA   Raha S.S., Loquellano N.A., Peters G.J., Abramson R.D., Mullahy S.J.,
RA   Bosak S.A., McEwan P.J., McKernan K.J., Malek J.A., Gunaratne P.H.,
RA   Richards S., Worley K.C., Hale S., Garcia A.M., Gay L.J., Hulyk S.W.,
RA   Villalon D.K., Muzny D.M., Sodergren E.J., Lu X., Gibbs R.A.,
RA   Fahey J., Helton E., Ketteman M., Madan A., Rodrigues S., Sanchez A.,
RA   Whiting M., Madan A., Young A.C., Shevchenko Y., Bouffard G.G.,
RA   Blakesley R.W., Touchman J.W., Green E.D., Dickson M.C.,
RA   Rodriguez A.C., Grimwood J., Schmutz J., Myers R.M., Butterfield Y.S.,
RA   Krzywinski M.I., Skalska U., Smailus D.E., Schnerch A., Schein J.E.,
RA   Jones S.J., Marra M.A.;
RT   "Generation and initial analysis of more than 15,000 full-length human
RT   and mouse cDNA sequences.";
RL   Proc. Natl. Acad. Sci. U.S.A. 99:16899-16903(2002).
RN   [3]
RP   SEQUENCE FROM N.A.
RC   STRAIN=FVB/N; TISSUE=Kidney;
RA   Strausberg R.;
RL   Submitted (MAR-2002) to the EMBL/GenBank/DDBJ databases.
RN   [4]
RP   SEQUENCE FROM N.A.
RA   Miyazato M.;
RL   Submitted (AUG-1996) to the EMBL/GenBank/DDBJ databases.
RN   [5]
RP   SEQUENCE FROM N.A.
RC   STRAIN=C57BL/6J; TISSUE=Kidney;
RX   MEDLINE=99279253; PubMed=10349636; DOI=10.1016/S0076-6879(99)03004-9;
RA   Carninci P., Hayashizaki Y.;
RT   "High-efficiency full-length cDNA cloning.";
RL   Meth. Enzymol. 303:19-44(1999).
RN   [6]
RP   SEQUENCE FROM N.A.
RC   STRAIN=C57BL/6J; TISSUE=Kidney;
RX   MEDLINE=21085660; PubMed=11217851; DOI=10.1038/35055500;
RA   RIKEN FANTOM Consortium;
RT   "Functional annotation of a full-length mouse cDNA collection.";
RL   Nature 409:685-690(2001).
RN   [7]
RP   SEQUENCE FROM N.A.
RC   STRAIN=C57BL/6J; TISSUE=Kidney;
RA   The FANTOM Consortium,
RA   the RIKEN Genome Exploration Research Group Phase I & II Team;
RT   "Analysis of the mouse transcriptome based on functional annotation of
RT   60,770 full-length cDNAs.";
RL   Nature 420:563-573(2002).
RN   [8]
RP   SEQUENCE FROM N.A.
RC   STRAIN=C57BL/6J; TISSUE=Kidney;
RX   MEDLINE=20499374; PubMed=11042159; DOI=10.1101/gr.145100;
RA   Carninci P., Shibata Y., Hayatsu N., Sugahara Y., Shibata K., Itoh M.,
RA   Konno H., Okazaki Y., Muramatsu M., Hayashizaki Y.;
RT   "Normalization and subtraction of cap-trapper-selected cDNAs to
RT   prepare full-length cDNA libraries for rapid discovery of new genes.";
RL   Genome Res. 10:1617-1630(2000).
RN   [9]
RP   SEQUENCE FROM N.A.
RC   STRAIN=C57BL/6J; TISSUE=Kidney;
RX   MEDLINE=20530913; PubMed=11076861; DOI=10.1101/gr.152600;
RA   Shibata K., Itoh M., Aizawa K., Nagaoka S., Sasaki N., Carninci P.,
RA   Konno H., Akiyama J., Nishi K., Kitsunai T., Tashiro H., Itoh M.,
RA   Sumi N., Ishii Y., Nakamura S., Hazama M., Nishine T., Harada A.,
RA   Yamamoto R., Matsumoto H., Sakaguchi S., Ikegami T., Kashiwagi K.,
RA   Fujiwake S., Inoue K., Togawa Y., Izawa M., Ohara E., Watahiki M.,
RA   Yoneda Y., Ishikawa T., Ozawa K., Tanaka T., Matsuura S., Kawai J.,
RA   Okazaki Y., Muramatsu M., Inoue Y., Kira A., Hayashizaki Y.;
RT   "RIKEN integrated sequence analysis (RISA) system-384-format
RT   sequencing pipeline with 384 multicapillary sequencer.";
RL   Genome Res. 10:1757-1771(2000).
RN   [10]
RP   SEQUENCE FROM N.A.
RC   STRAIN=C57BL/6J; TISSUE=Kidney;
RA   Adachi J., Aizawa K., Akahira S., Akimura T., Arai A., Aono H.,
RA   Arakawa T., Bono H., Carninci P., Fukuda S., Fukunishi Y., Furuno M.,
RA   Hanagaki T., Hara A., Hayatsu N., Hiramoto K., Hiraoka T., Hori F.,
RA   Imotani K., Ishii Y., Itoh M., Izawa M., Kasukawa T., Kato H.,
RA   Kawai J., Kojima Y., Konno H., Kouda M., Koya S., Kurihara C.,
RA   Matsuyama T., Miyazaki A., Nishi K., Nomura K., Numazaki R., Ohno M.,
RA   Okazaki Y., Okido T., Owa C., Saito H., Saito R., Sakai C., Sakai K.,
RA   Sano H., Sasaki D., Shibata K., Shibata Y., Shinagawa A., Shiraki T.,
RA   Sogabe Y., Suzuki H., Tagami M., Tagawa A., Takahashi F., Tanaka T.,
RA   Tejima Y., Toya T., Yamamura T., Yasunishi A., Yoshida K., Yoshino M.,
RA   Muramatsu M., Hayashizaki Y.;
RL   Submitted (JUL-2000) to the EMBL/GenBank/DDBJ databases.
DR   EMBL; AF006668; AAD09311.1; -.
DR   EMBL; BC024373; AAH24373.1; -.
DR   EMBL; U67800; AAD09215.1; -.
DR   EMBL; AK002364; BAB22042.1; -.
DR   HSSP; Q16661; 1UYA.
DR   MGD; MGI:1270851; Guca2b.
DR   GO; GO:0005615; C:extracellular space; TAS.
DR   GO; GO:0006182; P:cGMP biosynthesis; IMP.
DR   GO; GO:0007589; P:fluid secretion; IMP.
DR   GO; GO:0045776; P:negative regulation of blood pressure; IMP.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PIRSF; PIRSF001849; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
DR   SMART; SM00183; GUANYLIN; 1.
SQ   SEQUENCE   106 AA;  11627 MW;  30FF1CCE9D293DA8 CRC64;

  Query Match             88.4%;  Score 84;  DB 2;  Length 106;
  Best Local Similarity   92.9%;  Pred. No. 6.6e-05;
  Matches   13;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGC 15
              ||||||:|||||||
Db         93 DECELCINVACTGC 106


RESULT 6
Q8R5G8
ID   Q8R5G8      PRELIMINARY;      PRT;   107 AA.
AC   Q8R5G8;
DT   01-JUN-2002 (TrEMBLrel. 21, Created)
DT   01-JUN-2002 (TrEMBLrel. 21, Last sequence update)
DT   01-JUN-2003 (TrEMBLrel. 24, Last annotation update)
DE   Uroguanylin.
OS   Notomys alexis (Spinifex hopping mouse).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Rodentia; Sciurognathi; Muridae; Murinae; Notomys.
OX   NCBI_TaxID=184396;
RN   [1]
RP   SEQUENCE FROM N.A.
RA   Donald J.A., Bartolo R.C.;
RL   Submitted (JAN-2002) to the EMBL/GenBank/DDBJ databases.
DR   EMBL; AF469496; AAL77417.1; -.
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DR   HSSP; Q16661; 1UYA.
DR   GO; GO:0008047; F:enzyme activator activity; IEA.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PIRSF; PIRSF001849; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
SQ   SEQUENCE   107 AA;  11618 MW;  735110CACE60DA97 CRC64;

  Query Match             88.4%;  Score 84;  DB 2;  Length 107;
  Best Local Similarity   92.9%;  Pred. No. 6.7e-05;
  Matches   13;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGC 15
              ||||||:|||||||
Db         94 DECELCINVACTGC 107


