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(54) Title: BIMATOPROST FOR ENHANCEMENT OF LEPTIN PRODUCTION

(57) Abstract: Prostamides such as bimatoprost and its pro-drugs for enhancement of leptin production and appetite suppression.

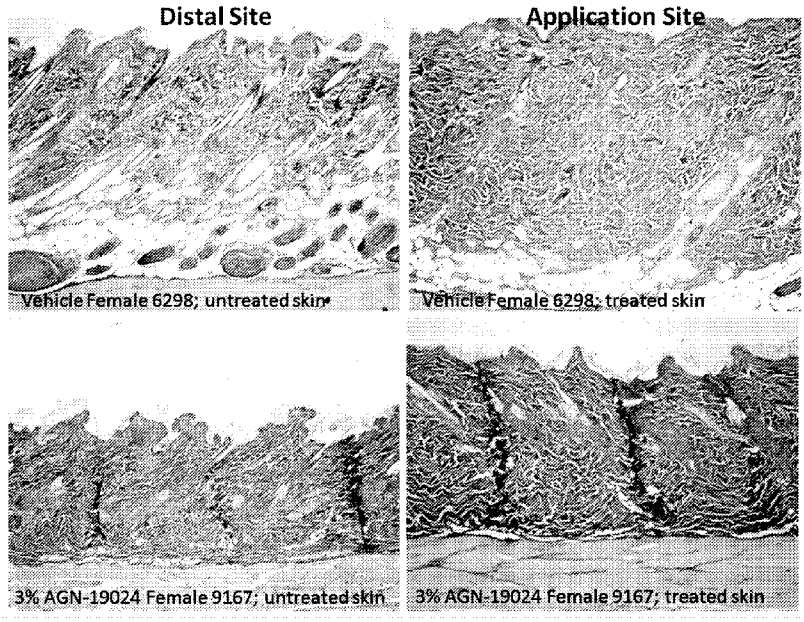

FIGURE 1

WO 2014/143629 A1

UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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BIMATOPROST FOR ENHANCEMENT OF LEPTIN PRODUCTION

Cross Reference to Related Application

This application claims the benefit of United States Provisional Patent Application Serial No. 61/793,132, filed March 15, 2013, the entire disclosure of which is incorporated herein by reference.

Field of the Invention

The present invention is directed to the use of prostamides such as bimatoprost and its pro-drugs for the enhancement of leptin production and appetite suppression.

Background of the Invention:

Leptin is major hormone produced in adipose tissue that has been shown to regulate appetite [Halaas JL, Gajiwala KS, Maffei M, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. Science. 1995;269 (5223):543–546r] and alter the taste for sweetness of food [Kawai K, Sugimoto K, Nakashima K, Miura H, Ninomiya Y, Proc Natl Acad Sci U S A. 2000 Sep 26;97(20):11044-9]. Leptin is also a mediator of long-term regulation of energy balance, suppressing food intake and thereby inducing weight loss (Klok, "The Role of Leptin and Ghrelin in the Regulation of Food Intake and Body Weight in Humans: A Review." Obes. Rev. 2007, Jan; 8(1): 21-34).

Bimatoprost (AGN 192024) is a synthetic prostamide which has been used in intraocular pressure lowering therapeutics such as LUMIGAN® 0.03, LUMIGAN® 0.01 and GANFORT®. Bimatoprost has also been shown to induce eyelash and hair growth and is marketed for that purpose with the commercial product LATISSE®. Bimatoprost applied topically has also been shown to result in subcutaneous fat loss at sites distant from the application site (see Figure 1) in rats during a six month study of once a day topical application (~10% body surface coverage). This application also led to a reduction in weight over time (see Figure 2).

Summary of the Invention:

It is hereby proposed that in addition to other therapeutic uses, bimatoprost can mediate weight loss and gain through modulation of the appetite suppressing hormone leptin. An additional benefit may be maintaining weight control in non-obese individuals, that is in suppressing appetite in individuals with normal weight, use in conjunction with or without dieting, or as an adjunct to bariatric surgery, gastric banding (Lap-band) or other methods where weight control would be suitable (e.g., prolonged systemic steroid use, during smoking cessation programs to alleviate over-eating, or intake of foods high in sugar). Further, the use of bimatoprost as described in the present application can be applied to a wide range of disorders such as metabolic disease, type II diabetes, insulin resistance syndrome and non-alcoholic fatty liver. The delivery of bimatoprost may be topical, oral, systemic such as by skin patch, subcutaneous, sublingual and by suppository to obtain systemic exposure of the compound.

The term “prodrug” is used according to its plain ordinary meaning and is intended to mean compounds that require a chemical or enzymatic transformation in order to release the active parent drug *in vivo* prior to producing a pharmacological effect.

