



(12) **United States Patent**
Comiskey et al.

(10) **Patent No.:** **US 9,919,024 B2**
(45) **Date of Patent:** ***Mar. 20, 2018**

(54) **FORMULATIONS OF GUANYLATE
CYCLASE C AGONISTS AND METHODS OF
USE**

(58) **Field of Classification Search**
None
See application file for complete search history.

(71) Applicant: **SYNERGY PHARMACEUTICALS,
INC.**, New York, NY (US)

(56) **References Cited**

(72) Inventors: **Stephen Comiskey**, Doylestown, PA
(US); **Rong Feng**, Langhorne, PA (US);
John Foss, Doylestown, PA (US);
Kunwar Shailubhai, Audubon, PA
(US)

U.S. PATENT DOCUMENTS

(73) Assignee: **SYNERGY PHARMACEUTICALS,
INC.**, New York, NY (US)

5,106,834 A 4/1992 Bovy et al.
5,130,333 A 7/1992 Pan et al.
5,489,670 A 2/1996 Currie et al.
5,518,888 A 5/1996 Waldman et al.
5,578,709 A 11/1996 Woiszwilllo et al.
5,601,990 A 2/1997 Waldman et al.
5,721,238 A 2/1998 Heiker et al.
5,731,159 A 3/1998 Waldman et al.
5,817,624 A 10/1998 Yang et al.
5,879,656 A 3/1999 Waldman et al.
5,928,873 A 7/1999 Waldman et al.
5,969,097 A 10/1999 Wiegand et al.
6,060,037 A 5/2000 Waldman et al.
6,235,782 B1 5/2001 Pamukcu et al.
7,041,786 B2 5/2006 Shailubhai et al.
7,067,748 B1 7/2006 Whitmore, Jr. et al.
7,375,083 B2 5/2008 Mickle et al.
7,494,979 B2 2/2009 Currie et al.
7,799,897 B2 9/2010 Jacob et al.
7,879,802 B2 2/2011 Shailubhai et al.
8,034,782 B2 10/2011 Shailubhai
8,114,831 B2 2/2012 Shailubhai et al.

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-
claimer.

(21) Appl. No.: **15/467,648**

(22) Filed: **Mar. 23, 2017**

(65) **Prior Publication Data**
US 2017/0202904 A1 Jul. 20, 2017

(Continued)

FOREIGN PATENT DOCUMENTS

Related U.S. Application Data

JP 2006-022115 A 1/2006
JP 2009-519343 A 5/2009

(63) Continuation of application No. 14/845,644, filed on
Sep. 4, 2015, now Pat. No. 9,610,321, which is a
continuation of application No. 14/661,299, filed on
Mar. 18, 2015, now abandoned, which is a
continuation of application No. 13/421,769, filed on
Mar. 15, 2012, now Pat. No. 9,616,097, which is a
continuation-in-part of application No.
PCT/US2011/051805, filed on Sep. 15, 2011.

(Continued)

OTHER PUBLICATIONS

(60) Provisional application No. 61/383,156, filed on Sep.
15, 2010, provisional application No. 61/387,636,
filed on Sep. 29, 2010, provisional application No.
61/392,186, filed on Oct. 12, 2010.

Shailubhai, K.; Gerson, W.; Talluto, C.; Jacob, G. Digestive Disease
Week. San Diego: 2008. A randomized, double-blind, placebo-
controlled, single-, ascending-, oral-dose safety, tolerability and
pharmacokinetic study of SP-304 in healthy adult human male and
female volunteers.*
Advisory Committee Briefing document for Merida [sibutramine
hydrochloride monohydrate], Abbott, Aug. 13, 2010 (205 pages).
Alrefai , "Cholesterol modulates human intestinal sodium-depend-
ent bile acid transporter," Am. J. Physiol. Gastrointest. Liver
Physiol. 288:G978-G985 (2005).
Askling "Colorectal cancer rates among first degree relatives of
patients with inflammatory bowel disease: A population-based
cohort study" Lancet 357:262-266 (2001).
Bakre et al. "Expression and regulation of the cGMP-binding,
cGMP-specific phosphodiesterase (PDE5) in human colonic epi-
thelial cells: role in the induction of cellular refractoriness to the
heat-stable enterotoxin peptide" J. Cell Biol. 77:159-167 (2000).

