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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
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WO 2006/039256 A1

(54) Title: USE OF GPR103 AGONISTS FOR MODULATING FEEDING BEHAVIOUR

(57) Abstract: Methods for modulating feeding behavior and for the weight control treatment, utilizing GPR103 agonism, are provided.

USE OF GPR103 AGONISTS FOR MODULATING FEEDING BEHAVIOUR

FIELD OF THE INVENTION

The present invention relates to the use of GPR103 agonists to affect feeding behavior and weight gain, and to treat obesity.

BACKGROUND OF THE INVENTION

G-protein coupled receptors (GPCRs) are a super-family of membrane receptors that mediate a wide variety of biological functions. Upon binding of extracellular ligands, GPCRs interact with a specific subset of heterotrimeric G proteins that can, in their activated forms, inhibit or activate various effector enzymes and/or ion channels. All GPCRs are predicted to share a common molecular architecture consisting of seven transmembrane helices linked by alternating intracellular and extracellular loops. The extracellular receptor surface has been shown to be involved in ligand binding whereas the intracellular portions are involved in G protein recognition and activation.

RFamides are a family of neuropeptides terminating in Arg-Phe-NH2 which were first discovered in a molluscan nervous system (Price and Greenberg, Science 197:670 (1977)). Peptides of this family have been identified in invertebrates and vertebrates and have diverse physiological functions involving central and peripheral neurotransmission such as cardioexcitation, muscle contraction, nociception, and regulation of food intake (Dockray, Exp. Physiology 89:229 (2004)).

C. elegans possesses more than 20 genes which encode for at least 59 RFamide peptide products. *flp*-18 and *flp*-21 are two such peptides which are capable of modulating feeding behavior (Rogers et al., Nature Neuroscience 6:1178 (2003)). It has been demonstrated that these peptides are natural ligands for the nematode GPCR NPR-1 (Rogers et al., 2003; Kubiak et al., J. Biol. Chem. 278:33724 (2003)) which is homologous to the mammalian receptors for neuropeptide Y, an orexigenic agent. NPR-1 is important in regulation of social feeding in which the animals group together where food is abundant (de Bono and Bargmann, Cell 94:679 (1998)). A single amino acid substitution (Phe215Val) alters social behavior, to solitary feeding.

Five genes encoding RFamide peptides have been identified in mammals. These peptides act as ligands for several GPCRs that modulate diverse function such as pain, energy homeostasis, blood pressure and endocrine secretion (Dockray, Exp. Physiology 89:229 (2004)). Neuropeptide FF (NPFF) has been shown to inhibit food intake in rats after intracerebroventricular (ICV) injection (Murase et al., Peptides 17:353 (1996)). Both NPFF and its putative GPCR receptor, NPFF-2, are expressed in the hypothalamus, a key region of food intake regulation in the brain. Prolactin-Releasing Peptide (PrRP), in addition to its role in control of prolactin secretion, when administered ICV to rats inhibits food intake (Lawrence et al. Nature Neuroscience 3:645 (2000)). The putative GPCR receptor for PrRP was previously known as the orphan receptor GPR10 (Langmead et al, Br. J. Pharmacology 131:683 (2000)).

26RFa (P518, QRFP) was recently identified as a hypothalamic peptide belonging to the RFamide family (Chartrel et al, PNAS 100:15247 (2003)). In human and mouse tissues, this peptide is expressed most highly in brain (retina, trigeminal ganglion, hypothalamus and vestibular nucleus) and was either not expressed or expressed at low levels in peripheral tissues (Jiang et al, J. Biol. Chem. 278:27652 (2003)). In the rat hypothalamus, mRNA expression is located exclusively in the ventromedial nucleus and lateral hypothalamus, which are known to be involved in regulation of feeding behavior. Intracerebroventricular injection of 26RFa induced feeding in a dose-dependent manner over a 2 hour period in food-deprived mice (Chartrel et al., PNAS 100:15247 (2003)).