A "pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient" means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier/excipient" as used in the specification and claims includes both one and more than one such excipient.

The terms “treat” “treating” or “treatment” refers to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating;

improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. For example, the certain methods presented herein successfully treat cancer by decreasing the incidence of cancer, in inhibiting its growth and or causing remission of cancer.

An "effective amount" of a compound is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease. Where recited in reference to a disease treatment, an "effective amount" may also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) a disease, disorder or condition, or reducing the likelihood of the onset (or reoccurrence) of a disease, disorder or condition or symptoms thereof. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations.

The term "topical" in the context of methods described herein relates in the customary sense to the administration of a compound or pharmaceutical composition which is incorporated into a suitable pharmaceutical carrier and administered at a topical treatment site of a subject. Accordingly, the term "topical pharmaceutical composition" includes those pharmaceutical forms in which the compound is administered externally by direct contact with a topical treatment site, e.g., the skin. The term "topical epidermal pharmaceutical composition" refers to a pharmaceutical composition suitable for administering directed to the epidermal layer of the skin, e.g., the palpebra, the supercilium, the scalp, or the body. The term "topical administering" refers to administering externally by direct contact with a topical treatment site. The term "topical epidermal administering" refers to administering externally by direct contact with the epidermis.

Some embodiments of the invention are included in the following paragraphs:

1) A method of enhancing leptin levels in a human comprising administering bimatoprost to the human.

2) The method of paragraph 1, wherein the bimatoprost is administered systemically.

3) The method of paragraph 1, wherein the bimatoprost is administered topically.

4) The method of paragraphs 1 – 3, wherein the bimatoprost enhances leptin production in adipose tissue.

5) The method of paragraphs 2 – 4, wherein the method enhances leptin production in pre-adipocytes.

6) The method of paragraphs 1 – 5, wherein the method suppresses appetite in a human.

7) The method of paragraphs 1 and 2, wherein the method is useful in treating type II diabetes.

8) The method of paragraphs 1 and 2, wherein the method is useful for treating a condition selected from the group consisting of metabolic disease, type II diabetes, insulin resistance syndrome, metabolic syndrome and non-alcoholic fatty liver.

9) The method of paragraphs 1 and 2, wherein bimatoprost is administered orally.

10) The method of paragraph 3, wherein bimatoprost is administered by a transdermal skin patch.

11) The method of paragraph 2, wherein bimatoprost is administered subcutaneously.

12) The method of paragraphs 1 – 6, wherein the method is useful in treating obesity.

13) The methods of paragraphs 1 – 6, wherein bimatoprost is in the form of a bimatoprost prodrug.

14) The method of paragraph 1, wherein the method reduces or prevents differentiation of pre-adipocytes than would occur if the bimatoprost was not administered.

15) The method of paragraph 1, wherein the topical or subcutaneous application of bimatoprost results in fat reduction at the application site and distal to the application site.

16) A method of losing weight or causing systemic weight loss comprising administering bimatoprost to a patient.

17) The method of paragraph 16, where the bimatoprost is applied topically.

18) The method of paragraphs 1 – 17, wherein the bimatoprost is 0.1 - 3% w/v.

19) The method of paragraph 1, wherein the method prevents the onset of non-alcoholic fatty liver.

20) The method of paragraphs 1 and 16, wherein the bimatoprost concentration is selected from one consisting of .1%, .3%, 1%, 2% and 3% w/w bimatoprost.

21) The method of paragraph 1, wherein the bimatoprost is administered to the patient in a transdermal skin patch.

Brief Description of the Drawings:

Figure 1 shows subcutaneous fat reduction at sites distal to the application site of bimatoprost with vehicle and application of 3% w/v bimatoprost;

Figure 2 shows reduction in body weight after treatment with bimatoprost. Rats were treated topically with bimatoprost at doses shown in Figure 2;

Figure 3 shows that bimatoprost increases Leptin production in human pre-adipocytes. Vehicle is DMSO, bimatoprost treatment at 1 μM. Stimulation of leptin over 8-days of bimatoprost treatment;

Figure 4 shows that bimatoprost results in elevated leptin levels of rats on a cafeteria diet; and,

Figure 5 shows bimatoprost dose-dependently decreases cafeteria diet induced fatty liver changes.

Detailed Description of the Invention:

The present invention covers a novel use of bimatoprost including other known prostamides, and structural analogs of bimatoprost and its pro-drugs (non-limiting examples include acyl, acyl esters, amino acids and phosphates and prostamides as disclosed in U.S. Patent No. 5,688,819 which is herein incorporated by reference). Bimatoprost was examined for the effect on hormones released from adipose tissue.

