PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 38/26, 38/30, 38/27, 35/38, G01N 33/50, C12N 5/06, 5/08 // (A61K 38/30, 38:26) (A61K 38/27, 38:26) (A61K 38/26, 38:18)

A1

(11) International Publication Number: **WO 98/52600**

(43) International Publication Date: 26 November 1998 (26.11.98)

(21) International Application Number: PCT/CA98/00497

(22) International Filing Date: 15 May 1998 (15.05.98)

(30) Priority Data:

60/046,754	16 May 1997 (16.05.97)	US
9715481.9	23 July 1997 (23.07.97)	GB
09/059,504	13 April 1998 (13.04.98)	US

(71) Applicant: 1149336 ONTARIO INC. [CA/CA]; 19 Fernwood Road, Toronto, Ontario M6B 3G3 (CA).

(72) Inventor: DRUCKER, Daniel, J.; 19 Fernwood Road, Toronto, Ontario M6B 3G3 (CA).

(74) Agent: AITKEN, David, W.; Osler, Hoskin & Harcourt, Suite 1500, 50 O'Connor Street, Ottawa, Ontario K1P 6L2 (CA).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHODS OF ENHANCING FUNCTIONING OF THE UPPER GASTROINTESTINAL TRACT

(57) Abstract

The invention relates to glucagon–related peptides and their use for the prevention or treatment of disorders involving the upper gastrointestinal tract including the esophagus and stomach. In particular, it has now been demonstrated that GLP–2 and peptidic agonists of GLP–2 can cause proliferation of the tissue of the upper gastrointestinal tract. Thus, the invention provides methods of proliferating the upper gastrointestinal tract in a subject in need thereof. Further, the methods of the invention are useful to treat or prevent inflammatory conditions of the upper gastrointestinal tract, including inflammatory diseases. GLP–2 stimulates the growth of upper gastrointestinal tissue when administered in conjunction with other peptide hormones. The invention further provides pharmaceutical compositions of GLP–2 with at least one other peptide hormone, methods of enhancing the growth of upper gastrointestinal tissue and of gastrointestinal disorders by increasing serum levels of GLP–2 and at least one other peptide hormone, an kits for performing the methods of the invention.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

METHODS OF ENHANCING FUNCTIONING OF THE UPPER GASTROINTESTINAL TRACT

Field of Invention

This invention relates to glucagon-related peptides and their use, either alone or in combination with other peptide hormones, for the prevention or treatment of disorders involving the upper gastrointestinal tract.

Background of the Invention

Glucagon-like peptide-2 (GLP-2) is a 33 amino acid peptide expressed in a tissue-specific manner from the pleiotropic glucagon gene. GLP-2 shows remarkable homology in terms of amino acid sequence to glucagon and Glucagon-Like Peptide-1 (GLP-1). Further, different mammalian forms of GLP-2 are highly conserved. For example, the human GLP-2 and degu (a south American rodent) GLP-2 differ from rat GLP-2 by one and three amino acids respectively. When given exogenously, GLP-2 can produce a marked increase in the proliferation of small intestinal epithelium of test mice, apparently with no undesirable side effects (Drucker et al., 1996, *PNAS:USA* 93:7911-7916). Subsequently it was shown that peptide analogs of native GLP-2 with certain modifications to the peptide sequence possess enhanced trophic activity at the small intestine (see co-pending application U.S. Serial No. 08/669,791, filed June 28, 1996, incorporated herein by reference). It has further been demonstrated that GLP-2 can proliferate the tissue of the large intestine (co-pending applications U.S. Serial No. 08/763,177, filed December 10, 1996, and U.S. Serial No. 08/850,664, filed on May 2, 1997, and Litvak et al., 1997, *Gastroenterology*, vol. 112 (4 Suppl.), page A1455, all of which are incorporated herein by reference). Moreover, GLP-2 has also been shown to increase D-glucose maximal transport rate across the intestinal basolateral membrane (Cheeseman and Tseng, 1996, *American Journal of Physiology* 271:G477-G482).

A number of peptide hormones, structurally unrelated to

GLP-2, have been demonstrated to have varying degrees of trophic activity. For example, Insulin-Like Growth Factor-2 (IGF-2) has been shown to promote mitosis of the crypt cells of the small intestine *in vivo* (U.S. Patent No. 5,482,926). Insulin-Like Growth Factor-1 (IGF-1), which shares 64% sequence identity with IGF-2, and peptide analogs thereof have also been shown to increase the growth of gut tissue *in vivo* (WO 91/12018). Growth Hormone (GH) has been shown to have a number of physiological effects, including increasing proliferation of the intestinal mucosa (*see*, for example, Willmore, U.S. Patent No. 5,288,703), thereby enhancing the absorptive capacity of the gut. However, none of the above peptide hormones possess the efficacy or specificity of GLP-2 in promoting proliferation of the tissue of the lower gastrointestinal tract.

Summary of the Invention

The invention is based, in part, on the discovery that GLP-2 receptor agonists act to enhance functioning of the upper gastrointestinal tract. Specifically, it has been demonstrated that GLP-2 can proliferate the tissue of the esophagus and stomach. It is accordingly a general object of the present invention to exploit GLP-2 receptor agonists for therapeutic and related purposes.

In particular, it has been demonstrated that GLP-2 and peptidic analogs of GLP-2 can cause proliferation of the tissue of upper gastrointestinal tract. Thus, one aspect the invention provides a method of proliferating the tissue of the upper gastrointestinal tract in a subject in need thereof comprising delivering to the upper gastrointestinal tract of the subject an upper gastrointestinal tract proliferating amount of GLP-2 or a GLP-2 analog.

In addition, it has been demonstrated that GLP-2 can ameliorate nonsteroidal anti-inflammatory drug (NSAID) induced gastrointestinal toxicity. Thus, the invention provides methods of therapeutically or prophylactically treating a subject with or at risk of an inflammatory

condition of the gastrointestine involving the upper gastrointestinal tract, comprising delivering to the upper gastrointestinal tract an effective amount of GLP-2 or a GLP-2 analog.

More particularly, and according to one aspect of the invention, there is provided a method of treating a subject suffering from a condition involving the upper gastrointestinal tract, wherein GLP-2 or a GLP-2 analog is delivered to the upper gastrointestinal tract in an amount capable of ameliorating the condition.

In a related aspect of the invention, there is provided a method of treating a subject having a damaged, partially resected, eroded or inflamed esophagus comprising the step of delivering to the subject a upper gastrointestinal tract damage or inflammation ameliorating amount of GLP-2 or an analog of GLP-2 in a pharmaceutically or veterinarily acceptable carrier. In a further aspect, GLP-2 or a GLP-2 analog is provided in a pharmaceutically or veterinarily acceptable form in an amount effective to cause proliferation of the upper gastrointestinal tract.

In a further aspect of the invention, there is provided a method of treating a subject having a damaged, atrophic or inflamed stomach comprising the step of delivering to the subject a stomach damage or inflammation ameliorating amount of GLP-2 or an analog of GLP-2 in a pharmaceutically or veterinarily acceptable carrier. In a further aspect, GLP-2 is provided in a pharmaceutically or veterinarily acceptable form in an amount effective to cause proliferation of the tissue of the stomach.

In another aspect, the invention provides a method of prophylactically treating a subject at risk of developing an inflammatory condition of the gastrointestine involving the upper gastrointestinal tract comprising the steps of:

a) identifying a subject at risk of developing an inflammatory condition involving the upper gastrointestinal tract; and

DOCKET ALARM

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.