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# (54) METHODS AND COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS

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- (52) U.S. Cl. ...... 514/21.5; 530/327

(2006.01)

#### (56) References Cited

#### U.S. PATENT DOCUMENTS

| 5,140,102    | A  | 8/1992  | Currie            |
|--------------|----|---------|-------------------|
| 5,395,490    | A  | 3/1995  | Hoff              |
| 5,489,670    | A  | 2/1996  | Currie et al.     |
| 5,969,097    | A  | 10/1999 | Wiegand et al.    |
| 6,060,037    | Α  | 5/2000  | Waldman           |
| 7,304,036    | B2 | 12/2007 | Currie et al.     |
| 7,371,727    | B2 | 5/2008  | Currie et al.     |
| 7,704,947    | B2 | 4/2010  | Currie et al.     |
| 7,745,409    | B2 | 6/2010  | Currie et al.     |
| 7,772,188    | B2 | 8/2010  | Currie et al.     |
| 7,910,546    | B2 | 3/2011  | Currie et al.     |
| 2003/0073628 | A1 | 4/2003  | Shailubhai et al. |
| 2003/0232013 | A1 | 12/2003 | Siechman et al.   |
| 2004/0121961 | A1 | 6/2004  | Masferrer         |
| 2004/0152868 | A1 | 8/2004  | Larsen et al.     |
| 2004/0258687 | A1 | 12/2004 | Waldman et al.    |
| 2004/0266989 | A1 | 12/2004 | Currie et al.     |
| 2005/0032684 | A1 | 2/2005  | Cetin et al.      |
| 2006/0281682 | A1 | 12/2006 | Currie et al.     |
| 2009/0191611 | A1 | 7/2009  | Currie et al.     |

#### FOREIGN PATENT DOCUMENTS

| EP | 1012188        | 6/2000  |
|----|----------------|---------|
| WO | WO 99/14239    | 3/1999  |
| WO | WO 01/25266    | 4/2001  |
| WO | WO 02/062369   | 8/2002  |
| WO | WO 02/078683   | 10/2002 |
| WO | WO 02/079235   | 10/2002 |
| WO | WO 02/098912   | 12/2002 |
| WO | WO 03/072125   | 9/2003  |
| WO | WO 03/072754   | 9/2003  |
| WO | WO 2004/069165 | 8/2004  |
| WO | WO 2004/071436 | 8/2004  |
| WO | WO 2005/087797 | 9/2005  |

#### OTHER PUBLICATIONS

Amarante et al., "The k-opioid agonist (+)-bremazocine elicits peripheral antinociception by activation of the L-arginine/nitric oxide/cyclic GMP pathway" European Journal of Pharmacology, vol. 454: pp. 19-23 (2002).

Arita et al., "Purification and characterization of a heat-stable enterotoxin of *Vibrio mimicus*" FEMS Microbiology Letters, vol. 79/1: pp. 105-110 (1991).

Camilleri "Management of the Irritable Bowel Syndrome" Gastroenterology 120: 652-668 (2001).

Chan et al., "Amino Acid Sequence of Heat-stable Enterotoxin Produced by *Escherichia coli* Pathogenic for Man" The Journal of Biological Chemistry, vol. 256, No. 15: pp. 7744-7746 (1981).

Drossman, D.A., "The functional gastrointestinal disorders and the Rome II process" GUT 45: Supplement II: pp. 111-113 (1999).

Drossman, D.A., "Psychosocial aspects of the functional gastrointestinal disorders" GUT 45: Supplement II: pp. 1125-1130 (1999).

Drossman et al., "U.S. Householder Survey of Functional Gastrointestinal Disorders" Digestive Diseases and Sciences 38(9): pp. 1569-1580 (1993).

Forte et al., "Lymphoguanylin: Cloning and Characterization of a Unique Member of the Guanylin Peptide Family" Endocrinology, vol. 140, No. 4: pp. 1800-1806 (1999).