In Figure 1, bimatoprost was applied topically once per day for 6 months to rats. Treatment of rats resulted in substantial local subcutaneous fat reduction, as well as reduction at adjunct and distal sites. Figure 2 describes the systemic exposure (topically

applied) of bimatoprost by measuring blood levels of the compound after treatment. A major target of bimatoprost for action is the pre-adipocyte, as determined by its activity to inhibit differentiation. In conjunction, treatment of human pre-adipocytes result in an increase in leptin production. It was also discovered that application of bimatoprost to pre-adipocytes, but not mature adipocytes, led to an increase in leptin levels in vitro (Figure 3), a protein known to suppress appetite. The *in vivo* action of bimatoprost is likely a dual mechanism to inhibit food intake and suppress replenishment of fat cells during normal turnover. Figure 4 shows male rats on a cafeteria diet (CAF) were treated with topical bimatoprost in BSHG formulation (0.3%, 1%, or 3%) or vehicle (see Fig. 2) daily. Blood was drawn every 2 weeks and the serum was analyzed for leptin levels by luminex assay. Male rats dosed with 0.3% bimatoprost showed elevated levels of Leptin ($p<0.01$, 2-way ANOVA). A cafeteria diet is a high sugar and fat diet with typical "junk food":

Table I:

	1	2	3	4	5	6	7	8	9	10
Food Type	**Kcal**	**Fat (kcal)**	**Total Fat**	**Total Carb**	**Protein**	**Dietary fiber**	**Sugars**	**Sat. Fat**	**Chol.**	**Sodium**
Standard Chow®	4.07	0.36	0.04	0.49	0.24	0.05	0	0	0	4
Kellog's Fruit Loops®	4	0.33	0.03	0.87	0.03	0.03	0.43	0	0	4.7
General Mills Coca Puffs®	4.07	0.37	0.06	0.85	0.04	0.04	0.44	0	0	5.6
Little Debbie Fudge Rounds®	4.48	1.49	0.16	0.7	0.03	0.03	0.45	0.06	0.08	2.39
Peanut butter cookies	5	1.88	0.22	0.63	0.06	0	0.31	0.06	0	3.13
Hershey Reeses Pieces®	5.13	2.05	0.23	0.62	0.13	0.03	0.54	0.18	0	2.05
Hostess® blueberry mini-muffins	4.74	2.28	0.26	0.56	0.05	0.02	0.33	0.04	0.7	3.16
Nestle Crunch®	4.86	2.29	0.26	0.69	0.06	0.03	0.51	0.14	0.14	0.86
Cheez-it®	5.33	2.33	0.27	0.6	0.13	0.03	0.03	0.07	0	8.33
General Mills Coca Puffs®	4.39	2.46	0.28	0.44	0.05	0.02	0.26	0.04	0.53	2.46
Keebler TownHouse Butter Crackers®	5.36	2.5	0.29	0.61	0.07	0.04	0.04	0.05	0	6.43
Sugar wafers	5.16	2.58	0.29	0.65	0.03	0	0.48	0.06	0	0.65
Kroger® hot dog wieners	3.33	2.67	0.29	0.09	0.11	0	0.04	0.1	0.78	10.22
Kroger® mild cheddar/jack cheese	3.93	2.86	0.32	0.04	0.25	0	0	0.18	1.07	6.43
Kroger® wedding cakes	5.67	3	0.33	0.57	0.03	0	0.33	0.07	0	2.5

Frito-lay® Lay wavy	5.36	3.21	0.36	0.54	0.07	0.04	0	0.04	0	6.43
Kroger® pork rinds BBQ	5.71	3.21	0.36	0	0.57	0	0	0.11	1.43	28.57
Kroger® pepperoni slices	4.67	4	0.43	0	0.2	0	0	0.17	1	16.67

Figure 5 shows that rats receiving 0.3% and 1% bimatoprost formulations had reduced lipidosis as compared to the control. Topical administration of bimatoprost inhibited cafeteria diet induced fatty liver disease. Rats were fed the cafeteria diet for 10 weeks and administered bimatoprost daily. At the end of 10 weeks, livers were resected and examined by histology. This result shows bimatoprost can inhibit lipid droplet deposition in the liver due to the excess dietary consumption of fats and sugar from the cafeteria diet. This has important consequences in the potential treatment of non-alcoholic fatty liver disease (NAFLD).

The compounds and pharmaceutical compositions disclosed herein can be prepared and administered in a variety of forms including a dermal or transdermal skin patch, a transdermal implant, cream, lotion, shampoo, solution, emulsion, gel, colloid, or foam. Accordingly, pharmaceutical compositions contemplated herein include a pharmaceutically acceptable carrier or excipient and one or more compounds described herein.