26RFa has been identified as the putative endogenous ligand for GPR103 (also known as AQ27, SP9155, and AXOR16; Fukusumi et al., J. Biol. Chem. 278:46387 (2003); Jiang et al., J. Biol. Chem. 278:27652 (2003)). Human GPR103 encodes a 455 amino acid peptide with closest homology to the NPFF receptors 1 and 2 and orexin receptors 1 and 2 (approximately 50% similarity), receptors which modulate feeding behavior. The mouse and rat receptors share 90% amino acid identity with the human GPR103 receptor. Human GPR103 mRNA is most abundant in brain but is also expressed in heart, kidney, and testes, whereas murine GPR103 is expressed exclusively in brain (Jiang et al., J. Biol. Chem. 278:27652 (2003)).

Being overweight or obese substantially raises an individual's risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, and other conditions. Despite the expected medical benefits, many overweight individuals find it

difficult to successfully lose weight by diet management alone. Obesity is recognized as a complex multifactorial condition that develops from the interaction of genetic and environmental factors. See, e.g., Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, Am. J. Clin. Nutr. 68:899 (1998).

Various pharmaceutical compounds have been utilized in weight loss treatments. Serotonergic agents that inhibit the reuptake of serotonin are reported to act on the hypothalamus to decrease satiety. However, serious cardiovascular side effects have been reported in some individuals treated with such agents. Fenfluramine and dexfenfluramine, serotonergic agents previously utilized in the United States for the treatment of obesity, have been withdrawn from the U.S. market due to reports of valvular heart disease and primary pulmonary hypertension. (Davidoff et al., Arch Intern Med 161:1429 (2001); Michelakis et al., Am J Med Sci 321:292 (2001); Weissman, Am J Med Sci 321:285 (2001); 2001 PHYSICIANS DESK REFERENCE®, Medical Economics Co., (2000)).

In view of the need for medical weight loss therapies, additional pharmaceutical methods useful in weight control or weight loss are desirable.

SUMMARY OF THE INVENTION

A first aspect of the present invention is a method of reducing cumulative caloric intake over a period of at least six hours in a mammalian subject. The method comprises administering a GPR103 agonist to the subject in an amount effective to reduce cumulative caloric intake during that time, compared to the caloric intake which would occur in the absence of GPR103 administration.

A further aspect of the present invention is a method of reducing weight in a mammalian subject, comprising administering a GPR103 agonist to the subject for a period of time sufficient to reduce cumulative caloric intake and result in weight loss.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 graphs the effect of ICV administration of vehicle only, 26RFa peptide (0.31 or 3.1nmol), or MTII (10nmol) on non-restricted nocturnal feeding in C57BL/6J mice. Values represent cumulative food intake (grams) during the overnight period and are expressed as the mean of 8 mice/treatment. The inset in Figure 1 provides Area

Under the Curve (AUC) measurements for 15 hour values for food intake. Error bars=SEM; *p<0.05.

Figures 2A – 2C graph metabolic parameter measurements during the overnight feeding period of the mice treated with either vehicle, 26RFa peptide (0.31 or 3.1 nmol), or MTII (10nmol). **(A)** Oxygen consumption (vO2); **(B)** Carbon Dioxide production (vCO2) ; **(C)** Respiratory quotient (RQ). **Figures 2D-2F** provide Area Under the Curve (AUC) for the 15 hr values for vO2, VCO2 and RQ measurements, respectively. N=8mice/treatment; *p<0.05

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the use of GPR103 agonists to affect the feeding behavior of mammals, and as a pharmaceutical treatment for weight control and weight loss. As described herein, GPR103 agonists have been determined to have anti-orexigenic effects.

"Pharmaceutical weight loss treatment" as used herein refers to administration of a pharmaceutical compound to a subject whose weight is greater than a medically acceptable or medically desirable amount, to achieve a reduction in the subject's weight. "Pharmaceutical treatment of obesity" is an aspect of pharmaceutical weight loss treatment and refers to such treatment for individuals whose body mass meets an accepted medical definition of obesity. One commonly accepted measure of overweight in humans is the Body Mass Index (BMI); overweight may be defined as a BMI of at least 25 kg/m^2, with obesity defined as a BMI of at least $30kg/m^2$. Pharmaceutical weight loss treatment may be accompanied by a change in diet and/or other behavioral modifications such as support groups and/or patient education. As used herein, pharmaceutical weight loss treatment does not imply a "cure" for obesity or permanent weight loss. "Pharmaceutical weight maintenance treatment" as used herein refers to administration of a pharmaceutical compound to a subject as an aid in maintaining a desired weight. As described herein, GPR103 agonists are useful in such treatments described above. It will be apparent that the methods of the present invention will not result in immediate weight loss; administration of GPR103 agonists must be maintained for a sufficient period of time for reduced caloric intake to be manifested as weight loss.