RESULT 7
GUAU_PIG
ID   GUAU_PIG       STANDARD;      PRT;   113 AA.
AC   O13009;
DT   15-JUL-1999 (Rel. 38, Created)
DT   15-JUL-1999 (Rel. 38, Last sequence update)
DT   25-OCT-2004 (Rel. 45, Last annotation update)
DE   Uroguanylin precursor (UGN) (Guanylate cyclase activator 2B)
DE   (Guanylate cyclase C activating peptide II) (GCAP-II).
GN   Name=GUCA2B;
OS   Sus scrofa (Pig).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Cetartiodactyla; Suina; Suidae; Sus.
OX   NCBI_TaxID=9823;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   TISSUE=Jejunum;
RA   Hill O., Maegert H.J., Forssmann W.-G.;
RL   Submitted (MAY-1997) to the EMBL/GenBank/DDBJ databases.
CC   -!- FUNCTION: Endogenous activator of intestinal guanylate cyclase. It
CC       stimulates this enzyme through the same receptor binding region as
CC       the heat-stable enterotoxins. May be a potent physiological
CC       regulator of intestinal fluid and electrolyte transport. May be an
CC       autocrine/paracrine regulator of intestinal salt and water
CC       transport (By similarity).
CC   -!- SUBCELLULAR LOCATION: Secreted (By similarity).
CC   -!- SIMILARITY: Belongs to the guanylin family.
CC   ---------------------------------------------------------------------
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CC   ---------------------------------------------------------------------
DR   EMBL; Z83746; CAB06042.1; -.
DR   HSSP; Q16661; 1UYA.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PIRSF; PIRSF001849; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
KW   Signal.
FT   SIGNAL        1     27       Potential.
FT   PROPEP       28     89
FT   PEPTIDE      90    113       GCAP-II.
FT   PEPTIDE      98    113       Uroguanylin.
FT   DISULFID     68     81       By similarity.
FT   DISULFID    101    109       By similarity.
FT   DISULFID    104    112       By similarity.
SQ   SEQUENCE   113 AA;  12044 MW;  8160573287BAB642 CRC64;

  Query Match             86.3%;  Score 82;  DB 1;  Length 113;
  Best Local Similarity   92.9%;  Pred. No. 0.00014;
  Matches   13;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGC 15
              |:|||||||||||
Db         99 DDCELCVNVACTGC 112


RESULT 8
GUAU_DIDMA
ID   GUAU_DIDMA     STANDARD;      PRT;   109 AA.
AC   Q28358;
DT   01-NOV-1997 (Rel. 35, Created)
DT   01-NOV-1997 (Rel. 35, Last sequence update)
DT   25-OCT-2004 (Rel. 45, Last annotation update)
DE   Uroguanylin precursor (UGN) (Guanylate cyclase activator 2B).
GN   Name=GUCA2B;
OS   Didelphis marsupialis virginiana (North American opossum).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Metatheria; Didelphimorphia; Didelphidae; Didelphis.
OX   NCBI_TaxID=9267;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   TISSUE=Colon;
RX   MEDLINE=96193673; PubMed=8605009; DOI=10.1006/bbrc.1996.0255;
RA   Fan X., Hamra F.K., Freeman R.H., Eber S.L., Krause W.J., Lim R.W.,
RA   Pace V.M., Currie M.G., Forte L.R.;
RT   "Uroguanylin: cloning of preprouroguanylin cDNA, mRNA expression in
RT   the intestine and heart and isolation of uroguanylin and
RT   prouroguanylin from plasma.";
RL   Biochem. Biophys. Res. Commun. 219:457-462(1996).
RN   [2]
RP   SEQUENCE OF 95-109.
RC   TISSUE=Urine;
RX   MEDLINE=94068421; PubMed=7902563;
RA   Hamra F.K., Forte L.R., Eber S.L., Pidhorodeckyj N.V., Krause W.J.,
RA   Freeman R.H., Chin D.T., Tompkins J.A., Fok K.F., Smith C.E.,
RA   Duffin K.L., Siegel N.R., Currie M.G.;
RT   "Uroguanylin: structure and activity of a second endogenous peptide
RT   that stimulates intestinal guanylate cyclase.";
RL   Proc. Natl. Acad. Sci. U.S.A. 90:10464-10468(1993).
CC   -!- FUNCTION: Endogenous activator of intestinal guanylate cyclase. It
CC       stimulates this enzyme through the same receptor binding region as
CC       the heat-stable enterotoxins. May be a potent physiological
CC       regulator of intestinal fluid and electrolyte transport. May be an
CC       autocrine/paracrine regulator of intestinal salt and water
CC       transport.
CC   -!- SUBCELLULAR LOCATION: Secreted.
CC   -!- TISSUE SPECIFICITY: Small and large intestine and atria and
CC       ventricles of heart. Both uroguanylin and prouroguanylin are found
CC       in plasma.
CC   -!- SIMILARITY: Belongs to the guanylin family.
CC   ---------------------------------------------------------------------
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CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; U49353; AAB00553.1; -.
DR   HSSP; Q16661; 1UYA.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PIRSF; PIRSF001849; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
KW   Direct protein sequencing; Signal.
FT   SIGNAL        1     23       Potential.
FT   PROPEP       24     94
FT   PEPTIDE      95    109       Uroguanylin.
FT   DISULFID     65     78       Potential.
FT   DISULFID     98    106       By similarity.
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FT   DISULFID    101    109       By similarity.
SQ   SEQUENCE   109 AA;  12040 MW;  AE948E210CA3AE7A CRC64;

  Query Match             81.1%;  Score 77;  DB 1;  Length 109;
  Best Local Similarity   78.6%;  Pred. No. 0.00074;
  Matches   11;  Conservative    3;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGC 15
              ::||||:|||||||
Db         96 EDCELCINVACTGC 109


RESULT 9
Q98TI0
ID   Q98TI0      PRELIMINARY;      PRT;   108 AA.
AC   Q98TI0;
DT   01-JUN-2001 (TrEMBLrel. 17, Created)
DT   01-JUN-2001 (TrEMBLrel. 17, Last sequence update)
DT   01-MAR-2004 (TrEMBLrel. 26, Last annotation update)
DE   Guanylin.
GN   Name=GUCA2I;
OS   Anguilla anguilla (European freshwater eel).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Actinopterygii; Neopterygii; Teleostei; Anguilliformes; Anguillidae;
OC   Anguilla.
OX   NCBI_TaxID=7936;
RN   [1]
RP   SEQUENCE FROM N.A.
RX   MEDLINE=21139737; PubMed=11243845; DOI=10.1006/bbrc.2001.4485;
RA   Comrie M.M., Cutler C.P., Cramb G.;
RT   "Cloning and Expression of Guanylin from the European eel (Anguilla
RT   anguilla).";
RL   Biochem. Biophys. Res. Commun. 281:1078-1085(2001).
RN   [2]
RP   SEQUENCE FROM N.A.
RA   Comrie M.M.;
RL   Thesis (2000), Department of School of Biology, University of St
RL   Andrews, St Andrews, United Kingdom.
DR   EMBL; AJ301672; CAC35448.1; -.
DR   HSSP; Q02747; 1O8R.
DR   GO; GO:0008047; F:enzyme activator activity; IEA.
DR   InterPro; IPR006058; 2Fe2S_fd_BS.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PIRSF; PIRSF001849; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
DR   PROSITE; PS00197; 2FE2S_FERREDOXIN; UNKNOWN_1.
SQ   SEQUENCE   108 AA;  11584 MW;  8A3B6D490E7C858D CRC64;

  Query Match             76.8%;  Score 73;  DB 2;  Length 108;
  Best Local Similarity   73.3%;  Pred. No. 0.0029;
  Matches   11;  Conservative    1;  Mismatches    3;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGCL 16
              | ||:| | ||||||
Db         94 DPCEICANAACTGCL 108


RESULT 10
Q7ZZS0
ID   Q7ZZS0      PRELIMINARY;      PRT;   108 AA.
AC   Q7ZZS0;
DT   01-JUN-2003 (TrEMBLrel. 24, Created)
DT   01-JUN-2003 (TrEMBLrel. 24, Last sequence update)
DT   01-MAR-2004 (TrEMBLrel. 26, Last annotation update)
DE   Preprouroguanylin.
GN   Name=uroguanylin;
OS   Anguilla japonica (Japanese eel).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Actinopterygii; Neopterygii; Teleostei; Anguilliformes; Anguillidae;
OC   Anguilla.
OX   NCBI_TaxID=7937;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   TISSUE=Intestine;
RX   MEDLINE=22692502; PubMed=12684514; DOI=10.1074/jbc.M303111200;
RA   Yuge S., Inoue K., Hyodo S., Takei Y.;
RT   "A novel guanylin family (guanylin, uroguanylin, and renoguanylin) in
RT   eels: possible osmoregulatory hormones in intestine and kidney.";
RL   J. Biol. Chem. 278:22726-22733(2003).
DR   EMBL; AB080642; BAC76011.1; -.
DR   HSSP; Q02747; 1O8R.
DR   GO; GO:0008047; F:enzyme activator activity; IEA.
DR   InterPro; IPR006058; 2Fe2S_fd_BS.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PIRSF; PIRSF001849; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
DR   PROSITE; PS00197; 2FE2S_FERREDOXIN; UNKNOWN_1.
SQ   SEQUENCE   108 AA;  11584 MW;  8A3B6D490E7C858D CRC64;

  Query Match             76.8%;  Score 73;  DB 2;  Length 108;
  Best Local Similarity   73.3%;  Pred. No. 0.0029;
  Matches   11;  Conservative    1;  Mismatches    3;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGCL 16
              | ||:| | ||||||
Db         94 DPCEICANAACTGCL 108