Pharmaceutical compositions contemplated herein may be prepared by combining a therapeutically effective amount of bimatoprost or another prostamide in combination with one or more pharmaceutically acceptable excipients. Pharmaceutical admixtures suitable for use in the present invention include those described in, for example, in PHARMACEUTICAL SCIENCES (17th Ed., Mack Pub. Co., Easton, PA) and WO 96/05309, the teachings of both of which are hereby incorporated by reference.

The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides, and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes.

Table 2: Some bimatoprost formulations include:

Ingredient (% w/w)	Function	Bimatoprost 0.3% (Propylene Glycol) Solution	Bimatoprost 1.0% (Propylene Glycol) Solution	Bimatoprost 3.0% (Propylene Glycol) Solution	Bimatoprost 2.0% (Propylene Glycol) Solution
Bimatoprost	Active	0.3	1.0	3.0	2.0
Propylene glycol	Penetration enhancer	10.0	10.0	10.0	10.0
Diethylene glycol monoethyl ether		10.0	10.0	10.0	10.0
Ethyl alcohol		30.0	30.0	30.0	30.0
Glycerin		2.0	2.0	2.0	2.0
Carbomer (Ultrez 10)	Thickener	0.15	0.15	0.15	0.15
Triethanolamine	Neutralizing agent	0.16	0.16	0.16	0.16
Purified water	Vehicle	47.66	47.59	47.39	47.49

Table 3: Example Components with Function and Concentration Ranges

Ingredient	Function	Composition (% w/w)
bimatoprost	Active	0.03 — 5.0
carbomer	Thickener	0.05 — 1.0
base	Neutralizing Agent	0.01 — 2.0
ethanol	Penetration enhancers	10 - 90
glycerin		1.0 — 20
diethylene glycol monoethyl ether		1.0 - 50
propylene glycol		1- 50
polysorbate 20		0.1 — 5.0
polysorbate 40		0.1 — 5.0
polysorbate 60		0.1— 5.0
polysorbate 80		0.1 — 5.0
PPG-5 ceteth-20		0.1— 5.0
oleic acid		0.1 — 5.0
isostearyl isostearate		0.1 - 10
isopropyl myristate		0.1 - 10
dipropylene glycol dimethyl ether		1-50
diethylene glycol		1-50
dipropylene glycol		1-50

caprylic/capric triglycerides		0.1-10
benzyl alcohol	Preservative	0.1 — 2.0
silicone	Occlusive Agent	0.1 - 10
water	Vehicle	0 - 90

Bimatoprost or another prostamide can be included in compositions of the embodiments disclosed herein in an amount of between 0.0001 and 15% (w/v), between 0.0001 and 10% (w/v), between 0.0001 and 5% (w/v), between 0.0005 and 3% (w/v), between 0.00075 and 2% (w/v), between 0.001 and 1.0% (w/v), between 0.001 and 0.1 (w/v), between 0.005 and .05%(w/v), or 0.01% (w/v) of the composition. In some embodiments, an amount of the active compound such as bimatoprost or another prostamide is 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0%, 7.5%, 8.0%, 9% and 10% w/w.

In some embodiments, an effective amount, e.g., a therapeutically effective amount, of the active compound in a pharmaceutical composition is afforded at a concentration of about $1x10^{-7}$ to 50% (w/w), about 0.001 to 50% (w/w), about 0.01 to 50% (w/w), about 0.1 to 50% (w/w), or about 1 to 50% (w/w). In some embodiments, the therapeutically effective amount of the active compound such as bimatoprost or another prostamide in a pharmaceutical composition is 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9% and 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 3.0%, 4.0% and 5.0% w/w.

Example 1: Use of bimatoprost patch for enhancing leptin production and weight loss.

A 51 year old Caucasian male who is morbidly obese applies a bimatoprost transdermal skin patch on his arm, which uniformly releases a 5% w/w bimatoprost formulation over a thirty day period. During the thirty-day period, the patient's leptin levels increase leading to suppressed appetite and weight loss. The patient loses 6

pounds more than he would have otherwise lost without using the bimatoprost transdermal skin patch.

Example 2: Use of topical bimatoprost to maintain weight.

A 43 year old Hispanic female applies a 3% w/w bimatoprost gel to her skin once a day. After several days, the 43 year old Hispanic female experiences elevated leptin levels which suppresses appetite. Over a sixty (60) day period, the patient maintains her weight through appetite suppression.

Example 3: Use of a bimatoprost patch to control glucose levels in a prediabetes patient.

A 61 year old African-American male with elevated blood pressure has been determined by doctors to have prediabetes. In addition to being on a low fat, low sugar diet, the patient uses a transdermal bimatoprost patch which releases a 3% w/w bimatoprost formulation through the dermis and into the blood stream. The patient experiences an immediate increase in blood leptin levels and a reduction in appetite and experiences weight loss while using the bimatoprost patch.