(51) **Int. Cl.**
A61K 38/10 (2006.01)
A61K 47/38 (2006.01)
A61K 47/12 (2006.01)
A61K 45/06 (2006.01)
A61K 9/00 (2006.01)
C07K 7/08 (2006.01)
C07K 7/64 (2006.01)
A61K 9/16 (2006.01)
A61K 9/48 (2006.01)

(Continued)

Primary Examiner — Satyanarayana R Gudibande
Assistant Examiner — Jia-Hai Lee

(52) **U.S. Cl.**
CPC **A61K 38/10** (2013.01); **A61K 9/0053**
(2013.01); **A61K 9/1623** (2013.01); **A61K**
9/1652 (2013.01); **A61K 9/1676** (2013.01);
A61K 9/4858 (2013.01); **A61K 9/4866**
(2013.01); **A61K 45/06** (2013.01); **A61K 47/12**
(2013.01); **A61K 47/38** (2013.01); **C07K 7/08**

(74) *Attorney, Agent, or Firm* — Cynthia A. Kozakiewicz;
Ivor Elrifi

(57) **ABSTRACT**

The invention provides low-dose formulations of guanylate
cyclase-C ("GCC") agonist peptides and methods for their
use. The formulations of the invention can be administered
either alone or in combination with one or more additional
therapeutic agents, preferably an inhibitor of cGMP-depend-
ent phosphodiesterase or a laxative.

(56)

References Cited

U.S. PATENT DOCUMENTS

8,207,295	B2	6/2012	Shailubhai et al.	
8,357,775	B2	1/2013	Shailubhai et al.	
8,367,800	B2	2/2013	Shailubhai	
8,497,348	B2	7/2013	Shailubhai et al.	
8,569,246	B2	10/2013	Shailubhai	
8,637,451	B2	1/2014	Shailubhai et al.	
8,664,354	B2	3/2014	Shailubhai	
8,716,224	B2	5/2014	Shailubhai et al.	
8,901,075	B2	12/2014	Shailubhai et al.	
8,969,514	B2	3/2015	Shailubhai	
9,238,677	B2	1/2016	Shailubhai et al.	
9,266,926	B2	2/2016	Shailubhai et al.	
9,486,494	B2	11/2016	Shailubhai	
9,545,446	B2	1/2017	Riff et al.	
9,610,321	B2*	4/2017	Comiskey	A61K 9/1623
9,616,097	B2*	4/2017	Comiskey	A61K 9/1623
2002/0128176	A1	9/2002	Forssmann et al.	
2002/0133168	A1	9/2002	Smeldley et al.	
2002/0143015	A1	10/2002	Fryburg et al.	
2003/0073628	A1	4/2003	Shailubhai et al.	
2004/0015140	A1	1/2004	Shields	
2005/0016244	A1	1/2005	Hergemoller	
2005/0032684	A1	2/2005	Cetin et al.	
2005/0107734	A1	5/2005	Coroneo	
2005/0145351	A1	7/2005	Schaible et al.	
2005/0266047	A1	12/2005	Tu et al.	
2005/0267297	A1	12/2005	Berlin	
2006/0086653	A1	4/2006	St. Germain	
2006/0094658	A1	5/2006	Currie	
2007/0101158	A1	5/2007	Elliott	
2008/0137318	A1	6/2008	Rangaraj et al.	
2008/0151257	A1	6/2008	Yasuda et al.	
2009/0048175	A1	2/2009	Shailubhai et al.	
2009/0192083	A1	7/2009	Currie	
2009/0253634	A1	10/2009	Currie et al.	
2010/0048489	A1	2/2010	Fretzen	
2010/0069306	A1	3/2010	Shailubhai et al.	
2010/0093635	A1	4/2010	Shailubhai	
2010/0120694	A1	5/2010	Shailubhai et al.	
2010/0152118	A1	6/2010	Shailubhai	
2010/0221329	A1	9/2010	Shailubhai et al.	
2012/0196797	A1	8/2012	Currie et al.	
2012/0237593	A1	9/2012	Comiskey et al.	
2012/0289460	A1	11/2012	Shailubhai	
2013/0274204	A1	10/2013	Shailubhai et al.	
2014/0024605	A1	1/2014	Shailubhai et al.	
2014/0121169	A1	5/2014	Shailubhai et al.	
2014/0135274	A1	5/2014	Shailubhai	
2014/0187470	A1	7/2014	Jacob et al.	
2014/0287002	A1	9/2014	Shailubhai	
2014/0329738	A1	11/2014	Shailubhai et al.	
2015/0359749	A1	12/2015	Shailubhai et al.	
2015/0366935	A1	12/2015	Comiskey et al.	
2016/0367623	A1	12/2016	Shailubhai	
2017/0202903	A1	7/2017	Comiskey et al.	