RESULT 11
Q98TH9
ID   Q98TH9      PRELIMINARY;      PRT;   116 AA.
AC   Q98TH9;
DT   01-JUN-2001 (TrEMBLrel. 17, Created)
DT   01-JUN-2001 (TrEMBLrel. 17, Last sequence update)
DT   01-MAR-2004 (TrEMBLrel. 26, Last annotation update)
DE   Guanylin.
GN   Name=GUCA2II;
OS   Anguilla anguilla (European freshwater eel).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Actinopterygii; Neopterygii; Teleostei; Anguilliformes; Anguillidae;
OC   Anguilla.
OX   NCBI_TaxID=7936;
RN   [1]
RP   SEQUENCE FROM N.A.
RX   MEDLINE=21139737; PubMed=11243845; DOI=10.1006/bbrc.2001.4485;
RA   Comrie M.M., Cutler C.P., Cramb G.;
RT   "Cloning and Expression of Guanylin from the European eel (Anguilla
RT   anguilla).";
RL   Biochem. Biophys. Res. Commun. 281:1078-1085(2001).
RN   [2]
RP   SEQUENCE FROM N.A.
RA   Comrie M.M.;
RL   Thesis (2000), Department of School of Biology, University of St
RL   Andrews, St Andrews, United Kingdom.
DR   EMBL; AJ301673; CAC35449.1; -.
DR   PIR; JC7620; JC7620.
DR   HSSP; Q02747; 1O8R.
DR   GO; GO:0008047; F:enzyme activator activity; IEA.
DR   InterPro; IPR006058; 2Fe2S_fd_BS.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PIRSF; PIRSF001849; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
DR   PROSITE; PS00197; 2FE2S_FERREDOXIN; UNKNOWN_1.
SQ   SEQUENCE   116 AA;  12547 MW;  38B3DAF0AC0B39E0 CRC64;

  Query Match             76.8%;  Score 73;  DB 2;  Length 116;
  Best Local Similarity   73.3%;  Pred. No. 0.0031;
  Matches   11;  Conservative    1;  Mismatches    3;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGCL 16
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Db        102 DPCEICANAACTGCL 116
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RESULT 12
Q7ZZS2
ID   Q7ZZS2      PRELIMINARY;      PRT;   109 AA.
AC   Q7ZZS2;
DT   01-JUN-2003 (TrEMBLrel. 24, Created)
DT   01-JUN-2003 (TrEMBLrel. 24, Last sequence update)
DT   01-MAR-2004 (TrEMBLrel. 26, Last annotation update)
DE   Preproguanylin.
GN   Name=guanylin;
OS   Anguilla japonica (Japanese eel).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Actinopterygii; Neopterygii; Teleostei; Anguilliformes; Anguillidae;
OC   Anguilla.
OX   NCBI_TaxID=7937;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   TISSUE=Intestine;
RX   MEDLINE=22692502; PubMed=12684514; DOI=10.1074/jbc.M303111200;
RA   Yuge S., Inoue K., Hyodo S., Takei Y.;
RT   "A novel guanylin family (guanylin, uroguanylin, and renoguanylin) in
RT   eels: possible osmoregulatory hormones in intestine and kidney.";
RL   J. Biol. Chem. 278:22726-22733(2003).
DR   EMBL; AB080640; BAC76009.1; -.
DR   HSSP; Q02747; 1O8R.
DR   GO; GO:0008047; F:enzyme activator activity; IEA.
DR   InterPro; IPR006058; 2Fe2S_fd_BS.
DR   InterPro; IPR000879; Guanylin.
DR   Pfam; PF02058; Guanylin; 1.
DR   PRINTS; PR00774; GUANYLIN.
DR   ProDom; PD005588; Guanylin; 1.
DR   PROSITE; PS00197; 2FE2S_FERREDOXIN; UNKNOWN_1.
SQ   SEQUENCE   109 AA;  11773 MW;  A25C40D085A556C7 CRC64;

  Query Match            70.5%;  Score 67;  DB 2;  Length 109;
  Best Local Similarity  71.4%;  Pred. No. 0.022;
  Matches   10;  Conservative    2;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGC 15
              ||||:|:  |||||
Db         96 DECEICMFAACTGC 109
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RESULT 13
Q93G01
ID   Q93G01      PRELIMINARY;      PRT;    78 AA.
AC   Q93G01;
DT   01-DEC-2001 (TrEMBLrel. 19, Created)
DT   01-DEC-2001 (TrEMBLrel. 19, Last sequence update)
DT   01-JUN-2003 (TrEMBLrel. 24, Last annotation update)
DE   Heat-stable enterotoxin.
OS   Vibrio mimicus.
OC   Bacteria; Proteobacteria; Gammaproteobacteria; Vibrionales;
OC   Vibrionaceae; Vibrio.
OX   NCBI_TaxID=674;
RN   [1]
RP   SEQUENCE FROM N.A.
RA   Teixeira L.F., Vicente A.C.;
RL   Submitted (AUG-2000) to the EMBL/GenBank/DDBJ databases.
DR   EMBL; AF302048; AAL02159.1; -.
DR   GO; GO:0005576; C:extracellular; IEA.
DR   GO; GO:0009405; P:pathogenesis; IEA.
DR   InterPro; IPR001489; Enterotoxin_HS.
DR   Pfam; PF02048; Enterotoxin_HS; 1.
SQ   SEQUENCE   78 AA;  8820 MW;  21947FBBC0F6FD4B CRC64;

  Query Match            67.4%;  Score 64;  DB 2;  Length 78;
  Best Local Similarity  66.7%;  Pred. No. 0.046;
  Matches   10;  Conservative    1;  Mismatches    4;  Indels    0;  Gaps    0;
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Qy          2 DECELCVNVACTGCL 16
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Db         63 DRCEICCNPACFGCL 77
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RESULT 14
Q6VEG7
ID   Q6VEG7      PRELIMINARY;      PRT;    61 AA.
AC   Q6VEG7;
DT   05-JUL-2004 (TrEMBLrel. 27, Created)
DT   05-JUL-2004 (TrEMBLrel. 27, Last sequence update)
DT   05-JUL-2004 (TrEMBLrel. 27, Last annotation update)
DE   Heat-stable enterotoxin ST Ib (Fragment).
OS   Escherichia coli.
OC   Bacteria; Proteobacteria; Gammaproteobacteria; Enterobacteriales;
OC   Enterobacteriaceae; Escherichia.
OX   NCBI_TaxID=562;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   STRAIN=R544;
RX   PubMed=15364995;
RA   Reischl U., Youssef M.T., Wolf H., Hyytia-Trees E., Strockbine N.A.;
RT   "Real-time fluorescence PCR assays for detection and characterization
RT   of heat-labile I and heat-stable I enterotoxin genes from
RT   enterotoxigenic Escherichia coli.";
RL   J. Clin. Microbiol. 42:4092-4100(2004).
DR   EMBL; AY342059; AAQ92976.1; -.
DR   GO; GO:0005576; C:extracellular; IEA.
DR   GO; GO:0009405; P:pathogenesis; IEA.
DR   InterPro; IPR001489; Enterotoxin_HS.
DR   Pfam; PF02048; Enterotoxin_HS; 1.
DR   PROSITE; PS00273; ENTEROTOXIN_H_STABLE; 1.
FT   NON_TER       1      1
SQ   SEQUENCE   61 AA;  6556 MW;  89788D3FAB3DCA0A CRC64;

  Query Match            66.3%;  Score 63;  DB 2;  Length 61;
  Best Local Similarity  83.3%;  Pred. No. 0.051;
  Matches   10;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db         49 CELCCNPACTGC 60
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Q6VEG8
ID   Q6VEG8      PRELIMINARY;      PRT;    61 AA.
AC   Q6VEG8;
DT   05-JUL-2004 (TrEMBLrel. 27, Created)
DT   05-JUL-2004 (TrEMBLrel. 27, Last sequence update)
DT   05-JUL-2004 (TrEMBLrel. 27, Last annotation update)
DE   Heat-stable enterotoxin ST Ib (Fragment).
OS   Escherichia coli.
OC   Bacteria; Proteobacteria; Gammaproteobacteria; Enterobacteriales;
OC   Enterobacteriaceae; Escherichia.
OX   NCBI_TaxID=562;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   STRAIN=C4046;
RX   PubMed=15364995;
RA   Reischl U., Youssef M.T., Wolf H., Hyytia-Trees E., Strockbine N.A.;
RT   "Real-time fluorescence PCR assays for detection and characterization
RT   of heat-labile I and heat-stable I enterotoxin genes from
RT   enterotoxigenic Escherichia coli.";
RL   J. Clin. Microbiol. 42:4092-4100(2004).
DR   EMBL; AY342058; AAQ92975.1; -.
DR   GO; GO:0005576; C:extracellular; IEA.
DR   GO; GO:0009405; P:pathogenesis; IEA.
DR   InterPro; IPR001489; Enterotoxin_HS.
DR   Pfam; PF02048; Enterotoxin_HS; 1.
DR   PROSITE; PS00273; ENTEROTOXIN_H_STABLE; 1.
FT   NON_TER       1      1
SQ   SEQUENCE   61 AA;  6658 MW;  1D75955D7AF0DED2 CRC64;
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Query Match 66.3%; Score 63; DB 2; Length 61;
Best Local Similarity 83.3%; Pred. No. 0.051;
Matches 10; Conservative 0; Mismatches 2; Indels 0; Gaps 0;