Example 4: Use of topically delivered bimatoprost to treat non-alcoholic fatty liver.

A 70 year old Caucasian male is diagnosed with non-alcoholic fatty liver. The patient applies a transdermal bimatoprost patch which releases a 2% w/w bimatoprost formulation. The patient experiences a reduction in lipidosis in the liver that would have occurred had the patient not been administered bimatoprost.

Example 5: Use of topically delivered bimatoprost in dieting.

A healthy 27 year old Caucasian female in an effort to lose weight is on a low fat diet. In order to suppress her appetite, the 27 year old Caucasian female applies a

bimatoprost transdermal patch which continually releases 1% w/w bimatoprost for 30 days. As a result, her leptin levels rise and she experiences suppression of her appetite and greater weight loss in comparison to had she not applied the transdermal patch with bimatoprost.

Claims:

1) A method of enhancing leptin levels in a human comprising administering bimatoprost to the human.

2) The method of claim 1, wherein the bimatoprost is administered systemically.

3) The method of claim 1, wherein the bimatoprost is administered topically.

4) The method of claim 3, wherein the bimatoprost enhances leptin production in adipose tissue.

5) The method of claim 3, wherein the method enhances leptin production in pre-adipocytes.

6) The method of claim 1, wherein the method suppresses appetite in a human.

7) The method of claim 3, wherein the method is useful in treating type II diabetes.

8) The method of claim 3, wherein the method is useful for treating a condition selected from the group consisting of metabolic disease, type II diabetes, insulin resistance syndrome, metabolic syndrome and non-alcoholic fatty liver.

9) The method of claim 1, wherein the method results in weight loss.

10) The method of claim 3, wherein bimatoprost is administered by a transdermal skin patch.

11) The method of claim 2, wherein bimatoprost is administered subcutaneously.

12) The method of claim 1, wherein the method is useful in treating obesity.

13) The methods of claim 1, wherein bimatoprost is a bimatoprost prodrug.

14) The method of claim 1, wherein the method reduces or prevents differentiation of pre-adipocytes.

15) The method of claim 1, wherein the topical or subcutaneous application of bimatoprost results in fat reduction at the application site and distal to the application site.

16) The method of claim 1, wherein the method prevents and reduces the onset of non-alcoholic fatty liver.

17) The method of claim 1, wherein the bimatoprost concentration is selected from one consisting of .1%, .3%, 1%, 2% and 3% w/w bimatoprost.

18) The method of claim 1, wherein the bimatoprost is administered to the patient in a transdermal patch.

