



US007704947B2

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

(10) **Patent No.:** **US 7,704,947 B2**
(45) **Date of Patent:** ***Apr. 27, 2010**

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

(75) Inventors: **Mark G. Currie**, Sterling, MA (US); **Shalina Mahajan-Miklos**, Stanford, CA (US); **Thea Norman**, San Diego, CA (US); **G. Todd Milne**, Brookline, MA (US)

(73) Assignee: **Ironwood Pharmaceuticals, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 51 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/930,696**

(22) Filed: **Oct. 31, 2007**

(65) **Prior Publication Data**

US 2009/0005534 A1 Jan. 1, 2009

Related U.S. Application Data

(62) Division of application No. 10/766,735, filed on Jan. 28, 2004, now abandoned.

(60) Provisional application No. 60/443,098, filed on Jan. 28, 2003, provisional application No. 60/471,288, filed on May 15, 2003, provisional application No. 60/519,460, filed on Nov. 12, 2003.

(51) **Int. Cl.**
C07K 7/08 (2006.01)

(52) **U.S. Cl.** **514/2; 530/327**

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

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,140,102	A	8/1992	Currie	530/326
5,395,490	A	3/1995	Hoff	204/132
5,489,670	A	2/1996	Currie et al.	530/326
5,969,097	A	10/1999	Wiegand et al.	530/326
6,060,037	A	5/2000	Waldman	424/1.65
7,304,036	B2	12/2007	Currie et al.	
7,371,727	B2*	5/2008	Currie et al.	514/14
2003/0073628	A1	4/2003	Shailubhai et al.	514/12
2003/0232013	A1	12/2003	Siechman et al.	424/1.69
2004/0121961	A1	6/2004	Masferrer	514/15
2004/0152868	A1	8/2004	Larsen et al.	530/317
2004/0258687	A1	12/2004	Waldman et al.	424/143.1
2004/0266989	A1	12/2004	Currie et al.	530/326
2005/0032684	A1	2/2005	Cetin et al.	514/12
2006/0281682	A1	12/2006	Currie et al.	
2008/0227685	A1	9/2008	Currie et al.	
2009/0062207	A1	3/2009	Currie et al.	
2009/0191611	A1	7/2009	Currie et al.	

FOREIGN PATENT DOCUMENTS

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	WO03/072754	9/2003
WO	WO2004/069165	8/2004
WO	WO 2004/071436	8/2004
WO	WO2005/087797	9/2005

OTHER PUBLICATIONS

Amarante et al., "The κ -opioid agonist (\pm)-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).

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).

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

Giannela, "*Escherichia coli* heat-stable enterotoxins, guanylin, 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).

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

(Continued)

Primary Examiner—Christopher R. Tate

Assistant Examiner—Roy Teller

(74) *Attorney, Agent, or Firm*—Honigman Miller Schwartz and Cohn LLP; Kelly T. Murphy; Johnathan 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

- 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-sensitive 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 enterotoxin *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).
- 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).
- 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 Science of the U.S.A.*, vol. 77, No. 7 [Part 2: Biological Sciences]: pp. 4011-4015 (1980).
- Soares, et al., "Dibutyl-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).
- 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).
- 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, 2001.
- GenBank Accession No. A54534; GI:628844; Arita et al., May 3, 1996.
- 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; Stieglitz et al., Jun. 15, 2004.
- Camilleri, "Management of the Irritable Bowel Syndrome" *Gastroenterology* 120:652-668, 2001.
- Drossman, D.A., "The functional gastrointestinal disorders and the Rome II process" *Gut* 45:Supp. 11:111-113, 1999.
- Drossman, D.A., "Psychosocial aspects of the functional gastrointestinal disorders" *Gut* 45:Supp. 11:1125-1130, 1999.
- Drossman et al., "U.S. Householder Survey of Functional Gastrointestinal Disorders" *Digestive Diseases and Sciences* 38(9):1569-1580, 1993.
- Ringel, et al., "Irritable Bowel Syndrome" *Annu. Rev. Med.* 52:319-38, 2001.
- Santos-Neto, et al., "Guanylin and its Lysine-Containing Analogue in the Isolated Perfused Rat Kidney" *Pharmacol. & Toxicol.* 92:114-120, 2003.
- Talley, et al., "Irritable Bowel Syndrome. In a Community: Symptom Subgroups, Risk." *Am. J. of Epidemiology* 142(1):76-83, 1995.
- Talley, et al., "Medical Costs in Community Subjects with Irritable Bowel Syndrome" *Gastroenterology* 109(6):1736-1741, 1995.
- Abandonment for U.S. Appl. No. 10/766,735 dated Nov. 28, 2007.
- Abandonment for U.S. Appl. No. 10/845,895 dated Mar. 09, 2009.
- Office Action for U.S. Appl. No. 11/054,071 dated Jul. 6, 2009.
- Notice of Allowance for U.S. Appl. No. 11/949,340 dated Sep. 3, 2009.
- Forte, L., "Uroguanylin and guanylin peptides; pharmacology and experimental therapeutics", *Pharmacology & Therapeutics*, vol. 104, (2004), pp. 137-162.