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Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db         49 CELCCNPACTGC 60
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Search completed: August 26, 2005, 19:03:48
Job time : 170 secs

GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: August 26, 2005, 18:55:22 ; Search time 42 Seconds
(without alignments)
28.438 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 513545 seqs, 74649064 residues

Total number of hits satisfying chosen parameters: 513545

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : Issued_Patents_AA:*
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2: /cgn2_6/ptodata/1/iaa/5B_COMB.pep:*
3: /cgn2_6/ptodata/1/iaa/6A_COMB.pep:*
4: /cgn2_6/ptodata/1/iaa/6B_COMB.pep:*
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6: /cgn2_6/ptodata/1/iaa/backfiles1.pep:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	92	96.8	16	1	US-08-145-940-1	Sequence 1, Appli
2	92	96.8	16	2	US-08-583-447A-56	Sequence 56, Appl
3	86	90.5	15	1	US-08-145-940-2	Sequence 2, Appli
4	77	81.1	15	2	US-08-583-447A-55	Sequence 55, Appl
5	63	66.3	13	1	US-08-141-892A-32	Sequence 32, Appl
6	63	66.3	13	2	US-08-583-447A-32	Sequence 32, Appl
7	63	66.3	13	2	US-08-467-920-32	Sequence 32, Appl
8	63	66.3	13	3	US-08-635-930-32	Sequence 32, Appl
9	63	66.3	13	3	US-09-193-997-32	Sequence 32, Appl
10	63	66.3	13	3	US-09-138-237A-32	Sequence 32, Appl
11	63	66.3	14	1	US-08-141-892A-31	Sequence 31, Appl
12	63	66.3	14	1	US-08-141-892A-37	Sequence 37, Appl
13	63	66.3	14	2	US-08-583-447A-31	Sequence 31, Appl
14	63	66.3	14	2	US-08-583-447A-37	Sequence 37, Appl
15	63	66.3	14	2	US-08-467-920-31	Sequence 31, Appl
16	63	66.3	14	2	US-08-467-920-37	Sequence 37, Appl
17	63	66.3	14	3	US-08-635-930-31	Sequence 31, Appl
18	63	66.3	14	3	US-08-635-930-37	Sequence 37, Appl
19	63	66.3	14	3	US-09-193-997-31	Sequence 31, Appl
20	63	66.3	14	3	US-09-193-997-37	Sequence 37, Appl
21	63	66.3	14	3	US-09-138-237A-31	Sequence 31, Appl
22	63	66.3	14	3	US-09-138-237A-37	Sequence 37, Appl
23	63	66.3	15	1	US-08-141-892A-30	Sequence 30, Appl
24	63	66.3	15	1	US-08-141-892A-36	Sequence 36, Appl
25	63	66.3	15	2	US-08-583-447A-30	Sequence 30, Appl
26	63	66.3	15	2	US-08-583-447A-36	Sequence 36, Appl
27	63	66.3	15	2	US-08-467-920-30	Sequence 30, Appl
28	63	66.3	15	2	US-08-467-920-36	Sequence 36, Appl
29	63	66.3	15	3	US-08-635-930-30	Sequence 30, Appl
30	63	66.3	15	3	US-08-635-930-36	Sequence 36, Appl
31	63	66.3	15	3	US-09-193-997-30	Sequence 30, Appl
32	63	66.3	15	3	US-09-193-997-36	Sequence 36, Appl
33	63	66.3	15	3	US-09-138-237A-30	Sequence 30, Appl
34	63	66.3	15	3	US-09-138-237A-36	Sequence 36, Appl
35	63	66.3	16	1	US-08-141-892A-29	Sequence 29, Appl
36	63	66.3	16	1	US-08-141-892A-35	Sequence 35, Appl
37	63	66.3	16	2	US-08-583-447A-29	Sequence 29, Appl
38	63	66.3	16	2	US-08-583-447A-35	Sequence 35, Appl
39	63	66.3	16	2	US-08-467-920-29	Sequence 29, Appl
40	63	66.3	16	2	US-08-467-920-35	Sequence 35, Appl
41	63	66.3	16	3	US-08-635-930-29	Sequence 29, Appl
42	63	66.3	16	3	US-08-635-930-35	Sequence 35, Appl
43	63	66.3	16	3	US-09-193-997-29	Sequence 29, Appl
44	63	66.3	16	3	US-09-193-997-35	Sequence 35, Appl
45	63	66.3	16	3	US-09-138-237A-29	Sequence 29, Appl

ALIGNMENTS

```
RESULT 1
US-08-145-940-1
; Sequence 1, Application US/08145940
; Patent No. 5489670
;  GENERAL INFORMATION:
;    APPLICANT:  Currie, Mark G.
;    APPLICANT:  Kita, Toshihiro
;    APPLICANT:  Smith, Christine E.
;    APPLICANT:  Fok, Kam F.
;    TITLE OF INVENTION:  Human Uroguanylin
;    NUMBER OF SEQUENCES:  2
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Dennis A. Bennett, G.D. Searle & Co.,
;      ADDRESSEE:  Corporate Patent Dept.
;      STREET:  P. O. Box 5110
;      CITY:  Chicago
;      STATE:  Illinois
;      COUNTRY:  USA
;      ZIP:  60680
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.25
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/145,940
;      FILING DATE:
;      CLASSIFICATION:  530
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Bennett, Dennis A.
;      REGISTRATION NUMBER:  34,547
;      REFERENCE/DOCKET NUMBER:  07-21(808)A
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (708)470-6501
;      TELEFAX:  (708)470-6881
;  INFORMATION FOR SEQ ID NO:  1:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  16 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-145-940-1

  Query Match             96.8%;  Score 92;  DB 1;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 2.9e-06;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
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Db          1 NDDCELCVNVACTGCL 16
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RESULT 2
US-08-583-447A-56
; Sequence 56, Application US/08583447A
; Patent No. 5879656
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and
;    TITLE OF INVENTION:  Methods of Using the Same
;    NUMBER OF SEQUENCES:  56
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz & No. 5879656ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  Windows
;      SOFTWARE:  WordPerfect 6.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/583,447A
;      FILING DATE:  05-JAN-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US 08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1702
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  56:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  16 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-583-447A-56

  Query Match             96.8%;  Score 92;  DB 2;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 2.9e-06;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
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Db          1 NDDCELCVNVACTGCL 16


RESULT 3
US-08-145-940-2
; Sequence 2, Application US/08145940
; Patent No. 5489670
;  GENERAL INFORMATION:
;    APPLICANT:  Currie, Mark G.
;    APPLICANT:  Kita, Toshihiro
;    APPLICANT:  Smith, Christine E.
;    APPLICANT:  Fok, Kam F.
;    TITLE OF INVENTION:  Human Uroguanylin
;    NUMBER OF SEQUENCES:  2
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Dennis A. Bennett, G.D. Searle & Co.,
;      ADDRESSEE:  Corporate Patent Dept.
;      STREET:  P. O. Box 5110
;      CITY:  Chicago
;      STATE:  Illinois
;      COUNTRY:  USA
;      ZIP:  60680
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.25
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/145,940
;      FILING DATE:
;      CLASSIFICATION:  530
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Bennett, Dennis A.
;      REGISTRATION NUMBER:  34,547
;      REFERENCE/DOCKET NUMBER:  07-21(808)A
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (708)470-6501
;      TELEFAX:  (708)470-6881
;  INFORMATION FOR SEQ ID NO:  2:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  15 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-145-940-2

  Query Match             90.5%;  Score 86;  DB 1;  Length 15;
  Best Local Similarity   93.3%;  Pred. No. 1.7e-05;
  Matches   14;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGCL 16
              |:|||||||||||||
Db          1 DDCELCVNVACTGCL 15


RESULT 4
US-08-583-447A-55
; Sequence 55, Application US/08583447A
; Patent No. 5879656
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and
;    TITLE OF INVENTION:  Methods of Using the Same
;    NUMBER OF SEQUENCES:  56
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz & No. 5879656ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  Windows
;      SOFTWARE:  WordPerfect 6.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/583,447A
;      FILING DATE:  05-JAN-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US 08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1702
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  55:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  15 amino acids
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;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-583-447A-55

  Query Match             81.1%;  Score 77;  DB 2;  Length 15;
  Best Local Similarity   78.6%;  Pred. No. 0.00027;
  Matches   11;  Conservative    3;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGC 15
              ::||||:|||||||
Db          2 EDCELCINVACTGC 15


RESULT 5
US-08-141-892A-32
; Sequence 32, Application US/08141892A
; Patent No. 5518888
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and Methods
;    TITLE OF INVENTION:  of Using the Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz and No. 5518888ris
;      STREET:  One Liberty Place - 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  U.S.A.
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  3.5 inch disk, 720 Kb
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  WordPerfect 5.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/141,892A
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:
;      FILING DATE:
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-0903
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  32:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  13 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-141-892A-32

  Query Match             66.3%;  Score 63;  DB 1;  Length 13;
  Best Local Similarity   83.3%;  Pred. No. 0.017;
  Matches   10;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db          2 CELCCNPACTGC 13


RESULT 6
US-08-583-447A-32
; Sequence 32, Application US/08583447A
; Patent No. 5879656
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and
;    TITLE OF INVENTION:  Methods of Using the Same
;    NUMBER OF SEQUENCES:  56
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz & No. 5879656ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  Windows
;      SOFTWARE:  WordPerfect 6.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/583,447A
;      FILING DATE:  05-JAN-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US 08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1702
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  32:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  13 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-583-447A-32

  Query Match             66.3%;  Score 63;  DB 2;  Length 13;
  Best Local Similarity   83.3%;  Pred. No. 0.017;
  Matches   10;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db          2 CELCCNPACTGC 13


RESULT 7
US-08-467-920-32
; Sequence 32, Application US/08467920
; Patent No. 5962220
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  Compositions That Specifically
;    TITLE OF INVENTION:  Bind To Colorectal Cancer Cells
;    TITLE OF INVENTION:  And Methods Of Using The Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz &
;      ADDRESSEE:  No. 5962220ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  WordPerfect 5.0
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/467,920
;      FILING DATE:
;      CLASSIFICATION:  435
```