Forte et al., "Uroguanylin and guanylin peptides; pharmacology and experimental therapeutics", Pharmacology & Therapeutics, vol. 104: pp. 137-162 (2004).

#### (Continued)

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(74) Attorney, Agent, or Firm — Honigman Miller Schwartz
and Cohn LLP; Kelly T. Murphy; Jonathan P. O'Brien

#### (57) ABSTRACT

The present invention features compositions and related methods for treating IBS and other gastrointestinal disorders and conditions (e.g., gastrointestinal motility disorders, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), Crohn's disease, ulcerative colitis, Inflammatory bowel disease, functional heartburn, dyspepsia (including functional dyspepsia or nonulcer dyspepsia), gastroparesis, chronic intestinal pseudo-obstruction (or colonic pseudo-obstruction), and disorders and conditions associated with constipation, e.g., constipation associated with use of opiate pain killers, post-surgical constipation, and constipation associated with neuropathic disorders as well as other conditions and disorders using peptides and other agents that activate the guanylate cyclase C (GC-C) receptor.



#### OTHER PUBLICATIONS

Giannela, "Escherichia coli heat-stable enterotoxins, guanylins, and their receptors: What are they and what do they do?" The Journal of Laboratory and Clinical Medicine, vol. 125, No. 2: pp. 173-181 (1995).

Gualillo et al., "Ghrelin, a widespread hormone: insights into molecular and cellular regulation of its expression and mechanism of action" FEBS Letters, vol. 552: pp. 105-109 (2003).

Guarino et al., "Citrobacter freundii Produces an 18-Amino-Acid Heat-Stable Enterotoxin Identical to the 18-Amino-Acid Escherichia coli Heat-Stable Enterotoxin (ST la)" Infection and Immunity, vol. 57, No. 2: pp. 649-652 (1989).

Hasegawa et al. "Identification of a binding region on *Escherichia coli* heat-stable enterotoxin to intestinal guanylyl cyclase C," Letters in Peptide Sci., 4, pp. 1-11 (1997).

Hasegawa et al. "Determination of the binding site on the extracellular domain of guanylyl cyclase C to heat-stable enterotoxin," J of Biol. Chem., 274(44), pp. 31713-31718 (1999).

Huang et al., "Nucleotide sequence of a gene encoding the novel *Yersinia enterocolitica* heat-stable enterotoxin that includes a proregion-like sequence in its mature toxin molecule" Microbial Pathogenesis, vol. 22: pp. 89-97 (1997).

Jain et al., "Sildenafil-induced peripheral analgesia and activation of the nitric oxide-cyclic GMP pathway" Brain Research, vol. 909: pp. 170-178 (2001).

Kim et al., "Changes in ghrelin and ghrelin receptor expression according to feeding status" NeuroReport, vol. 14, No. 10: pp. 1317-1320 (2003)

Lazaro-Ibanez et al., "Participation of the nitric oxide-cyclic GMP-ATP-senstive K+ channel pathway in the antinociceptive action of ketorolac" European Journal of Pharmacology, vol. 426: pp. 39-44 (2001).

Moseley et al., "Isolation and Nucleotide Sequence Determination of a Gene Encoding a Heat-Stable Enterotoxin of *Escherichia coli*" Infection and Immunity, vol. 39, No. 3: pp. 1167-1174 (1983).

Nzegwu et al., "Luminal capsaicin inhibits fluid secretion induced by exterotoxin *E. coli* STa, but not by carbachol, in vivo in rat small and large intestines" Experimental Physiology, vol. 81, No. 2: pp. 313-315 (1996).

Ringel et al., "Irritable Bowel Syndrome" Annual Review of Medicine, vol. 52: pp. 319-338 (2001).

Rolfe et al., "Enterotoxin *Escherichia coli* STa activates a nitric oxide-dependent myenteric plexus secretory reflex in the rat ileum" The Journal of Physiology, vol. 475, No. 3: pp. 531-537 (1994).