FOREIGN PATENT DOCUMENTS

JP	2009-537535	A	10/2009	
JP	2010-519217	A	6/2010	
WO	WO 1988/005306	A1	7/1988	
WO	WO 1993/012068	A1	6/1993	
WO	WO 1999/026567	A1	6/1999	
WO	WO 2001/025266	A1	4/2001	
WO	WO 2002/062369	A2	8/2002	
WO	WO 2002/078683	A1	10/2002	
WO	WO 2002/098912	A3	12/2002	
WO	WO 2004/069165	A2	8/2004	
WO	WO 2005/087797	A1	9/2005	
WO	WO 2006/086653	A2	8/2006	
WO	WO 2007/022531	A2	2/2007	
WO	WO 2007/070562	A2	6/2007	
WO	WO 2007/101158	A2	9/2007	

WO	WO 2008/102264	A2	8/2008	
WO	WO 2008/106429	A2	9/2008	
WO	WO 2008/137318	A1	11/2008	
WO	WO 2008/151257	A2	12/2008	
WO	WO2008151257	A2 *	12/2008	
WO	WO 2009/149278	A1	12/2009	
WO	WO 2009/149279	A2	12/2009	
WO	WO 2010/009319	A2	1/2010	
WO	WO 2010/027404	A2	3/2010	
WO	WO 2010/065751	A2	6/2010	
WO	WO 2011/020054	A1	2/2011	
WO	WO 2012/037380	A2	3/2012	
WO	WO 2013/138352	A1	9/2013	

OTHER PUBLICATIONS

Barbara "A role for inflammation in irritable bowel syndrome": Gut, 51(Suppl. 1): 141-144 (2002).

Basoglu In: Proceedings of the Second FEPS Congress, Jun. 29-Jul. 4, 1999, Prague, Czech Republic, If2.cuni.cz/physiolres/feeps/basoglu.htm. (3 pages).

Baxter "The natriuretic peptides: An introduction" Basic Res. Cardiol. 99(2):71-75 (2004).

Beltowski "Guanlylin and related peptides" J. Physiol. Pharmacol 52(3):351-375 (2001).

Bergers "Extrinsic regulators of epithelial tumor progression: metalloproteinases" Cur. Opin. Gen. and Develop. 10:120-127 (2000).

Bhakdi "Release of interleukin-1 beta associated with potent cytotoxic action of staphylococcal alpha-toxin on human monocytes" Infect. Immun. 57(11): 3512-3519 (1989).

Brown "A receptor-mediated pathway for cholesterol homeostasis" Sci. 232:34-47 (1986).

Burnham "Polymers for delivering peptides and proteins" Am. J. Hosp. Pharm. 51:210-218 (1994).

Caliceti "Synthesis and biopharmaceutical characterisation of new poly(hydroxyethylaspartamide) copolymers as drug carriers" Biochimica et Biophysica Acta 1528:177-189 (2001).

Camilleri "Management of the irritable bowel syndrome" Gastroenterol. 120:652-668 (2001).

Carrithers, "Guanylyl cyclase C is a selective marker for metastatic colorectal tumors in human extraintestinal tissues" Proc. Natl. Acad. Sci. U.S.A. 93:14827-14832. (1996).

Cermak "Natriuretic peptides increase a K+ conductance in rat mesangial cells" Pflugers Arch. Eur. J. Physiol. 431:571-577 (1996).

Cheng "Defective intracellular transport and processing of CFTR is the molecular basis of most cystic fibrosis" Cell, 63:827-834 (1990).

Chino "Topological isomers of human uroguanylin: interconversion between biologically active and inactive isomers" FEBS Letters 421:27-31 (1998).

Cohen "Guanylin mRNA expression in human intestine and colorectal adenocarcinoma" Lab. Invest. 78:101-108 (1998).

Collins "The relationship of enteric microbial infection and functional bowel disorders" J. Clin. Gastroenterol 41 Suppl. 1:S30-32 (2007).

Cui The permissive effect of zinc deficiency on uroguanylin and inducible nitric oxide synthase gene upregulation in rat intestine induced by interleukin 1 α is rapidly reversed by zinc repletion. J. Nutri. 133(1):51-56 (2003).

Currie, "Guanylin: An endogenous activator of intestinal guanylate cyclase," Proc. Natl. Acad. Sci. U.S.A. 89:947-951 (1992).

Database Biosis (Online), biosciences Information Service, Philadelphia, PA, U.S., Apr. 2006, Refaat "SP304, an analog of uroguanylin, ameliorates inflammation in a model of experimental colitis" XP002540570, Database Accession No. PREV200600503788, 2 pages.

De Luca "Inflammation and insulin resistance" FEBS Letter 582:97-105 (2008).

Delvaux "Effect of alosetron on responses to colonic distension in patients with irritable bowel syndrome" Aliment Pharmacol. Ther 12:849-855 (1998).

Dennis "Off by a whisker" Nature 442:739-741 (2006).