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;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1589
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  32:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  13 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-467-920-32

  Query Match             66.3%;  Score 63;  DB 2;  Length 13;
  Best Local Similarity   83.3%;  Pred. No. 0.017;
  Matches   10;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db          2 CELCCNPACTGC 13


RESULT 8
US-08-635-930-32
; Sequence 32, Application US/08635930
; Patent No. 6060037
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  Compositions That Specifically Bind To
;    TITLE OF INVENTION:  Colorectal Cancer Cells And Methods Of Using
;    TITLE OF INVENTION:  The Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz & No. 6060037ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  WINDOWS 3.1
;      SOFTWARE:  WordPerfect 6.0/6.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/635,930
;      FILING DATE:  26-APR-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  08/305,056
;      FILING DATE:  13-SEP-1994
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1360
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  32:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  13 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-635-930-32

  Query Match             66.3%;  Score 63;  DB 3;  Length 13;
  Best Local Similarity   83.3%;  Pred. No. 0.017;
  Matches   10;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db          2 CELCCNPACTGC 13


RESULT 9
US-09-193-997-32
; Sequence 32, Application US/09193997
; Patent No. 6087109
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  Compositions That Specifically
;    TITLE OF INVENTION:  Bind To Colorectal Cancer Cells
;    TITLE OF INVENTION:  And Methods Of Using The Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz &
;      ADDRESSEE:  No. 6087109ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  WordPerfect 5.0
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/09/193,997
;      FILING DATE:
;      CLASSIFICATION:
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  08/467,920
;      FILING DATE:
;      CLASSIFICATION:
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1589
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  32:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  13 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-09-193-997-32

  Query Match             66.3%;  Score 63;  DB 3;  Length 13;
  Best Local Similarity   83.3%;  Pred. No. 0.017;
  Matches   10;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db          2 CELCCNPACTGC 13


RESULT 10
US-09-138-237A-32
; Sequence 32, Application US/09138237A
; Patent No. 6268159
;  GENERAL INFORMATION:
```

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;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and Methods
;    TITLE OF INVENTION:  of Using the Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz and No. 6268159ris
;      STREET:  One Liberty Place - 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  U.S.A.
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  3.5 inch disk, 720 Kb
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  WordPerfect 5.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/09/138,237A
;      FILING DATE:
;      CLASSIFICATION:
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  08/141,892
;      FILING DATE:
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-0903
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  32:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  13 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-09-138-237A-32

  Query Match             66.3%;  Score 63;  DB 3;  Length 13;
  Best Local Similarity   83.3%;  Pred. No. 0.017;
  Matches   10;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db          2 CELCCNPACTGC 13


RESULT 11
US-08-141-892A-31
; Sequence 31, Application US/08141892A
; Patent No. 5518888
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and Methods
;    TITLE OF INVENTION:  of Using the Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz and No. 5518888ris
;      STREET:  One Liberty Place - 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  U.S.A.
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  3.5 inch disk, 720 Kb
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  WordPerfect 5.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/141,892A
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:
;      FILING DATE:
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-0903
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  31:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  14 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-141-892A-31

  Query Match             66.3%;  Score 63;  DB 1;  Length 14;
  Best Local Similarity   83.3%;  Pred. No. 0.018;
  Matches   10;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db          3 CELCCNPACTGC 14


RESULT 12
US-08-141-892A-37
; Sequence 37, Application US/08141892A
; Patent No. 5518888
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and Methods
;    TITLE OF INVENTION:  of Using the Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz and No. 5518888ris
;      STREET:  One Liberty Place - 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  U.S.A.
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  3.5 inch disk, 720 Kb
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  WordPerfect 5.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/141,892A
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:
;      FILING DATE:
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-0903
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  37:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  14 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-141-892A-37

  Query Match             66.3%;  Score 63;  DB 1;  Length 14;
  Best Local Similarity   83.3%;  Pred. No. 0.018;
  Matches   10;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;
```

```
Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db          2 CELCCNPACTGC 13


RESULT 13
US-08-583-447A-31
; Sequence 31, Application US/08583447A
; Patent No. 5879656
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and
;    TITLE OF INVENTION:  Methods of Using the Same
;    NUMBER OF SEQUENCES:  56
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz & No. 5879656ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  Windows
;      SOFTWARE:  WordPerfect 6.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/583,447A
;      FILING DATE:  05-JAN-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US 08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1702
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  31:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  14 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-583-447A-31

  Query Match             66.3%;  Score 63;  DB 2;  Length 14;
  Best Local Similarity   83.3%;  Pred. No. 0.018;
  Matches   10;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db          3 CELCCNPACTGC 14


RESULT 14
US-08-583-447A-37
; Sequence 37, Application US/08583447A
; Patent No. 5879656
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  ST Receptor Binding Compounds and
;    TITLE OF INVENTION:  Methods of Using the Same
;    NUMBER OF SEQUENCES:  56
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz & No. 5879656ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  Windows
;      SOFTWARE:  WordPerfect 6.1
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/583,447A
;      FILING DATE:  05-JAN-1996
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US 08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1702
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  37:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  14 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  peptide
US-08-583-447A-37

  Query Match             66.3%;  Score 63;  DB 2;  Length 14;
  Best Local Similarity   83.3%;  Pred. No. 0.018;
  Matches   10;  Conservative    0;  Mismatches    2;  Indels    0;  Gaps    0;

Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db          2 CELCCNPACTGC 13


RESULT 15
US-08-467-920-31
; Sequence 31, Application US/08467920
; Patent No. 5962220
;  GENERAL INFORMATION:
;    APPLICANT:  Waldman, Scott A.
;    TITLE OF INVENTION:  Compositions That Specifically
;    TITLE OF INVENTION:  Bind To Colorectal Cancer Cells
;    TITLE OF INVENTION:  And Methods Of Using The Same
;    NUMBER OF SEQUENCES:  54
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz &
;      ADDRESSEE:  No. 5962220ris
;      STREET:  One Liberty Place, 46th Floor
;      CITY:  Philadelphia
;      STATE:  Pennsylvania
;      COUNTRY:  USA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  WordPerfect 5.0
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/467,920
;      FILING DATE:
;      CLASSIFICATION:  435
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  08/141,892
;      FILING DATE:  26-OCT-1993
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  DeLuca, Mark
;      REGISTRATION NUMBER:  33,229
;      REFERENCE/DOCKET NUMBER:  TJU-1589
```

; TELECOMMUNICATION INFORMATION:
; TELEPHONE: 215-568-3100
; TELEFAX: 215-568-3439
; INFORMATION FOR SEQ ID NO: 31:
; SEQUENCE CHARACTERISTICS:
; LENGTH: 14 amino acids
; TYPE: amino acid
; TOPOLOGY: linear
; MOLECULE TYPE: peptide
US-08-467-920-31

Query Match 66.3%; Score 63; DB 2; Length 14;
Best Local Similarity 83.3%; Pred. No. 0.018;
Matches 10; Conservative 0; Mismatches 2; Indels 0; Gaps 0;