* cited by examiner

LCMS ANALYSIS OF RECOMBINANT PEPTIDE VARIANTS

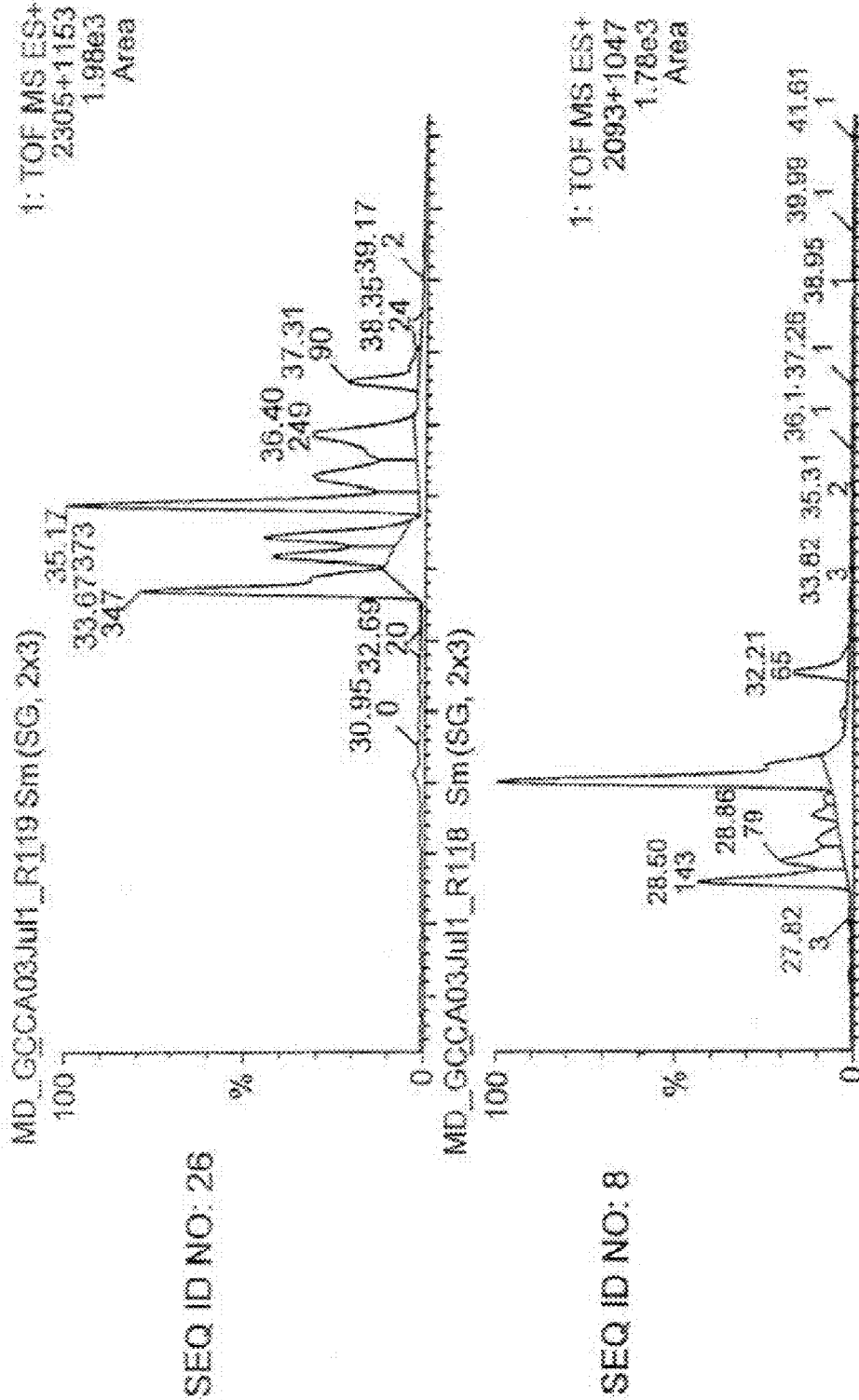


