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CLERK U.S. DISTRICT COURT
CENTRAL DIST. OF CALIF.
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ALLERGAN, INC., MURRAY A. JOHNSTONE, M.D., and DUKE UNIVERSITY

UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

SOUTHERN DIVISION

ALLERGAN, INC.; MURRAY A. JOHNSTONE, M.D.; and DUKE UNIVERSITY,

Plaintiffs,

v.

ATHENA COSMETICS, INC.; PHARMA TECH INTERNATIONAL, INC.; DIMENSIONAL MERCHANDISING, INC.; STELLA INTERNATIONAL, LLC; PRODUCT INNOVATIONS, LLC; METICS, LLC; NUTRA-LUXE M.D., LLC; SKIN RESEARCH LABORATORIES, INC.; LIFETECH RESOURCES LLC; ROCASUBA, INC.; LA CANADA VENTURES, INC.; SUSAN F. LIN, M.D.; PETER THOMAS ROTH LABS LLC; and PETER THOMAS ROTH, INC.,

Defendants.

CASE NO. SACV09 -328 CJC (ANx)

COMPLAINT FOR PATENT INFRINGEMENT AND DEMAND FOR JURY TRIAL

UNITED STATES DISTRICT COURT, CENTRAL DISTRICT OF CALIFORNIA
CIVIL COVER SHEET

VIII(a). IDENTICAL CASES: Has this action been previously filed in this court and dismissed, remanded or closed? ☒ No ☐ Yes
If yes, list case number(s): _____

VIII(b). RELATED CASES: Have any cases been previously filed in this court that are related to the present case? ☐ No ☒ Yes
If yes, list case number(s): SACV07-1316 JVS (RNBx)

Civil cases are deemed related if a previously filed case and the present case:
(Check all boxes that apply) ☒ A. Arise from the same or closely related transactions, happenings, or events; or
☒ B. Call for determination of the same or substantially related or similar questions of law and fact; or
☒ C. For other reasons would entail substantial duplication of labor if heard by different judges; or
☒ D. Involve the same patent, trademark or copyright, and one of the factors identified above in a, b or c also is present.

IX. VENUE: (When completing the following information, use an additional sheet if necessary.)

(a) List the County in this District; California County outside of this District; State if other than California; or Foreign Country, in which EACH named plaintiff resides.
☐ Check here if the government, its agencies or employees is a named plaintiff. If this box is checked, go to item (b).

County in this District:*	California County outside of this District; State, if other than California; or Foreign Country
Orange County	Washington; North Carolina

(b) List the County in this District; California County outside of this District; State if other than California; or Foreign Country, in which EACH named defendant resides.
☐ Check here if the government, its agencies or employees is a named defendant. If this box is checked, go to item (c).

County in this District:*	California County outside of this District; State, if other than California; or Foreign Country
Los Angeles County	Nevada; New Jersey; Arizona; Contra Costa County, California; Florida; Connecticut; Massachusetts; San Mateo County. California; New York

(c) List the County in this District; California County outside of this District; State if other than California; or Foreign Country, in which EACH claim arose.
Note: In land condemnation cases, use the location of the tract of land involved.

County in this District:*	California County outside of this District; State, if other than California; or Foreign Country
Orange	

* Los Angeles, Orange, San Bernardino, Riverside, Ventura, Santa Barbara, or San Luis Obispo Counties
Note: In land condemnation cases, use the location of the tract of land involved

X. SIGNATURE OF ATTORNEY (OR PRO PER): J Kevin Rooney Date March 16, 2009

Notice to Counsel/Parties: The CV-71 (JS-44) Civil Cover Sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law. This form, approved by the Judicial Conference of the United States in September 1974, is required pursuant to Local Rule 3-1 is not filed but is used by the Clerk of the Court for the purpose of statistics, venue and initiating the civil docket sheet. (For more detailed instructions, see separate instructions sheet.)

Key to Statistical codes relating to Social Security Cases:

Nature of Suit Code	Abbreviation	Substantive Statement of Cause of Action
861	HIA	All claims for health insurance benefits (Medicare) under Title 18, Part A, of the Social Security Act, as amended. Also, include claims by hospitals, skilled nursing facilities, etc., for certification as providers of services under the program. (42 U.S.C. 1935FF(b))
862	BL	All claims for "Black Lung" benefits under Title 4, Part B, of the Federal Coal Mine Health and Safety Act of 1969. (30 U.S.C. 923)
863	DIWC	All claims filed by insured workers for disability insurance benefits under Title 2 of the Social Security Act, as amended; plus all claims filed for child's insurance benefits based on disability. (42 U.S.C. 405(g))
863	DIWW	All claims filed for widows or widowers insurance benefits based on disability under Title 2 of the Social Security Act, as amended. (42 U.S.C. 405(g))
864	SSID	All claims for supplemental security income payments based upon disability filed under Title 16 of the Social Security Act, as amended.
865	RSI	All claims for retirement (old age) and survivors benefits under Title 2 of the Social Security Act, as amended. (42 U.S.C. (g))