Rolfe et al., "Vagotomy inhibits the jejunal fluid secretion activated by luminal ileal *Escherichia coli* STa in the rat in vivo" GUT, vol. 44: pp. 615-619 (1999).

Santos-Neto et al., "Guanylin and its Lysine-Containing Analogue in the Isolated Perfused Rat Kidney" Pharmacology & Toxicology, vol. 92: pp. 114-120 (2003).

Shailubhai, "Therapeutic applications of guanylate cyclase-C receptor agonists" Drug Discovery & Development, vol. 5, No. 2: pp. 261-268 (2002).

So et al., "Nucleotide Sequence of the Bacterial Transposon Tn1681 Encoding a Heat-Stable (ST) Toxin and Its Identification in Enterotoxigenic *Escherichia coli* Strains" Proceedings of the National Academy of Sciences of the USA, vol. 77, No. 7 [Part 2: Biological Sciences]: pp. 4011-4015 (1980).

Soares et al., "Dibutyryl-cyclic GMP induces peripheral antinociception via activation of ATP-sensitive K+ channels in the RAT PGE2-induced hyperalgesic paw" British Journal of Pharmacology, vol. 134: pp. 127-131 (2001).

Takao et al., "Amino acid sequence of heat-stable enterotoxin produced by Vibrio cholerae non-01" FEBS, vol. 193, No. 2: pp. 250-254 (1985).

Takao et al., "Isolation, primary structure and synthesis of heat-stable enterotoxin produced by Yersinia enterocolitica" European Journal of Biochemistry, vol. 152, No. 1: pp. 199-206 (1985).

Talley et al., "Irritable Bowel Syndrome in a Community: Symptom Subgroups, Risk" American Journal of Epidemiology vol. 142(1): pp. 76-83 (1995).

Talley et al., "Medical Costs in Community Subjects with Irritable Bowel Syndrome" Gastroenterology vol. 109(6): pp. 1736-1741 (1995).

Vaandrager et al., "Structure and function of the heat-stable enterotoxin receptor/guanylyl cyclase C" Molecular and Cellular Biochemistry, vol. 230, Nos. 1&2: pp. 73-83 (2002).

Yoshimura et al., "Essential structure for full enterotoxigenic activity of heat-stable enterotoxin produced by enterotoxigenic *Escherichia coli*," FEBS Letters, 181(1), pp. 138-142 (1985).

GenBank Accession No. QHECIB; GI:69638; Aimoto et al., Jun. 18, 1999.

GenBank Accession No. P01559; GI:123711; So et al., Oct. 25, 2004. GenBank Accession No. AAA24653; GI:147878; Sekizaki et al., Apr. 26, 1993.

GenBank Accession No. P01560; GI:123707; Chan et al., Jun. 15, 2004.

GenBank Accession No. AAA27561; GI:295439; Ogawa et al., Jun. 12, 1993.

GenBank Accession No. P04429; GI:123712; Ogawa et al., Jun. 15, 2004

GenBank Accession No. S34671; GI:421286; Rossolini et al., Apr. 12, 1995.

GenBank Accession No. CAA52209; GI:395161; Guglielmetti et al., Jul. 27, 1995.

GenBank Accession No. A54534; GI:628844; Arita et al., May 3,

GenBank Accession No. AAL02159; GI:15592919; Teixeira et al., Sep. 13, 2001.

GenBank Accession No. AAA18472; GI:487395; Mikulskis et al., May 26,1994.