As used herein, a GPR103 agonist pharmaceutical compound for the treatment of obesity or for weight loss treatment is one in which administration (in an appropriate pharmaceutical formulation and in a therapeutically effective amount) to a mammal, and preferably to humans, has been shown to increase weight loss over time, compared to the change in weight that would have occurred had the subject not been administered the compound. Therapeutically effective amounts of such compounds for use in treatment of obesity or for weight loss can be readily determined by those skilled in the art using, e.g., dose-response studies.

"GPR103 agonist" as used herein refers to an agent that directly binds to and upregulates the activity of GPR103. In the present methods, preferred GPR103 agonists are small molecule organic compounds, preferably synthetic small molecule organic compounds, and may be non-steroidal synthetic small molecule organic compounds. Preferred GPR103 agonist compounds for use in the present methods do not include compounds that are naturally found in the human body.

As used herein, the term "small molecule organic compound" refers to a chemical compound that is an organic compound having a molecular weight less than about 10,000 daltons, and more preferably having a molecular weight less than about 7,500 daltons, less than about 5,000 daltons, or less than about 2,500 daltons. As used herein, the term "synthetic compound" refers to a chemical compound where the compound structure is not known to occur in nature, whereas the term "naturally-occurring compound" refers to a chemical compound isolated from or known to occur in natural sources, such as cells, plants, fungi, animals and the like.

As used herein, the term "GPR103 agonist" refers to compounds that achieve at least about 25% activation of GPR103 relative to 26Rfa peptide. Preferably, the compounds used in the methods of this invention achieve at least about 50% activation of GPR103 relative to that of 26Rfa peptide; more preferably, the compounds achieve at least about 75%, 80%, 90%, 95%, 97% or greater activation of GPR103 relative to 26Rfa peptide.

Additional GPR103 ligands useful in the present inventions can be identified by those of skill in the art using screening assays to identify compounds with GPR103 agonist or antagonist properties.

Preferred subjects for the methods of the present invention are mammals, including but not limited to humans, primates, rodents, canines and felines.

As used herein, a 'therapeutically effective amount' of a GPR103 agonist, in the treatment of weight gain or obesity, indicates an amount of GPR103 agonist that decreases feeding over a given time period (and thus decreases the cumulative caloric intake over that time period). The 'decrease' in feeding/caloric intake is as compared to the feeding/caloric intake which would occur over that time period in the absence of GPR103 agonist treatment. A reduction in weight, a slowing of the rate of weight gain, and/or a reduction in food/caloric intake may be measured or ascertained using any suitable means as are known in the art.

Formulations, pharmaceutical compositions

GPR103 agonists used in the methods of the present invention are administered in the form of pharmaceutical compositions. Such pharmaceutical compositions comprising a GPR103 agonist may be presented for use in a conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

It will be appreciated that suitable dosages of GPR103 will be determined by standard methods for each treatment modality and indication, taking into account the indication, its severity, route of administration, complicating conditions and the like.

The following nonlimiting examples are provided to further illustrate the present invention.

EXAMPLE 1

Materials and Methods

Intracerebroventricular (ICV) cannulated male C57BL/6J mice (21-25g) (Charles River, Wilmington, MA, USA) were individually housed in a Comprehensive Laboratory Animal Monitoring System (CLAMS) (Columbus Instruments, Columbus, OH, USA) in a vivarium under a 12:12-h light dark cycle. Ground 45% high fat diet (D12451) (Research Diets, New Brunswick, New Jersey, USA) and water were available ad libitum. The experimental protocols used conform to institutional standards of animal care and the Guide for the Care and Use of Laboratory Animals (National Research Council 1996).