FIG. 1A

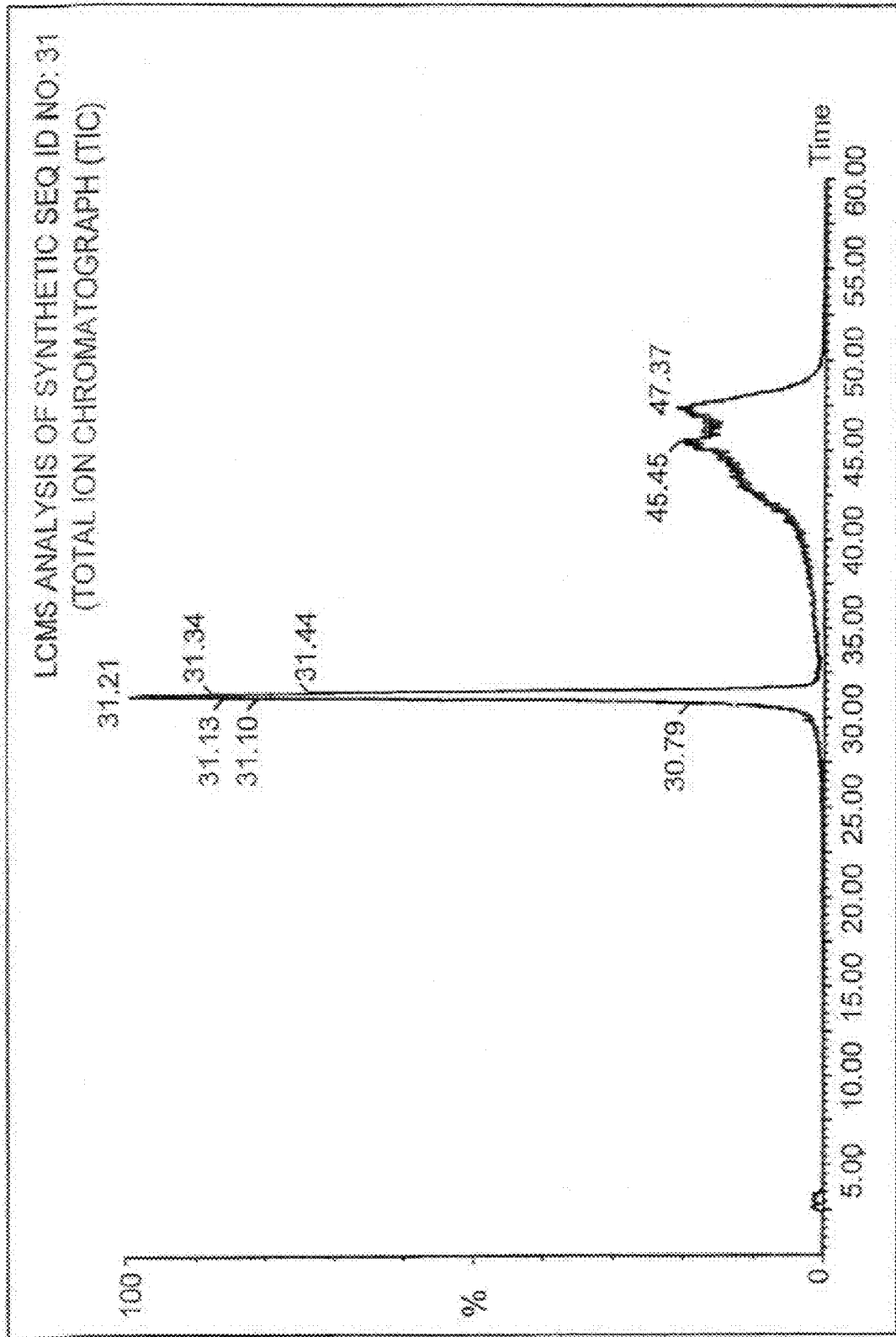


FIG. 1B