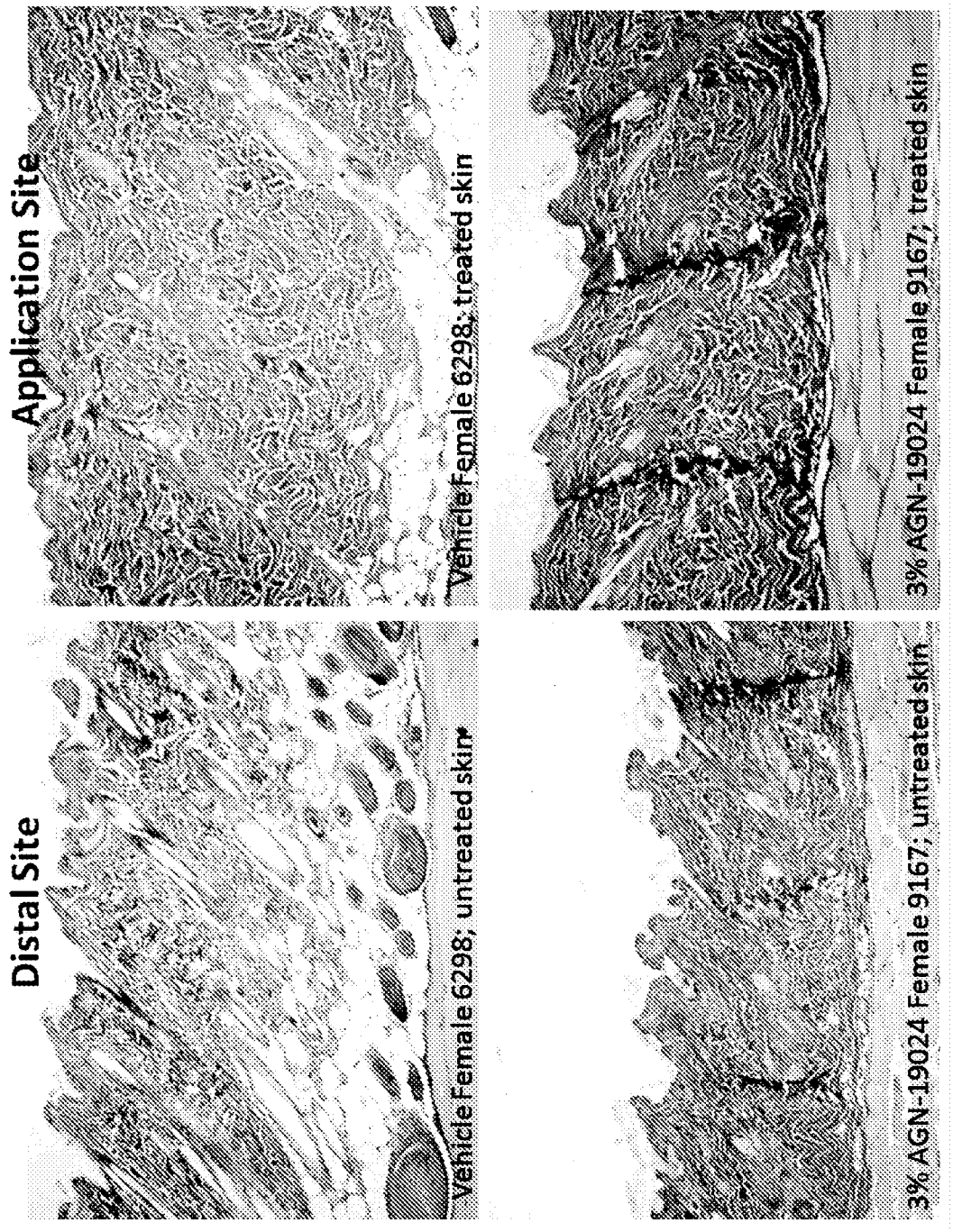
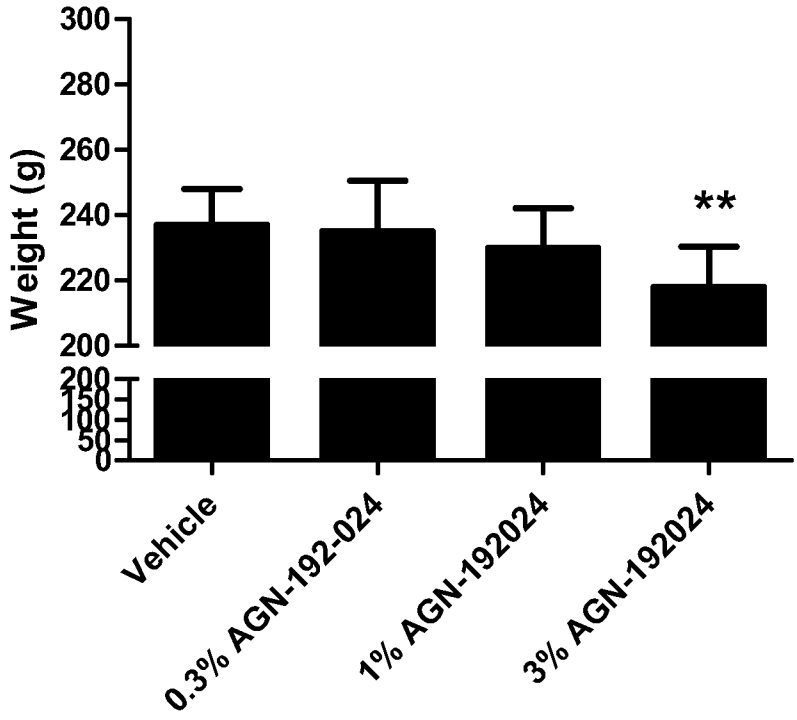

Application Site
Distal Site
Vehicle Female 6298; treated skin
3% AGN-19024 Female 9167; treated skin
Vehicle Female 6298; untreated skin
3% AGN-19024 Female 9167; untreated skin