DeSavage "Precursor structure, expression and tissue distribution

(56)

References Cited

OTHER PUBLICATIONS

- Deschner "Proliferative defects in ulcerative colitis patients" *Can. Invest* 1:41-47 (1983).
- Duncan "Drug-polymer Conjugates: Potential for improved chemotherapy" *Anti-Can. Drugs* 3:175-210 (1992).
- Dunfield "Energy parameters in polypeptides. 8. Empirical potential energy algorithm for the conformational analysis of large molecules" *J. Phys. Chem.* 82:2609-2616 (1978).
- Eastwood "Epithelial renewal in premalignant conditions of the gastrointestinal tract: A review" *J. Clin. Gastroenterol* 14(1):S29-S33 (1992).
- Ettorre "Mucosal changes in ileal pouches after restorative proctocolectomy for ulcerative and Crohn's colitis" *Dis. Colon Rectum* 43:1743-1748 (2000).
- European Application No. 02721604.3: Office Communication dated Aug. 12, 2008 (3 pages).
- European Application No. 02721604.3: Response to European Patent Office Communication dated Mar. 16, 2007 (5 pages).
- European Patent 1,379,224: CombiMab, Inc. Annex to Notice of Opposition dated Apr. 22, 2010 (41 pages).
- European Patent 1,379,224: Opposition dated Apr. 22, 2010 (19 pages).
- European Patent 1,379,224: Response to Communication from Opposition division dated Oct. 8, 2010 (44 pages).
- European Patent 1,379,224: Written submission dated Dec. 7, 2011 (6 pages).
- European Patent 1,379,224: Written submission dated Nov. 18, 2011 by Ironwood (14 pages).
- European Patent 1,379,224: Written submission dated Nov. 22, 2011 (18 pages).
- European Patent 1,379,224: Written submission dated Oct. 14, 2011 (7 pages).
- European Patent 1,379,224: Written submission dated Oct. 14, 2011 by Ironwood (27 pages).
- European Patent 1,379,224: Written submission dated Oct. 25, 2011 (5 pages).
- European Patent 1,379,224: Written submission dated Oct. 7, 2011 in response to the Jun. 24, 2011 preliminary opinion of the Opposition Division (7 pages).
- European Patent 1,379,224: Summons to attend oral hearing dated Jun. 24, 2011 (23 pages).
- European Patent Application No. 11825961.3, Extended European Search Report dated Jun. 30, 2016, 6 pages.
- Evan "Proliferation, cell cycle and apoptosis in cancer" *Nature (London)* 411:342-348 (2001).
- Fan "Structure and activity of uroguanylin and guanylin from the intestine and urine of rats" *Am. J. Physiol. Endocrinol. Metab.* 273:957-964 (1997).
- Field, "Ezetimibe interferes with cholesterol trafficking from the plasma membrane to the endoplasmic reticulum in CaCo-2 cells," *Journal of Lipid Research*, 48:1735-1745 (2007).
- FMC BioPolymer of Avicel PH Production Instruction, 21 pages (2005).
- Fonteles "Natriuretic and kaliuretic activities of guanylin and uroguanylin in isolated perfused rat kidney" *Am. J. Physiol. Renal Physiol.* 275: 191-197 (1998).
- Forte, "Guanylin regulatory peptides: structures, biological activities mediated by cyclic GMP and pathobiology," *Regul. Pept.*, 81.1-3: 25-39 (1999).
- Forte, Jr., "Uroguanylin and guanylin peptides: pharmacology and experimental therapeutics," *Pharmacol. Ther.* 104(2):137-162 (2004).
- Galt et al., "In Vivo Evaluation of an 111 in -Labeled ST-Peptide Analog for Specific-Targeting of Human Colon Cancers." *Nuc. Med. Biol.*, 28.8: 903-909 (2001).
- Garcia "Processing and characterization of human proguanylin expressed in *Escherichia coli*." *J. Biol. Chem.* 268:22397-22401 (1993).
- Genbank IUyBA- Chain A, Solution Structure B—Form uroguanylin. Mar. 15, 2010. 2 pages.
- Genbank AAB18760.1 (rat, 1995) Mar. 11, 2010. 2 pages.
- Genbank AAB30324.1 Guca2B (human, 1994) Mar. 11, 2010. 2 pages.