All ICV cannulations and placements were conducted by Charles River (Research Triangle Park, NC). After a minimum period of 7 days post-surgery, cannula

placement was confirmed by measuring the dipsogenic response (immediate drinking of at least 2-3 mL of water 30-40 minutes) to an acute ICV injection of angiotensin II (50 ng, ICV) (Sigma Diagnostics, St. Louis, MO). Animals were used in peptide studies, 2 days after confirmation of cannula placement with angiotensin II. The animals were handled every day during recovery until the start of the peptide study, by picking them up and unscrewing the dummy cannula, removing it and then inserting an internal cannula. After the recovery period the mice were housed and acclimated (3 days) in individual CLAMS metabolic cages for determination of overnight food and water intake, oxygen consumption (vO2), CO2 production (vCO2), respiratory quotient (RQ) and activity.

Drug Preparation, Delivery and Metabolic Parameter Measurements:

MTII (Phoenix Pharmaceuticals, Belmont, Calif., USA) and the 26RFa peptide (Bachem, King of Prussia, Pa., USA) were prepared by dissolving the peptides in sterile 0.9% saline just prior to use. Injections were made through 23G stainless steel tubing that extended 2 mm below the guide cannula. A 3-µl volume of drug or vehicle was injected over 3 min using a Hamilton microsyringe. The injector was left in place for another minute before removal. All injections took place between 5:00-6:00 PM just prior to feeding. Treated animals (n=8 mice/treatment group) were then monitored in the CLAMS cages for overnight food and water intake, oxygen consumption (vO2), carbon dioxide production (vCO2), respiratory quotient (RQ) and activity.

Example 2

Results

The effect of ICV administration of 26RFa peptide (0, 0.31, or 3.1nmol) or MTII (10nmol) on non-restricted nocturnal feeding in C57BL/6J mice is shown in **Figures 1** and **2**. In **Figure 1A,** values represent cumulative food intake during the overnight period and are expressed as the mean of 8 mice/treatment. **(Inset figure:** Area under the curve (AUC) for 15 hr values for food intake. Error bars=SEM; *p<0.05)

Figures 2A-C show metabolic parameter measurements of mice treated with either 26RFa peptide or MTII, during the overnight feeding period. **Figure 2A:** Oxygen consumption (vO2). **Figure 2B:** Carbon Dioxide production (vCO2). **Figure 2C**: Respiratory quotient (RQ) measurements. **Figures 2D-F** show Area Under the Curve

(AUC) for 15 hr values for vO2, VCO2 and RQ measurements, respectively. N=8mice/treatment; *p<0.05.

The results demonstrate that ICV cannulated mice treated with 0.31 or 3.1 nmol of 26RFa peptide showed a dose-dependent inhibition of non-restricted nocturnal feeding (**Figure 1**). There was an acute phase orexigenic effect that lasted for 2-3hrs. These acute results are consistent with what has been previously reported (Chartrel *et al.,* PNAS 100:15247 (2003)). However, as shown in **Figure** 1, measuring chronic food intake beyond three hours clearly demonstrated an anti-orexigenic effect of the 26Rfa peptide consistent with those found for the anti-orexigenic peptide MTII (melanotan II, a melanocortin agonist). Measurement of metabolic respiratory parameters including oxygen consumption, carbon dioxide production, and respiratory quotient, revealed dose-dependent decreases in these parameters for both the 26Rfamide and MTII peptides (**Figure 2**). Both peptides demonstrated dose-dependent decreases in water intake and overall activity (data not shown).

What is Claimed is:

1. A method of reducing cumulative caloric intake over a period of at least six hours in a mammalian subject, comprising administering a GPR103 agonist to said subject in an amount effective to reduce cumulative caloric intake during said time period, compared to caloric intake which would occur in the absence of said GPR103 administration.

2. The method according to claim 1 where said period is at least nine hours.

3. The method according to claim 1 where said period is at least twelve hours.

4. The method according to claim 1 where said period is at least fifteen hours.

5. The method according to claim 1 where said period is selected from at least two weeks, at least six weeks, at least eight weeks, and at least twelve weeks.

6. The method according to claim 1 where said subject is a human.

7. The method according to claim 1 where said subject is selected from a rodent, a canine, and a feline.

8. A method of reducing weight, comprising administering a GPR103 agonist to a mammalian subject, for a period of time sufficient to reduce cumulative caloric intake and result in weight loss, compared to caloric intake which would occur in the absence of GPR103 administration.