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Qy          4 CELCVNVACTGC 15
              |||| | |||||
Db          3 CELCCNPACTGC 14
```

Search completed: August 26, 2005, 19:05:21
Job time : 42 secs

GenCore version 5.1.6

OM protein - protein search, using sw model

Run on: August 26, 2005, 19:03:58 ; Search time 162 Seconds
(without alignments)
38.808 Million cell updates/sec

Title: US-10-107-814-20
Perfect score: 95
Sequence: 1 NDECELCVNVACTGCL 16

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 1767149 seqs, 392926209 residues

Total number of hits satisfying chosen parameters: 1767149

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : Published_Applications_AA:*
1: /cgn2_6/ptodata/1/pubpaa/US07_PUBCOMB.pep:*
2: /cgn2_6/ptodata/1/pubpaa/PCT_NEW_PUB.pep:*
3: /cgn2_6/ptodata/1/pubpaa/US06_NEW_PUB.pep:*
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18: /cgn2_6/ptodata/1/pubpaa/US10_NEW_PUB.pep:*
19: /cgn2_6/ptodata/1/pubpaa/US11A_PUBCOMB.pep:*
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22: /cgn2_6/ptodata/1/pubpaa/US60_PUBCOMB.pep:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	95	100.0	16	14	US-10-107-814-20	Sequence 20, Appl
2	92	96.8	16	14	US-10-107-814-1	Sequence 1, Appli
3	92	96.8	16	14	US-10-197-954-141	Sequence 141, App
4	92	96.8	16	15	US-10-621-684-56	Sequence 56, Appl
5	92	96.8	16	17	US-10-479-606-2	Sequence 2, Appli
6	92	96.8	16	17	US-10-760-085-141	Sequence 141, App
7	92	96.8	112	16	US-10-775-481A-56	Sequence 56, Appl
8	92	96.8	112	17	US-10-479-606-5	Sequence 5, Appli
9	84	88.4	106	16	US-10-775-481A-55	Sequence 55, Appl
10	83	87.4	14	14	US-10-107-814-21	Sequence 21, Appl
11	77	81.1	15	15	US-10-621-684-55	Sequence 55, Appl
12	71	74.7	14	18	US-10-505-239-15	Sequence 15, Appl
13	68	71.6	15	17	US-10-479-606-3	Sequence 3, Appli
14	68	71.6	109	17	US-10-479-606-6	Sequence 6, Appli
15	66	69.5	16	14	US-10-107-814-2	Sequence 2, Appli
16	64	67.4	17	16	US-10-766-735-15	Sequence 15, Appl
17	64	67.4	17	17	US-10-796-719-15	Sequence 15, Appl
18	63	66.3	13	15	US-10-621-684-32	Sequence 32, Appl
19	63	66.3	13	16	US-10-775-481A-32	Sequence 32, Appl
20	63	66.3	14	15	US-10-621-684-31	Sequence 31, Appl
21	63	66.3	14	15	US-10-621-684-37	Sequence 37, Appl
22	63	66.3	14	16	US-10-775-481A-31	Sequence 31, Appl
23	63	66.3	14	16	US-10-775-481A-37	Sequence 37, Appl
24	63	66.3	14	16	US-10-766-735-29	Sequence 29, Appl
25	63	66.3	14	17	US-10-796-719-29	Sequence 29, Appl
26	63	66.3	15	15	US-10-371-966-3	Sequence 3, Appli
27	63	66.3	15	15	US-10-621-684-30	Sequence 30, Appl
28	63	66.3	15	15	US-10-621-684-36	Sequence 36, Appl
29	63	66.3	15	16	US-10-775-481A-30	Sequence 30, Appl
30	63	66.3	15	16	US-10-775-481A-36	Sequence 36, Appl
31	63	66.3	15	16	US-10-766-735-32	Sequence 32, Appl
32	63	66.3	15	17	US-10-796-719-32	Sequence 32, Appl
33	63	66.3	16	15	US-10-621-684-29	Sequence 29, Appl
34	63	66.3	16	15	US-10-621-684-35	Sequence 35, Appl
35	63	66.3	16	16	US-10-775-481A-29	Sequence 29, Appl
36	63	66.3	16	16	US-10-775-481A-35	Sequence 35, Appl
37	63	66.3	16	16	US-10-766-735-46	Sequence 46, Appl
38	63	66.3	16	17	US-10-796-719-46	Sequence 46, Appl
39	63	66.3	16	18	US-10-505-239-16	Sequence 16, Appl
40	63	66.3	17	15	US-10-621-684-28	Sequence 28, Appl
41	63	66.3	17	15	US-10-621-684-34	Sequence 34, Appl
42	63	66.3	17	16	US-10-775-481A-28	Sequence 28, Appl
43	63	66.3	17	16	US-10-775-481A-34	Sequence 34, Appl
44	63	66.3	17	16	US-10-766-735-53	Sequence 53, Appl
45	63	66.3	17	17	US-10-796-719-53	Sequence 53, Appl

ALIGNMENTS

RESULT 1
US-10-107-814-20
; Sequence 20, Application US/10107814
; Publication No. US20030073628A1
; GENERAL INFORMATION:
; APPLICANT: SHAILUBHAI, KUNWAR
; APPLICANT: NIKIFOROVICH, GREGORY
; APPLICANT: JACOB, GARY S.
; TITLE OF INVENTION: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT
; TITLE OF INVENTION: OF TISSUE INFLAMMATION AND CARCINOGENESIS
; FILE REFERENCE: 81361/284943/MAS
; CURRENT APPLICATION NUMBER: US/10/107,814
; CURRENT FILING DATE: 2002-03-28
; NUMBER OF SEQ ID NOS: 23
; SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 20
; LENGTH: 16
; TYPE: PRT
; ORGANISM: Artificial Sequence
; FEATURE:
; OTHER INFORMATION: Description of Artificial Sequence: Synthetic
; OTHER INFORMATION: guanylate cyclase receptor agonist peptide
; NAME/KEY: DISULFID
; LOCATION: (4)..(12)
; NAME/KEY: DISULFID
; LOCATION: (7)..(15)
US-10-107-814-20

Query Match 100.0%; Score 95; DB 14; Length 16;
Best Local Similarity 100.0%; Pred. No. 4e-06;
Matches 16; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 NDECELCVNVACTGCL 16
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Db          1 NDECELCVNVACTGCL 16


RESULT 2
US-10-107-814-1
; Sequence 1, Application US/10107814
; Publication No. US20030073628A1
; GENERAL INFORMATION:
;  APPLICANT: SHAILUBHAI, KUNWAR
;  APPLICANT:  NIKIFOROVICH, GREGORY
;  APPLICANT:  JACOB, GARY S.
;  TITLE OF INVENTION: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT
;  TITLE OF INVENTION:  OF TISSUE INFLAMMATION AND CARCINOGENESIS
;  FILE REFERENCE: 81361/284943/MAS
;  CURRENT APPLICATION NUMBER: US/10/107,814
;  CURRENT FILING DATE:  2002-03-28
;  NUMBER OF SEQ ID NOS: 23
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 1
;   LENGTH: 16
;   TYPE: PRT
;   ORGANISM: Homo sapiens
;   FEATURE:
;   NAME/KEY: DISULFID
;   LOCATION: (4)..(12)
;   NAME/KEY: DISULFID
;   LOCATION: (7)..(15)
US-10-107-814-1

  Query Match             96.8%;  Score 92;  DB 14;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 1e-05;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          1 NDDCELCVNVACTGCL 16


RESULT 3
US-10-197-954-141
; Sequence 141, Application US/10197954
; Publication No. US20030119021A1
; GENERAL INFORMATION:
;  APPLICANT: K"ster, Hubert
;  APPLICANT:  Siddiqi, Suhaib
;  APPLICANT:  Little, Daniel
;  TITLE OF INVENTION: Capture Compounds, Collections Thereof
;  TITLE OF INVENTION:  And Methods For Analyzing The Proteome And Complex
;  TITLE OF INVENTION:  Compositions
;  FILE REFERENCE: 24743-2305
;  CURRENT APPLICATION NUMBER: US/10/197,954
;  CURRENT FILING DATE:  2002-07-16
;  PRIOR APPLICATION NUMBER: 60/306,019
;  PRIOR FILING DATE: 2001-07-16
;  PRIOR APPLICATION NUMBER: 60/314,123
;  PRIOR FILING DATE: 2001-08-21
;  PRIOR APPLICATION NUMBER: 60/363,433
;  PRIOR FILING DATE: 2002-03-11
;  NUMBER OF SEQ ID NOS: 149
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 141
;   LENGTH: 16
;   TYPE: PRT
;   ORGANISM: Homo Sapien
US-10-197-954-141

  Query Match             96.8%;  Score 92;  DB 14;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 1e-05;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
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Db          1 NDDCELCVNVACTGCL 16


RESULT 4
US-10-621-684-56
; Sequence 56, Application US/10621684
; Publication No. US20040029182A1
;   GENERAL INFORMATION:
;        APPLICANT: Waldman, Scott A.
;        TITLE OF INVENTION: ST Receptor Binding Compounds and
;                            Methods of Using the Same
;        NUMBER OF SEQUENCES: 56
;        CORRESPONDENCE ADDRESS:
;             ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz & No. US20040029182A1ris
;             STREET: One Liberty Place, 46th Floor
;             CITY: Philadelphia
;             STATE: Pennsylvania
;             COUNTRY: USA
;             ZIP: 19103