- Genbank AAC50416.1; GUCA2B (human, 1994) Mar. 11, 2010. 2 pages.
- Genbank: AAD09215.1 (mouse, 1996) Mar. 11, 2010. 2 pages.
- Genbank: CAA98994.1 (guinea pig, 1996) Mar. 11, 2010. 2 pages.
- Genbank: CAB0642.1 (pig, 1996) Mar. 11, 2010. 2 pages.
- Genbank: PRF.738946 (opossum, 1993) Mar. 15, 2010. 1 page.
- Greenberg "Comparison of effects of uroguanylin, guanylin, and *Escherichia coli* heat-stable enterotoxin Sta mouse intestine and kidney: evidence that uroguanylin is an intestinal natriuretic hormone" *J. Invest. Med.* 45(5):276-282 (1997).
- Guba et al., "Guanylin Strongly Stimulates Rat Duodenal HCO₃-Secretion: Proposed Mechanism and Comparison With Other Secretagogues." *Gastroenterology*, 111.6: 1558-1568 (1996).
- Gulcan "Increased frequency of prediabetes in patients with irritable bowel syndrome" *Am. J. Med. Sci* 338:116-119 (2009).
- Gulcan The predictive value of CRP levels on future severe renal disease in overweight and obese subjects without diabetes mellitus and hypertension. *Am. J. Med. Sci* 334:444-451 (2007).
- Gura, "Systems for Identifying New Drugs Are Often Faulty," *Science* 278:1041-1042 (1997).
- Hamman et al., "Oral Delivery of Peptide Drugs." *Biodrugs*, 19.3: 165-177 (2005).
- Hamra et al., "Uroguanylin: Structure and Activity of a Second Endogenous Peptide That Stimulates Intestinal Guanylate Cyclase." *PNAS*, 90.22: 10464-10468 (1993).
- Harris et al., "Drug Evaluation: Linaclotide, a New Direction in the Treatment of Irritable Bowel Syndrome and Chronic Constipation." *Curr. Opin. Mol. Ther.*, 9.4: 403-410 (2007).
- Hess, "GCAP-II: isolation and characterization of the circulating form of human uroguanylin." *FEBS Letters* 374:34-38 (1995).
- Hidaka "Dual Function of the Propeptide of Prouroguanylin in the Folding of the Mature Peptide" *J. Biol. Chem.* 275:25155-25162 (2000).
- Hidaka "In Vitro Disulfide-Coupled Folding of Guanylyl Cyclase-Activating Peptide and Its Precursor Protein" *Biochem.* 37:8498-8507 (1998).
- Hill, "Analysis of the human guanylin gene and the processing and cellular localization of the peptide" *Proc. Natl. Acad. Sci U.S.A.* 92:2046-2050 (1995).
- Hill et al., "A New Human Guanylate Cyclase-Activating Peptide (GCAP-II, Uroguanylin): Precursor cDNA and Colonic Expression." *Biochim. Biophys. Acta.*, 1253: 146-149 (1995).
- Hinds "Synthesis and Characterization of Poly (ethylene glycol)—Insulin Conjugates" *Bioconjug. Chem.* 11:195-201 (2000).
- Howard "Obesity and dyslipidemia" *Endocrinol. Metab. Clin. N. Am.* 32:855-867 (2003).
- http://www.merckmanuals.com/home/childrens_health_issues/hereditary_metabolic_disorders/disorders_of_Lipid_metabolism.html: last updated 2009; last visited Sep. 25, 2012 (1 page).
- <http://www.nlm.nih.gov/medlineplus/obesity.html>: 1999-2011; last visited Sep. 25, 2012 (6 pages).
- Hudson "Rethinking cystic fibrosis pathology: the critical role of abnormal reduced glutathione (GSH) transport caused by CFTR mutation" *Free Rad. Biol. Med.* 30:1441-1461 (2001).
- Huff, "Inhibition of the Apical Sodium-Dependent Bile Acid Transporter Reduces LDL Cholesterol and ApoB by Enhanced Plasma Clearance of LDL ApoB," *Arterioscler. Thromb. Vasc. Biol* 22:1884-1891 (2002).
- Hughes "Intracellular K⁺ suppresses the activation of apoptosis in lymphocytes" *J. Biol. Chem* 272(48):30567-30576 (1997).
- Hui, "Developmental and Physiological Regulation of Intestinal Lipid Absorption. III. Intestinal transporters and cholesterol absorption." *Am. J. Physiol. Gastrointest. Liver Physiol.* 294:G839-G843 (2008).
- International Preliminary Report on Patentability, PCT Appl. No. PCT/US2011/051805, 17 pages (dated Dec. 15, 2012).