9. The method according to claim 8 where said subject is a human.

10. The method according to claim 8 where said subject is selected from a rodent, a canine, and a feline.

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INTERNATIONAL SEARCH REPORT

ıtional application No
/US2005/034541

A. CLASSIFICATION OF SUBJECT MATTER
A61K38/16 A61K38/02 A61P3/04 A61K45/00

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)
A61K A61P

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)
EPO-Internal, WPI Data, BIOSIS, PAJ, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/78809 A (SMITHKLINE BEECHAM CORPORATION) 28 December 2000 (2000-12-28) page 1, lines 3-6 page 3, lines 9-29	1-10
X	DATABASE WPI Section Ch, Week 200467 Derwent Publications Ltd., London, GB; Class B04, AN 2004-248372 XP002364553 & WO 2004/022086 A (TAKEDA CHEM IND LTD) 18 March 2004 (2004-03-18) abstract	1-10
X	WO 03/087134 A (SCHERING CORPORATION) 23 October 2003 (2003-10-23)	1-10
Y	page 1, lines 8-12,27 - page 5, line 16 page 30, lines 10-19	1-10
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family 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)

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"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
26 January 2006	10/02/2006

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/026904 A (INPHARMATICA LIMITED; MICHALOVICH, DAVID; KAMP, SARAH, HELEN) 1 April 2004 (2004-04-01) page 1, lines 2-5	1-10
Y	page 9, lines 2-21 page 12, lines 1-5 page 33, lines 13-16 page 35, line 28 - page 36, line 5	1-10
Y	CHARTREL N ET AL: "Identification of 26RFa, a hypothalamic neuropeptide of the" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC, US, vol. 200, no. 25, 9 December 2003 (2003-12-09), pages 15247-15252, XP002992131 ISSN: 0027-8424 cited in the application abstract page 15247, column 2, paragraph 1-3 page 15250, column 1, paragraph 3 - page 15252, column 2, paragraph 1	1-10
Y	FUKUSUMI S ET AL: "A new peptidic ligand and its receptor regulating adrenal function in rats" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOCHEMICAL BIOLOGISTS, BIRMINGHAM,, US, vol. 278, no. 47, 5 September 2003 (2003-09-05), pages 46387-46395, XP002267777 ISSN: 0021-9258 cited in the application abstract page 46394, column 1, paragraph 2 page 46394, column 2, paragraph 2	1-10
Y	JIANG YING ET AL: "Identification and characterization of a novel RF-amide peptide ligand for orphan G-protein-coupled receptor SP9155" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOCHEMICAL BIOLOGISTS, BIRMINGHAM,, US, vol. 278, no. 30, 25 July 2003 (2003-07-25), pages 27652-27657, XP002267776 ISSN: 0021-9258 cited in the application abstract page 27655, column 2, paragraph 2 - page 27656, column 2, paragraph 4	1-10

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3

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BONINI JAMES A ET AL: "Identification and characterization of two G protein-coupled receptors for neuropeptide FF" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 275, no. 50, 15 December 2000 (2000-12-15), pages 39324-39331, XP002364550 ISSN: 0021-9258 abstract page 39331, column 1, paragraph 2	1-10
P,X	BENOIT S C ET AL: "The role of previous exposure in the appetitive and consummatory effects of orexigenic neuropeptides" PEPTIDES, ELSEVIER, AMSTERDAM, US, vol. 26, no. 5, May 2005 (2005-05), pages 751-757, XP004820283 ISSN: 0196-9781 abstract page 755, column 1, paragraph 2 - page 756, column 2, paragraph 1	1-10
P,X	DATABASE WPI Section Ch, Week 200551 Derwent Publications Ltd., London, GB; Class B04, AN 2005-506787 XP002364554 & WO 2005/065703 A1 (TAISHO PHARM CO LTD) 21 July 2005 (2005-07-21) abstract	1-10
P,X	WO 2004/106935 A (BAYER HEALTHCARE AG; GOLZ, STEFAN; BRUEGGEMEIER, ULF; SUMMER, HOLGER) 9 December 2004 (2004-12-09) page 1, lines 5-12 page 5, lines 14-24 page 75, lines 20-22	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/034541

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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:

Although claims 1-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] 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:

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 No. III Observations where unity of invention is lacking (Continuation of item 3 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 allsearchable claims.

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

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers 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 and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

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

INTERNATIONAL SEARCH REPORT

nformation on patent family members

ational application No
/US2005/034541

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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