;        COMPUTER READABLE FORM:
;             MEDIUM TYPE: Floppy disk
;             COMPUTER: IBM PC compatible
;             OPERATING SYSTEM: Windows
;             SOFTWARE: WordPerfect 6.1
;        CURRENT APPLICATION DATA:
;             APPLICATION NUMBER: US/10/621,684
;             FILING DATE: 17-Jul-2003
;             CLASSIFICATION: 435
;        PRIOR APPLICATION DATA:
;             APPLICATION NUMBER: US/08/583,447A
;             FILING DATE: 05-JAN-1996
;             APPLICATION NUMBER: US 08/141,892
;             FILING DATE: 26-OCT-1993
;        ATTORNEY/AGENT INFORMATION:
;             NAME: DeLuca, Mark
;             REGISTRATION NUMBER: 33,229
;             REFERENCE/DOCKET NUMBER: TJU-1702
;        TELECOMMUNICATION INFORMATION:
;             TELEPHONE: 215-568-3100
;             TELEFAX: 215-568-3439
;   INFORMATION FOR SEQ ID NO: 56:
;        SEQUENCE CHARACTERISTICS:
;             LENGTH: 16 amino acids
;             TYPE: amino acid
;             TOPOLOGY: linear
;        MOLECULE TYPE: peptide
;        SEQUENCE DESCRIPTION: SEQ ID NO: 56:
US-10-621-684-56

  Query Match             96.8%;  Score 92;  DB 15;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 1e-05;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          1 NDDCELCVNVACTGCL 16


RESULT 5
US-10-479-606-2
; Sequence 2, Application US/10479606
; Publication No. US20050032684A1
; GENERAL INFORMATION:
;  APPLICANT: Cetin, Yalcin
;  APPLICANT:  Savas, Yuksel
;  TITLE OF INVENTION: Guanylate-cyclase C ligand, administered via the airways, for th
;  TITLE OF INVENTION:  treatment of respiratory airway problems
;  FILE REFERENCE: 03100192aa
;  CURRENT APPLICATION NUMBER: US/10/479,606
;  CURRENT FILING DATE:  2003-12-04
;  PRIOR APPLICATION NUMBER: DE10127119.0
;  PRIOR FILING DATE: 2001-06-05
;  PRIOR APPLICATION NUMBER: PCT/DE02/02040
;  PRIOR FILING DATE: 2002-06-05
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;  NUMBER OF SEQ ID NOS: 7
;  SOFTWARE: PatentIn version 3.2
; SEQ ID NO 2
;   LENGTH: 16
;   TYPE: PRT
;   ORGANISM: Homo sapiens
US-10-479-606-2

  Query Match             96.8%;  Score 92;  DB 17;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 1e-05;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          1 NDDCELCVNVACTGCL 16


RESULT 6
US-10-760-085-141
; Sequence 141, Application US/10760085
; Publication No. US20050042771A1
; GENERAL INFORMATION:
;  APPLICANT: Hubert K"ster
;  APPLICANT:  Daniel Paul Little
;  APPLICANT:  Suhaib Mahmood Siddiqi
;  APPLICANT:  Mattew Peter Grealish
;  APPLICANT:  Subramaniam Marappan
;  APPLICANT:  Chester Frederick Hassman III
;  APPLICANT:  Ping Yip
;  TITLE OF INVENTION: Capture Compounds, Collections Thereof
;  TITLE OF INVENTION:  And Methods For Analyzing The Proteome And Complex
;  TITLE OF INVENTION:  Compositions
;  FILE REFERENCE: 24743-2309
;  CURRENT APPLICATION NUMBER: US/10/760,085
;  CURRENT FILING DATE:  2004-01-16
;  PRIOR APPLICATION NUMBER: 60/441,398
;  PRIOR FILING DATE: 2003-01-16
;  NUMBER OF SEQ ID NOS: 149
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 141
;   LENGTH: 16
;   TYPE: PRT
;   ORGANISM: Homo Sapien
US-10-760-085-141

  Query Match             96.8%;  Score 92;  DB 17;  Length 16;
  Best Local Similarity   93.8%;  Pred. No. 1e-05;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db          1 NDDCELCVNVACTGCL 16


RESULT 7
US-10-775-481A-56
; Sequence 56, Application US/10775481A
; Publication No. US20040258687A1
; GENERAL INFORMATION:
;  APPLICANT: Waldman, Scott A.
;  APPLICANT:  Pitari, Giovanni Mario
;  APPLICANT:  Park, Jason
;  APPLICANT:  Schulz, Stephanie
;  APPLICANT:  Wolfe, Henry R.
;  APPLICANT:  Lubbe, Wilhelm
;  TITLE OF INVENTION: The Use Of GCC Ligands
;  FILE REFERENCE: 08321-0168 US1
;  CURRENT APPLICATION NUMBER: US/10/775,481A
;  CURRENT FILING DATE:  2004-02-10
;  PRIOR APPLICATION NUMBER: US 60/446,730
;  PRIOR FILING DATE: 2003-02-10
;  NUMBER OF SEQ ID NOS: 56
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 56
;   LENGTH: 112
;   TYPE: PRT
;   ORGANISM: Homo sapiens
US-10-775-481A-56

  Query Match             96.8%;  Score 92;  DB 16;  Length 112;
  Best Local Similarity   93.8%;  Pred. No. 5.9e-05;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
              ||:|||||||||||||
Db         97 NDDCELCVNVACTGCL 112


RESULT 8
US-10-479-606-5
; Sequence 5, Application US/10479606
; Publication No. US20050032684A1
; GENERAL INFORMATION:
;  APPLICANT: Cetin, Yalcin
;  APPLICANT:  Savas, Yuksel
;  TITLE OF INVENTION: Guanylate-cyclase C ligand, administered via the airways, for th
;  TITLE OF INVENTION:  treatment of respiratory airway problems
;  FILE REFERENCE: 03100192aa
;  CURRENT APPLICATION NUMBER: US/10/479,606
;  CURRENT FILING DATE:  2003-12-04
;  PRIOR APPLICATION NUMBER: DE10127119.0
;  PRIOR FILING DATE: 2001-06-05
;  PRIOR APPLICATION NUMBER: PCT/DE02/02040
;  PRIOR FILING DATE: 2002-06-05
;  NUMBER OF SEQ ID NOS: 7
;  SOFTWARE: PatentIn version 3.2
; SEQ ID NO 5
;   LENGTH: 112
;   TYPE: PRT
;   ORGANISM: homo sapiens
US-10-479-606-5

  Query Match             96.8%;  Score 92;  DB 17;  Length 112;
  Best Local Similarity   93.8%;  Pred. No. 5.9e-05;
  Matches   15;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
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Db         97 NDDCELCVNVACTGCL 112


RESULT 9
US-10-775-481A-55
; Sequence 55, Application US/10775481A
; Publication No. US20040258687A1
; GENERAL INFORMATION:
;  APPLICANT: Waldman, Scott A.
;  APPLICANT:  Pitari, Giovanni Mario
;  APPLICANT:  Park, Jason
;  APPLICANT:  Schulz, Stephanie
;  APPLICANT:  Wolfe, Henry R.
;  APPLICANT:  Lubbe, Wilhelm
;  TITLE OF INVENTION: The Use Of GCC Ligands
;  FILE REFERENCE: 08321-0168 US1
;  CURRENT APPLICATION NUMBER: US/10/775,481A
;  CURRENT FILING DATE:  2004-02-10
;  PRIOR APPLICATION NUMBER: US 60/446,730
;  PRIOR FILING DATE: 2003-02-10
;  NUMBER OF SEQ ID NOS: 56
;  SOFTWARE: FastSEQ for Windows Version 4.0
; SEQ ID NO 55
;   LENGTH: 106
;   TYPE: PRT
;   ORGANISM: Rattus norvegicus
US-10-775-481A-55
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  Query Match             88.4%;  Score 84;  DB 16;  Length 106;
  Best Local Similarity   92.9%;  Pred. No. 0.00066;
  Matches   13;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGC 15
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Db         93 DECELCINVACTGC 106


RESULT 10
US-10-107-814-21
; Sequence 21, Application US/10107814
; Publication No. US20030073628A1
; GENERAL INFORMATION:
;  APPLICANT: SHAILUBHAI, KUNWAR
;  APPLICANT:  NIKIFOROVICH, GREGORY
;  APPLICANT:  JACOB, GARY S.
;  TITLE OF INVENTION: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT
;  TITLE OF INVENTION:  OF TISSUE INFLAMMATION AND CARCINOGENESIS
;  FILE REFERENCE: 81361/284943/MAS
;  CURRENT APPLICATION NUMBER: US/10/107,814
;  CURRENT FILING DATE:  2002-03-28
;  NUMBER OF SEQ ID NOS: 23
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 21
;   LENGTH: 14
;   TYPE: PRT
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Description of Artificial Sequence: Synthetic
;   OTHER INFORMATION: guanylate cyclase receptor agonist peptide
;   NAME/KEY: DISULFID
;   LOCATION: (2)..(10)
;   NAME/KEY: DISULFID
;   LOCATION: (5)..(13)
US-10-107-814-21