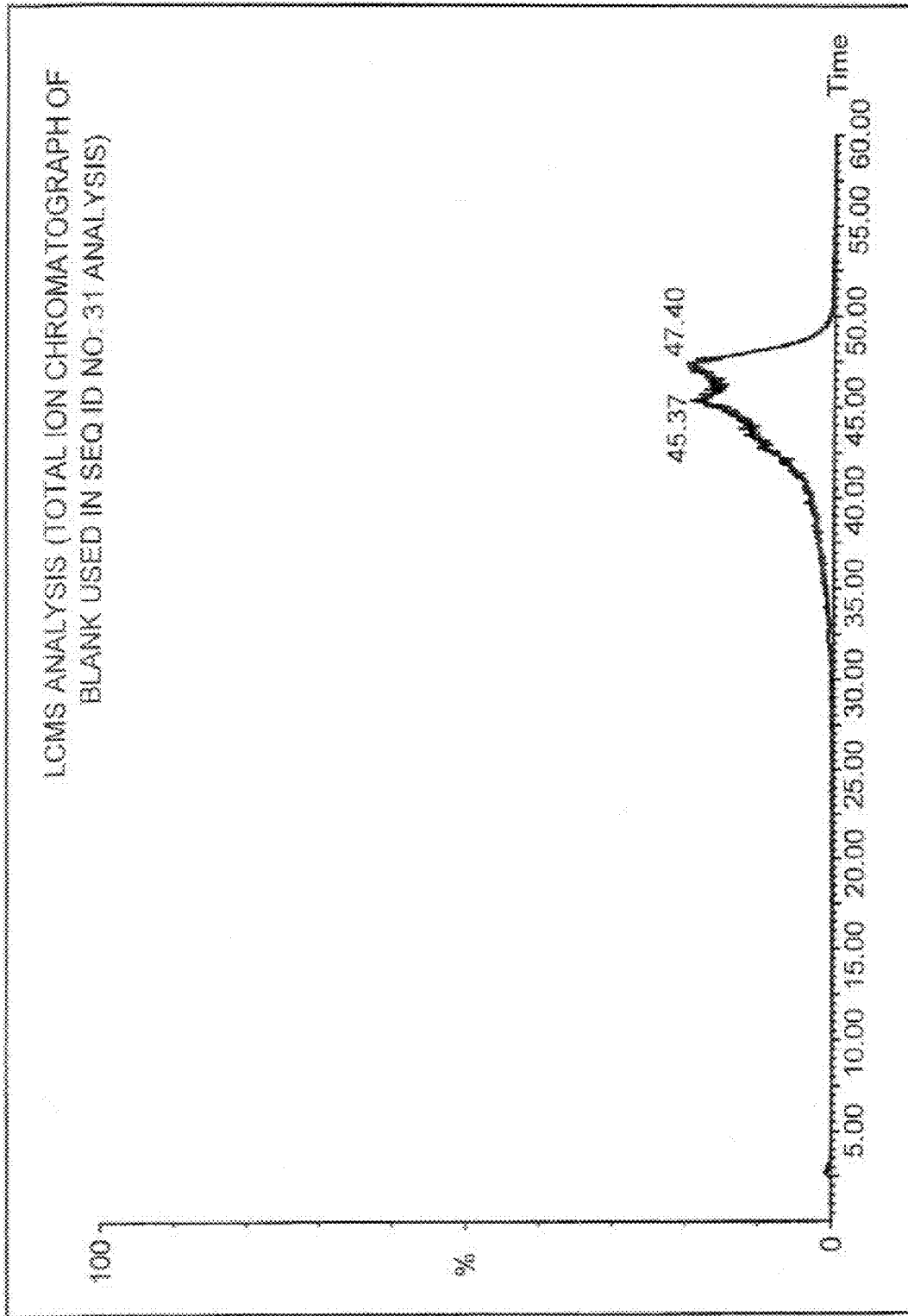


FIG.1C

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.