(56)

References Cited

OTHER PUBLICATIONS

- International Search Report in International Application No. PCT/US2009/046287, 5 pages (dated Nov. 10, 2009).
- International Search Report in International Application No. PCT/US2009/046288, 9 pages (dated Dec. 9, 2009).
- International Search Report, PCT Appl. No. PCT/US2011/051805, 6 pages (dated Jun. 21, 2012).
- International Search Report, PCT Appl. No. PCT/US2013/030551, 5 pages (dated Jun. 18, 2013).
- Joo et al., "Regulation of Intestinal Cl and HCO₃ Secretion by Uroguanylin." *Am. J. Physiol.*, 274.4: G633-G644 (1998).
- Kelland "Of mice and men": values and liabilities of the athymic nude mouse model in anticancer drug development" *Eur. J. Cancer* 40(6):827-836 (2004).
- Kita :Characterization of human uroguanylin: A member of the guanylin peptide family *Am. J. Physiol.* 266:F342-8 (1994).
- Klodt , "Synthesis, biological activity and isomerism of guanylate cyclase C-activating peptides guanylin and uroguanylin," *J. Pep. Res.* 50(2):222-230 (1997).
- Krause "The guanylin and uroguanylin peptide hormones and their receptors" *Acta Anat.* 160:213-231 (1997).
- Lai and Topp, "Solid-State Chemical Stability of Proteins and Peptides", *Journal of Pharmaceutical Sciences, MiniReview*, 88(5): 489-500 (1999).
- Lam "Serotonin and energy balance: molecular mechanisms and implications for type 2 diabetes" *Expert Rev. Mol. Med.* 9:1-24 (2007).
- Leister "Human colorectal cancer: High frequency of deletions at chromosome 1p35" *Can. Res.* 50:7232-7235 (1990).
- Li "Purification, cDNA sequence and tissue distribution of rat uroguanylin" *Reg. Pep.* 68:45-56 (1997).
- Li and Chiang, "Bile Acid Signaling in Liver Metabolism and Diseases", *Journal of Lipids, Hindawi Publishing Corporation*, 2012:1-9, Article ID 754067 (2011).
- Lipkin "Gastric cell regeneration" *Arch. Fr. Mal. Appl. Dig. (Paris)* 61(10-11):691-693 (1972).
- Lorenz "Uroguanylin knockout mice have increased blood pressure and impaired natriuretic response to enteral NaCl load" *J. Clin. Invest.* 112(8):1244-1254 (2003).
- MacFarlane and MacFarlane, "Factors affecting fermentation reactions in the large bowel," *Proc. Nutr. Soc.* 52(2):367-373 (1993).
- Magert Porcine guanylin and uroguanylin: cDNA sequences, deduced amino acid sequences, and biological activity of the chemically synthesized peptides' *Biochem. Biophys. Res. Comm.* 259:141-148 (1999).
- Mahato et al., "Emerging Trends in Oral Delivery of Peptide and Protein Drugs." *Crit. Rev. Therapeutic Drug Carrier Sys.*, 20.2-3: 153-214 (2003).
- Marx et al., "One Peptide, Two Topologies: Structure and Interconversion Dynamics of Human Uroguanylin Isomers." *J. Pept. Res.*, 52: 229-240 (1998).
- Mihranyan et al., "Moisture sorption by cellulose powders of varying crystallinity", *International Journal of Pharmaceutics*, 269(2): 433-442 (2004).
- Miyazato "Uroguanylin gene expression in the alimentary tract and extra-gastrointestinal tissues" *FEBS Letters*, 398:170-174 (1996).
- Miyazato "Cloning and characterization of a cDNA encoding a precursor for human uroguanylin" *Biochem Biophys Res. Comm.* 219:644-648 (1996).
- Moon "Effects of age, ambient temperature, and heat-stable *Escherichia coli* enterotoxin of intestinal transit in infant mice" *Infect. Immun.* 25(1):127-132 (1979).
- Muller-Lissner "Safety, tolerability, and efficacy of tegaserod over 13 months in patients with chronic constipation" *Am. J. Gastroenterol.* 101:2558-2569 (2006).
- Nakazato "Tissue distribution, cellular source, and structural analy-
- Nathan "Copolymers of lysine and polyethylene glycol: a new family of functionalized drug carriers" *Bioconjug Chem.* 4(1):54-62 (1993).