  Query Match             87.4%;  Score 83;  DB 14;  Length 14;
  Best Local Similarity   100.0%;  Pred. No. 0.00014;
  Matches   14;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          3 ECELCVNVACTGCL 16
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Db          1 ECELCVNVACTGCL 14


RESULT 11
US-10-621-684-55
; Sequence 55, Application US/10621684
; Publication No. US20040029182A1
;   GENERAL INFORMATION:
;        APPLICANT: Waldman, Scott A.
;        TITLE OF INVENTION: ST Receptor Binding Compounds and
;                            Methods of Using the Same
;        NUMBER OF SEQUENCES: 56
;        CORRESPONDENCE ADDRESS:
;             ADDRESSEE: Woodcock Washburn Kurtz Mackiewicz & No. US20040029182A1ris
;             STREET: One Liberty Place, 46th Floor
;             CITY: Philadelphia
;             STATE: Pennsylvania
;             COUNTRY: USA
;             ZIP: 19103
;        COMPUTER READABLE FORM:
;             MEDIUM TYPE: Floppy disk
;             COMPUTER: IBM PC compatible
;             OPERATING SYSTEM: Windows
;             SOFTWARE: WordPerfect 6.1
;        CURRENT APPLICATION DATA:
;             APPLICATION NUMBER: US/10/621,684
;             FILING DATE: 17-Jul-2003
;             CLASSIFICATION: 435
;        PRIOR APPLICATION DATA:
;             APPLICATION NUMBER: US/08/583,447A
;             FILING DATE: 05-JAN-1996
;             APPLICATION NUMBER: US 08/141,892
;             FILING DATE: 26-OCT-1993
;        ATTORNEY/AGENT INFORMATION:
;             NAME: DeLuca, Mark
;             REGISTRATION NUMBER: 33,229
;             REFERENCE/DOCKET NUMBER: TJU-1702
;        TELECOMMUNICATION INFORMATION:
;             TELEPHONE: 215-568-3100
;             TELEFAX: 215-568-3439
;   INFORMATION FOR SEQ ID NO: 55:
;        SEQUENCE CHARACTERISTICS:
;             LENGTH: 15 amino acids
;             TYPE: amino acid
;             TOPOLOGY: linear
;        MOLECULE TYPE: peptide
;        SEQUENCE DESCRIPTION: SEQ ID NO: 55:
US-10-621-684-55

  Query Match             81.1%;  Score 77;  DB 15;  Length 15;
  Best Local Similarity   78.6%;  Pred. No. 0.00098;
  Matches   11;  Conservative    3;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTGC 15
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Db          2 EDCELCINVACTGC 15


RESULT 12
US-10-505-239-15
; Sequence 15, Application US/10505239
; Publication No. US20050171014A1
; GENERAL INFORMATION:
;  APPLICANT: TARASOVA, Nadya I
;  APPLICANT:  MICHEJDA, Christopher J
;  APPLICANT:  DYBA, Marcin
;  APPLICANT:  COHRAN, Carolyn
;  TITLE OF INVENTION: CONJUGATES OF LIGAND, LINKER AND CYTOTOXIC AGENT AND RELATED
;  TITLE OF INVENTION:  COMPOSITIONS AND METHODS OF USE
;  FILE REFERENCE: 229694
;  CURRENT APPLICATION NUMBER: US/10/505,239
;  CURRENT FILING DATE:  2004-08-19
;  PRIOR APPLICATION NUMBER: PCT/US03/06344
;  PRIOR FILING DATE: 2003-02-27
;  PRIOR APPLICATION NUMBER: 60/360,543
;  PRIOR FILING DATE: 2002-02-27
;  PRIOR APPLICATION NUMBER: 60/370,189
;  PRIOR FILING DATE: 2002-04-05
;  NUMBER OF SEQ ID NOS: 28
;  SOFTWARE: PatentIn version 3.2
; SEQ ID NO 15
;   LENGTH: 14
;   TYPE: PRT
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Synthetic
US-10-505-239-15

  Query Match             74.7%;  Score 71;  DB 18;  Length 14;
  Best Local Similarity   81.2%;  Pred. No. 0.0058;
  Matches   13;  Conservative    1;  Mismatches    0;  Indels    2;  Gaps    1;

Qy          1 NDECELCVNVACTGCL 16
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Db          1 NDDCELC--VACTGCL 14


RESULT 13
US-10-479-606-3
; Sequence 3, Application US/10479606
; Publication No. US20050032684A1
; GENERAL INFORMATION:
;  APPLICANT: Cetin, Yalcin
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;  APPLICANT:  Savas, Yuksel
;  TITLE OF INVENTION: Guanylate-cyclase C ligand, administered via the airways, for the
;  TITLE OF INVENTION:  treatment of respiratory airway problems
;  FILE REFERENCE: 03100192aa
;  CURRENT APPLICATION NUMBER: US/10/479,606
;  CURRENT FILING DATE:  2003-12-04
;  PRIOR APPLICATION NUMBER: DE10127119.0
;  PRIOR FILING DATE: 2001-06-05
;  PRIOR APPLICATION NUMBER: PCT/DE02/02040
;  PRIOR FILING DATE: 2002-06-05
;  NUMBER OF SEQ ID NOS: 7
;  SOFTWARE: PatentIn version 3.2
; SEQ ID NO 3
;   LENGTH: 15
;   TYPE: PRT
;   ORGANISM: oppossum (lymphoid tissue)
US-10-479-606-3

  Query Match             71.6%;  Score 68;  DB 17;  Length 15;
  Best Local Similarity   76.9%;  Pred. No. 0.016;
  Matches   10;  Conservative    3;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTG 14
              :|||||:|:||||
Db          2 EECELCINMACTG 14


RESULT 14
US-10-479-606-6
; Sequence 6, Application US/10479606
; Publication No. US20050032684A1
; GENERAL INFORMATION:
;  APPLICANT: Cetin, Yalcin
;  APPLICANT:  Savas, Yuksel
;  TITLE OF INVENTION: Guanylate-cyclase C ligand, administered via the airways, for the
;  TITLE OF INVENTION:  treatment of respiratory airway problems
;  FILE REFERENCE: 03100192aa
;  CURRENT APPLICATION NUMBER: US/10/479,606
;  CURRENT FILING DATE:  2003-12-04
;  PRIOR APPLICATION NUMBER: DE10127119.0
;  PRIOR FILING DATE: 2001-06-05
;  PRIOR APPLICATION NUMBER: PCT/DE02/02040
;  PRIOR FILING DATE: 2002-06-05
;  NUMBER OF SEQ ID NOS: 7
;  SOFTWARE: PatentIn version 3.2
; SEQ ID NO 6
;   LENGTH: 109
;   TYPE: PRT
;   ORGANISM: oppossum
US-10-479-606-6

  Query Match             71.6%;  Score 68;  DB 17;  Length 109;
  Best Local Similarity   76.9%;  Pred. No. 0.094;
  Matches   10;  Conservative    3;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          2 DECELCVNVACTG 14
              :|||||:|:||||
Db         96 EECELCINMACTG 108


RESULT 15
US-10-107-814-2
; Sequence 2, Application US/10107814
; Publication No. US20030073628A1
; GENERAL INFORMATION:
;  APPLICANT: SHAILUBHAI, KUNWAR
;  APPLICANT:  NIKIFOROVICH, GREGORY
;  APPLICANT:  JACOB, GARY S.
;  TITLE OF INVENTION: GUANYLATE CYCLASE RECEPTOR AGONISTS FOR THE TREATMENT
;  TITLE OF INVENTION:  OF TISSUE INFLAMMATION AND CARCINOGENESIS
;  FILE REFERENCE: 81361/284943/MAS
;  CURRENT APPLICATION NUMBER: US/10/107,814
;  CURRENT FILING DATE:  2002-03-28
;  NUMBER OF SEQ ID NOS: 23
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 2
;   LENGTH: 16
;   TYPE: PRT
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Description of Artificial Sequence: Synthetic
;   OTHER INFORMATION: guanylate cyclase receptor agonist peptide
;   NAME/KEY: DISULFID
;   LOCATION: (4)..(12)
;   NAME/KEY: DISULFID
;   LOCATION: (7)..(15)
;   NAME/KEY: MOD_RES
;   LOCATION: (2)
;   OTHER INFORMATION: Asp or Glu
;   NAME/KEY: MOD_RES
;   LOCATION: (3)
;   OTHER INFORMATION: Asp or Glu
;   NAME/KEY: MOD_RES
;   LOCATION: (10)
;   OTHER INFORMATION: Val or Pro
;   NAME/KEY: MOD_RES
;   LOCATION: (11)
;   OTHER INFORMATION: Ala or Aib
;   NAME/KEY: MOD_RES
;   LOCATION: (14)
;   OTHER INFORMATION: Gly or Ala
US-10-107-814-2

  Query Match             69.5%;  Score 66;  DB 14;  Length 16;
  Best Local Similarity   68.8%;  Pred. No. 0.031;
  Matches   11;  Conservative    0;  Mismatches    5;  Indels    0;  Gaps    0;

Qy          1 NDECELCVNVACTGCL 16
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Db          1 NXXCELCVNXXCTXCL 16


Search completed: August 26, 2005, 19:17:49
Job time : 163 secs
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