FIGURE 1

FIGURE 2



10% Coverage of skin

n=20

**< p 0.01using Dunnett's test

FIGURE 3

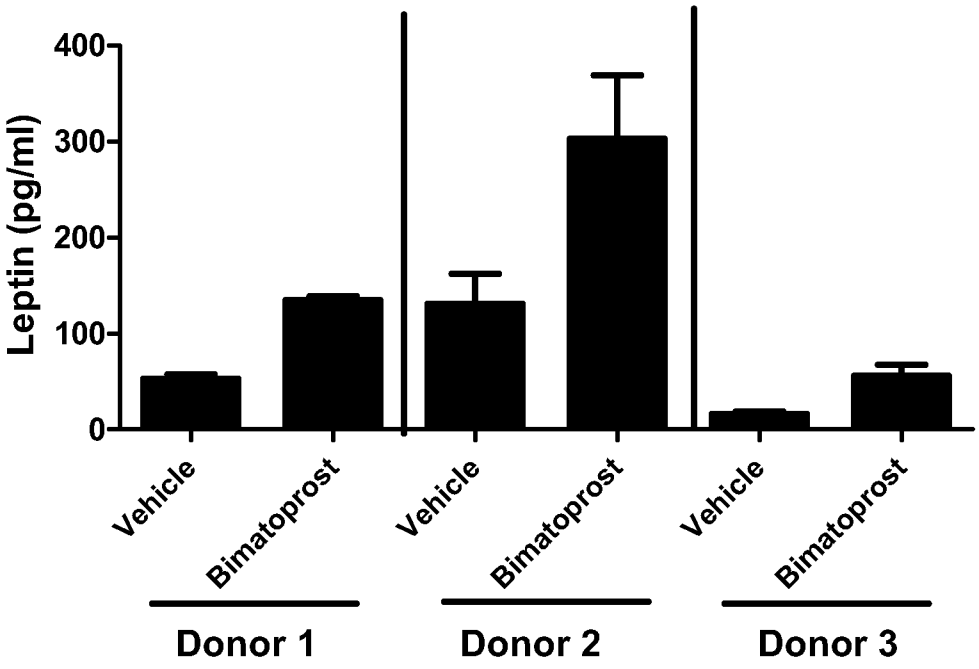
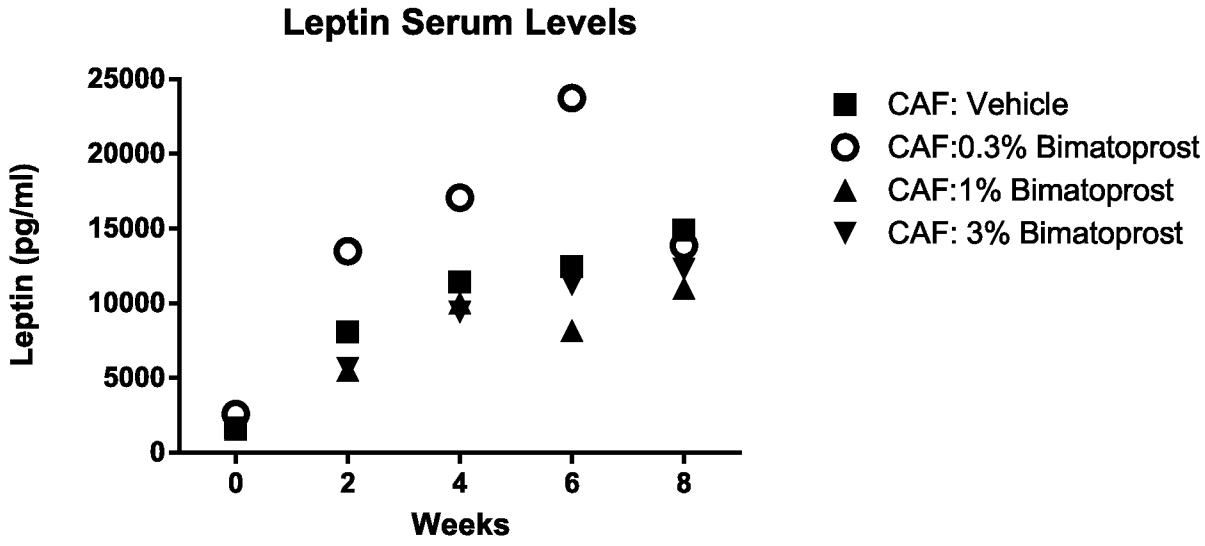

Leptin (pg/ml)
400
300
200
100
0
Vehicle
Bimatoprost
Vehicle
Bimatoprost
Vehicle
Bimatoprost
Donor 1
Donor 2
Donor 3

FIGURE 4


Leptin Serum Levels
Leptin (pg/ml)
25000
20000
15000
10000
5000
0
0
2
4
6
8
Weeks
CAF: Vehicle
CAF:0.3% Bimatoprost
CAF:1% Bimatoprost
CAF: 3% Bimatoprost

Rat #502. Vehicle. Liver has moderate fatty change (lipidosis) induced by CAF diet. Hepatocytes contain well defined vacuoles within the cell (arrow)

Rat #604. 0.3% Bim. Liver has mild-zonal fatty change (lipidosis) induced by CAF diet. Hepatocytes contain well vacuoles within the cell (arrow)

Rat #704. 0.1% Bim. Liver has minimal fatty change (lipidosis) induced by CAF diet. Hepatocytes contain well vacuoles within the cell (arrow)

Rat #801. 0.3% Bim. Normal

FIGURE 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/026110

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/5575 A61K9/70 A61P3/10 A61P3/04 A61P3/00
ADD.