- Nemethy "Energy parameters in polypeptides. 9. Updating of geometrical parameters non-bonded interactions, and hydrogen bond interactions for the naturally occurring amino acids" *J. Phys. Chem.* 87:1883-1887 (1983).
- Nikiforovich "Computation molecular modeling in peptide design" *Int. J. Pep. Prot. Res.* 44:513-531 (1994).
224. Nikiforovich "Topographical requirements for δ -selective opioid peptides" *Biopolymers*, 31:942-955 (1991).
- Nyburg "Some uses of best molecular fit routine" *Acta Crystallographica B30 (Part 1):251-253 (1974).*
- Ohbayashi , "Effects of uroguanylin and guanylin against antigen-induced bronchoconstriction and airway microvascular leakage in sensitized guinea-pigs" *Life Sci.*, 62(20):1883-1844 (1998).
- PCT/US2009/066600, International Preliminary Report on Patentability dated Aug. 2, 2011, 8 pages.
- Perkins "Uroguanylin is expressed by enterochromaffin cells in the rat gastrointestinal tract" *Gastroenterol* 113:1007-1014 (1997).
- Peterson "Integrating pharmacology and in vivo cancer models in preclinical and clinical drug development" *Eur. J. Cancer* 40:837-844 (2004).
- Pitari "Guanylyl cyclase C agonists regulate progression through the cell cycle of human colon carcinoma cells", *Proc. Natl. Acad. Sci. USA* 98(14):7546-7851 (2001).
- Potten "Regulation and significance of apoptosis in the stem cells of the gastrointestinal epithelium" *Stem Cells* 15:82-93 (2001).
- Provenzale "Surveillance issues in inflammatory bowel disease: ulcerative colitis" *J. Clin. Gastroenterol* 32:99-105 (2001).
- PubChem, CID 469, <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=469#x27>, (last visited Oct. 18, 2014). 19 pages.
- Ramamoorthy "Phosphorylation of threonine residue 276 is required for acute regulation of serotonin transporter by cyclic GMP" *J. Biol. Chem.* 282(16):11639-11647 (2007).
- Reddy and Rao "Lipid metabolism and liver inflammation II fatty liver disease and fatty acid oxidation" *Am. J. Physiol. Gastrointest. Liver Physiol.* 290:G852-G858 (2006).
- Refaat et al., "Sp304, an analog of uroguanylin, ameliorates inflammation in a model of experimental colitis", *Digestive Disease Week Conference, Abstract, May 2006.*
- Remington, JP "Remington's Pharmaceutical Sciences" Mack Pub. Co. 16th edition (1980) 7 pages.
- Roberts "Chemistry of peptide and protein PEGylation" *Adv. Drug. Deliv. Rev.* 54:459-476 (2002).
- Rolfé and Milla, "Nitric oxide stimulates cyclic guanosine monophosphate production and electrogenic secretion in Caco-2 colonocytes," *Clin. Sci. (Lond)*. 96(2):165-170 (1999).
- Samuel "Absorption of bile acids from the large bowel in man" *J. Clin. Invest.* 47:2070-2978 (1968).
- Schulz et al., "Guanylyl Cyclase is a Heat-Stable Enterotoxin Receptor." *Cell*, 63.5: 941-948 (1990).
- Schulz et al., "Side Chain Contributions to the Interconversion of the Topological Isomers of Guanylin-Like Peptides." *J. Peptide Sci.*, 11.6: 319-330 (2005).
- Sciaky "Mapping of guanylin to murine chromosome 4 and human chromosome 1p34p35" *Genomics* 26:427-429 (1995).
- Sellers "heat-stable enterotoxin of *Escherichia coli* stimulates a non-CFTR-mediated duodenal bicarbonate secretory pathway" *Am J. Physiol. Gastrointest. Liver Physiol.* 288:G654-G663 (2005).
- Shailubhai "Guanilib, an antagonist of guanylate C, is a new class of oral drug candidate that ameliorates inflammation in models of experimental colitis" [Abstract]: in Charon's and colitis foundation of America (2007) 1 page.
- Shailubhai "Guanilib, an agonist of Guanylate C, is a new class of oral drug candidate for GI disorders and colon cancer" [abstract] in *GTCbio*, 2008. 1 page.
- Shailubhai "Guanylate cyclase-C agonists as a new class of drug candidates for GI motility and inflammatory bowel disease" [Abstract] 2009 (1 page).