GenBank Accession No. S25659; GI:282047; Takao et al., Oct. 15, 1999

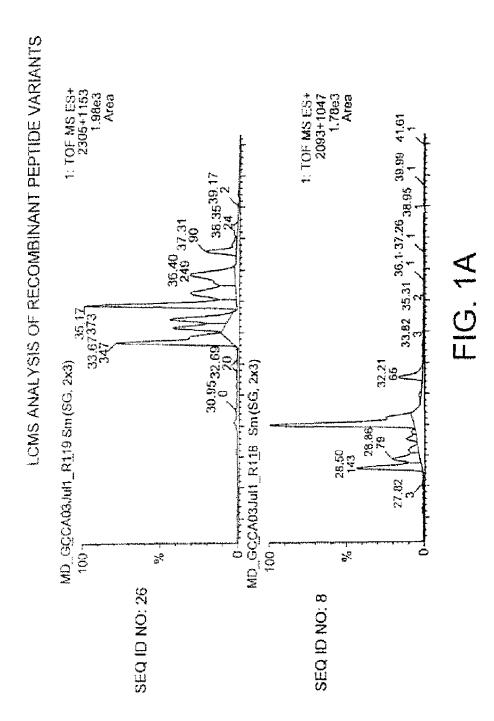
GenBank Accession No. P74977; GI:3913874; Ramamurthy et al., Jun. 15, 2004.

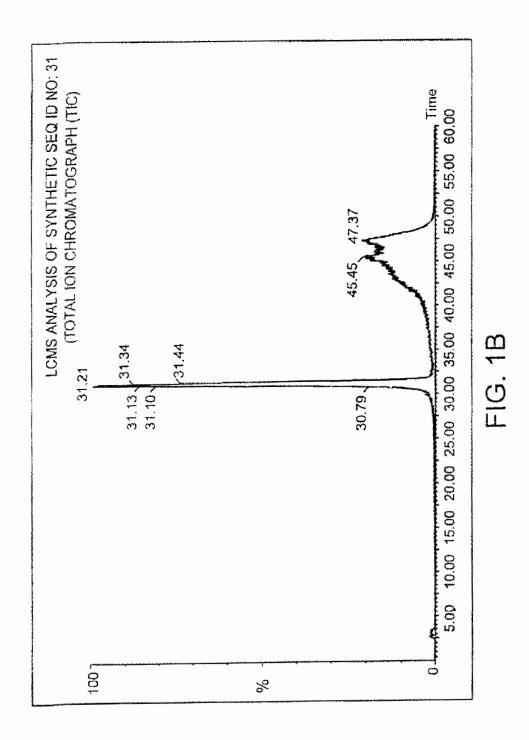
GenBank Accession No. BAA23656; GI:2662339; Huang et al., Feb. 13, 1999.

GenBank Accession No. P31518; GI:399947; Ibrahim et al., Mar. 15, 2004.

GenBank Accession No. P07965; GI:3915589; Steiglitz et al., Jun. 15, 2004.

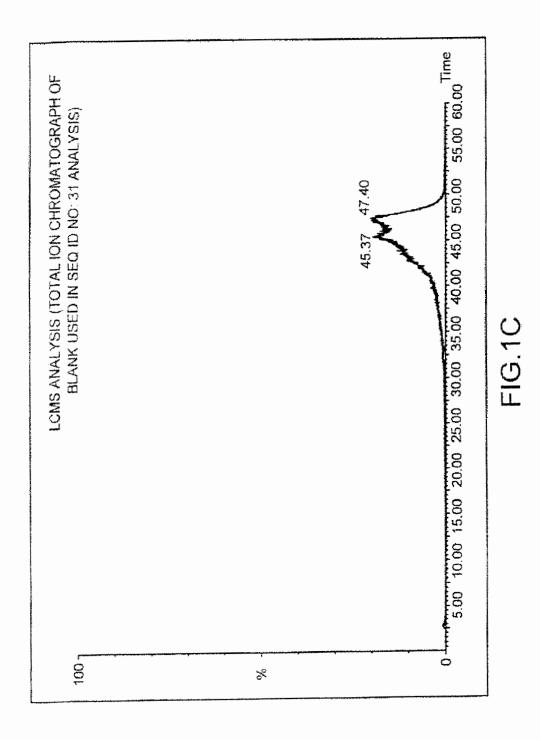








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