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 practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/111806 A2 (TERAKINE THERAPEUTICS INC [US]; KALAYOGLU MURAT V [US]) 4 October 2007 (2007-10-04) the whole document paragraph [0013] paragraph [0017] - paragraph [0018] paragraph [0023] - paragraph [0031] paragraph [0039] paragraph [0044] - paragraph [0063] paragraph [0064] - paragraph [0069] paragraph [0066] examples 1,3,4,7 claims 1,4,9,12,17,20,31-44 ----- -/--	1,3-5, 9-15,17, 18

[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 application or patent 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)

"O" document referring to an oral disclosure, use, exhibition or other means

"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
6 May 2014	15/05/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Economou, Dimitrios

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/026110

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 2012/099942 A2 (MASSACHUSETTS EYE & EAR INFIRM [US]; GROSSKREUTZ CYNTHIA L [US]; PASQU) 26 July 2012 (2012-07-26) the whole document paragraph [0018] - paragraph [0020] paragraph [0023] SEE: bimatoprost, bimatoprost isopropyl ester, bimatoprost free acid; page 8 paragraph [0030] - paragraph [0038] paragraph [0079] paragraph [0106] - paragraph [0109] paragraph [0218] - paragraph [0220] paragraph [0251] - paragraph [0338] paragraph [0301] - paragraph [0307] page 90, paragraph 0189 - paragraph 0190 claims 1,3-16,18,21-27 -----	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/026110

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007111806 A2	04-10-2007	CA 2681668 A1	04-10-2007
		US 2008015257 A1	17-01-2008
		US 2010234466 A1	16-09-2010
		WO 2007111806 A2	04-10-2007
WO 2012099942 A2	26-07-2012	CA 2824317 A1	26-07-2012
		EP 2665481 A2	27-11-2013
		JP 2014503560 A	13-02-2014
		US 2014045933 A1	13-02-2014
		WO 2012099942 A2	26-07-2012

摘要

本发明提供用于增加瘦素生成和食欲抑制的前列腺酰胺类，诸如比马前列素及其前药。

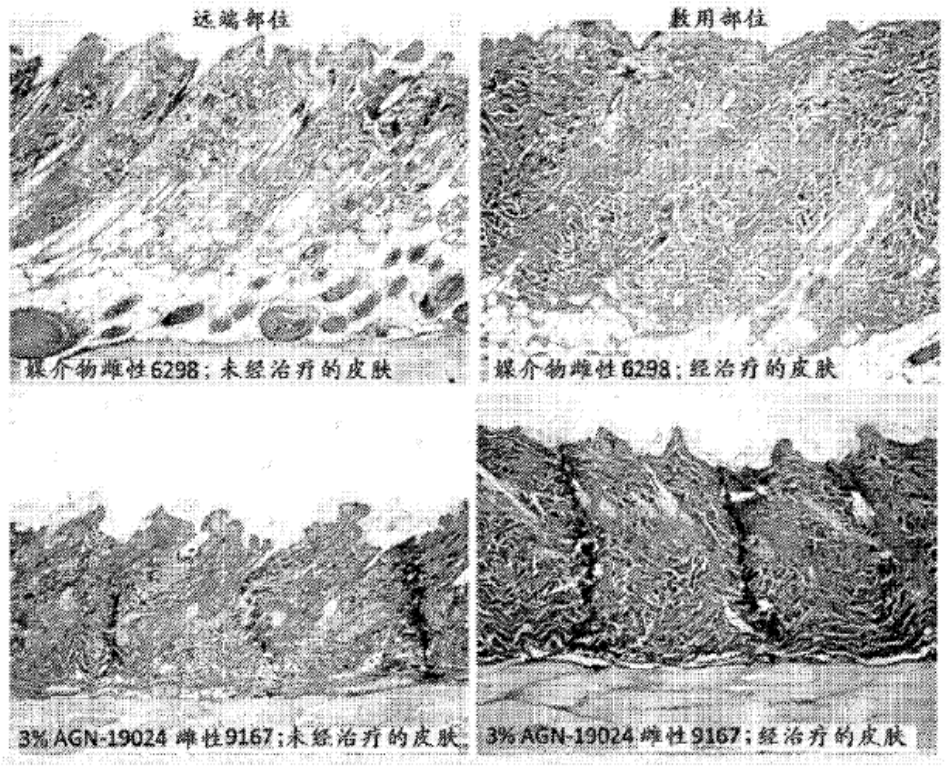


图 1