(56)

References Cited

OTHER PUBLICATIONS

- Shailubhai "Inflammatory bowel disease" Feb. 2008: S5 2007 IBD Abstract: Oral Presentation (1 page).
- Shailubhai "Phase II Clinical Evaluation of SP-304, a Guanylate Cyclase-C Agonist, for Treatment of Chronic Constipation," *Am. J. Gastroenterol.* 105(Suppl. 1):S487-S488 (2010).
- Shailubhai "SP-304 to treat GI disorders—effects of a single, oral dose of SP-304 in safety, tolerability, pharmacokinetics and pharmacodynamics in healthy volunteers" [Abstract]: in *Digestive Disease Week*, (2009) 1 page.
- Shailubhai "Therapeutic applications of guanylate cyclase-c receptor agonists" *Curr. Opin. Drug Disc. Devel.* 5(2):261-268 (2002).
- Shailubhai et al., "Uroguanylin Treatment Suppresses Polyp Formation in the ApcMin/+ Mouse and Induces Apoptosis in Human Colon Adenocarcinoma Cells via Cyclic GMP." *Cancer Res.*, 60: 5151-5157 (2000).
- Shinozaki "High proliferative activity is associated with dysplasia in ulcerative colitis" *Dis. Colon Rectum* 43:S34-S39 (2000).
- Sindice "Guanylin, Uroguanylin, and Heat-stable Enterotoxin Activate Guanylate Cyclase C and/or a Pertussis Toxin-sensitive G Protein in Human Proximal Tubule Cells". *J. Biol. Chem.* 277:17758-17764 (2002).
- Spranger "Inflammatory cytokines and the risk to develop Type 2 Diabetes: Results of the prospective population-based European prospective investigation into cancer and nutrition (EPIC)-Potsdam study" *Diabetes*, 52:812-817 (2003).
- St. John's Providence Health Center; Preventing Obesity, <http://www.stjohnprovidence.org/healthInfoLib/swArticle.aspx?85.P07863>; last visited Sep. 25, 2012 (2 pages).
- Takada , "Alteration of a Single Amino Acid in Peroxisome Proliferator-Activated Receptor- α (PPAR α) Generates a PPAR δ Phenotype" *Mol. Endocrinol.* 14(5):733-740 (2000).
- Talley "Medical costs in community subjects with irritable bowel syndrome" *Gastroenterol.* 109:1736-1741 (1995).
- Thomas , "Cholesterol dependent downregulation of mouse and human apical sodium dependent bile acid transporter (ASBT) gene expression: molecular mechanism and physiological consequences," *GUT* 55:1321-1331 (2006).
- Tian "STa peptide analogs for probing guanylyl cyclase C" *Biopolymers (Pept. Sci.)* 90(5):713-723 (2008).
- Tilg "Inflammatory mechanisms in the regulation of insulin resistance" *Mol. Med.* 14:222-231 (2008).
- Vaandrager, "Structure and Function of the Heat-Stable Enterotoxin Receptor/Guanylyl Cyclase C." *Mol. Cell. Biochem.*, 230.1-2: 73-83 (2002).
- Variyam, "Luminal bacteria and proteases together decrease adherence of *Entamoeba histolytica* trophozoites to Chinese hamster ovary epithelial cells: A novel host defense against an enteric pathogen," *GUT* 39(4):521-527 (1996).
- Venkatakrishnan Exaggerated activation of nuclear factor-B and altered I B-processing in cystic fibrosis bronchial epithelial cells. *Am. J. Resp. Cell Mol. Biol.* 23(3):396-403 (2000).
- Veronese "Bioconjugation in pharmaceutical chemistry" *Farmaco*, 54:497-516 (1999).
- Veronese "PEGylation, successful approach to drug deliver?" *Drug. Disc. Today.* 10(21):1451-1458 (2005).
- Veronese "Peptide and protein PEGylation: a review of problems and solutions" *Biomaterial*, 22:405-417 (2001).
- Waldman "Heterogeneity of guanylyl cyclase C expressed by human colorectal cancer cell lines in vitro" *Can. Epidemiol. Biomarkers & Prevention* 7:505-514 (1998).
- Weber "Activation of NF- κ B in airway epithelial cells is dependent on CFTR trafficking and Cl channel function" *Am. J. Physiol. Lung Cell Mol. Biol.* 281(1):L71-78 (2001).
- Welsh "Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis" *Cell* 73:1251-1254 (1993).
- Whitaker "The uroguanulin gene (Buca1b) is linked to guanylin (Guca2) on mouse chromosome 4" *Genomics* 45:348-354 (2002).
- Wong "Cell proliferation in gastrointestinal mucosa" *J. Clin. Pathol.* 52:321-333 (1999).
- Wong "Histogenesis of human colorectal adenomas and hyperplastic polyps: the role of cell proliferation and crypt fission" *Gut* 50:212-217 (2002).
- Written Opinion of the International Searching Authority, PCT Appl. No. PCT/US2011/051805, 5 pages (dated Jun. 21, 2012).
- Written Opinion of the International Searching Authority, PCT Appl. No. PCT/US2013/030551, 6 pages (dated Jun. 18, 2013).
- Wu "Atrial natriuretic peptide induces apoptosis in neonatal rat cardiac myocytes" *J. Biol. Chem.* 272(23):14860-14866 (1997).
- Zhang "Gene expression profiles in normal and cancer cells" *Science* 276:1268-1272 (1997).
- Zimmerman "Influence of local interactions on protein structure. I. Conformational energy studies of N-acetyl-N-methylamides of pro-X and X-pro dipeptides" *Biopolymers*, 16:811-843 (1977).

* cited by examiner

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.