Plaintiffs, Allergan, Inc. ("Allergan"); Murray A. Johnstone, M.D. ("Dr. Johnstone"); and Duke University (together "Plaintiffs"), for their Complaint against defendants, Athena Cosmetics, Inc. ("Athena Cosmetics"); Pharma Tech International, Inc. ("Pharma Tech"); Dimensional Merchandising, Inc. ("DMI"); Stella International, LLC ("Stella"); Product Innovations, LLC ("PI"); Metics, LLC ("Metics"); Nutra-Luxe M.D., LLC ("Nutra-Luxe"); Skin Research Laboratories, Inc. ("SRL"); Lifetech Resources LLC ("Lifetech"); Rocasuba, Inc. ("Rocasuba"); La Canada Ventures, Inc. ("La Canada"); Susan Lin, M.D. ("Dr. Lin"); and Peter Thomas Roth Labs LLC and Peter Thomas Roth, Inc. (together "PTR") (collectively "Defendants"), allege upon personal knowledge with respect to themselves and their own acts, and upon information and belief with respect to all other matters, as follows:

JURISDICTION AND VENUE

1. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338, in that this is a civil action for patent infringement arising under the Patent Laws of the United States, Title 35, United States Code.

2. Venue is proper in this district and division under 28 U.S.C. §§ 1391 and 1400.

3. This Court has personal jurisdiction over Defendants by virtue of Defendants' manufacture, marketing, promotion, offers for sale, sales, and distribution of products, including the products which are the subject of this Complaint, throughout the State of California, in this District and in this Division. Defendants have also placed or helped to place, and are continuing to place, products into the stream of commerce within the United States, within California, in this District and in this Division, and it is reasonable to expect that such products will continue to enter and be used by consumers in California, including in this District and in this Division. In addition, this Court has personal jurisdiction over La Canada by virtue of its incorporation in California, Lifetech and PI by virtue of their being California limited

liability companies, and Dr. Lin by virtue of her being a resident of the State of California.

THE PARTIES

4. Allergan is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 2525 Dupont Drive, Irvine, California.

5. Dr. Johnstone is an individual residing in Seattle, Washington.

6. Duke University is one of the world's leading institutions for education, research, and medical care, and is located in Durham, North Carolina.

7. Athena Cosmetics is a corporation organized and existing under the laws of the State of Nevada, with its principal place of business at 701 North Green Valley Parkway, Henderson, Nevada. Allergan is informed and believes and thereon alleges that Athena is the successor-in-interest to Athena Cosmetics Corporation.

8. Pharma Tech is a corporation organized and existing under the laws of the State of New Jersey, with its principal place of business at 21 Just Road, Fairfield, New Jersey.

9. DMI is a domestic profit corporation organized and existing under the laws of the State of New Jersey, with its principal place of business at 86 North Main Street, Wharton, New Jersey.

10. Stella is a limited liability company organized and existing under the laws of the State of Arizona, with its principal place of business at 21827 North Scottsdale Road, Scottsdale, Arizona.

11. PI is a limited liability company organized and existing under the laws of the State of California, with its principal place of business at 1850 Mt. Diablo Boulevard, Walnut Creek, California.

12. Metics is a limited liability company organized and existing under the laws of the State of Arizona, with its principal place of business at 2338 West Royal Palm Road, Phoenix, Arizona.

13. Nutra-Luxe is a limited liability company organized and existing under the laws of the State of Florida, with its principal place of business at 6835 International Center Boulevard, Fort Meyers, Florida.

14. SRL is a corporation organized and existing under the laws of the State of Connecticut.

15. Lifetech is a limited liability company organized and existing under the laws of the State of California, with its principal place of business at 9540 Cozycroft Avenue, Chatsworth, California.

16. Rocasuba is a corporation organized and existing under the laws of the State of Massachusetts, with its principal place of business at 133 Falmouth Road, Mashpee, Massachusetts.

17. La Canada is a corporation organized and existing under the laws of the State of California, with its principal place of business at 1265 La Canada Rd, Hillsborough, California.

18. Dr. Lin is an individual residing in San Mateo, California.

19. Peter Thomas Roth Labs LLC is a limited liability company organized and existing under the laws of the State of New York, with its principal place of business at 460 Park Avenue, New York, New York.

20. Peter Thomas Roth, Inc. is a corporation organized and existing under the laws of the State of New York, with its principal place of business at 131 West 35th Street, New York, New York.

GENERAL ALLEGATIONS

21. Allergan manufactures and sells LUMIGAN® ophthalmic solution ("Lumigan"), a medication approved by the Food and Drug Administration ("FDA") to lower intraocular eye pressure in people with open-angle glaucoma or ocular hypertension. Lumigan eye drops contain the active ingredient bimatoprost, which is in a category of compounds known as prostamides. Prostamides are related to a category of compounds known as prostaglandins ("PG").

22. There are several different types of PGs, which are categorized by their chemical structures and are named by letters. For example, there are PGAs, PGEs, PGFs, PGIs, etc. In addition to natural PGs, there are synthetic (i.e., man-made) compounds that have chemical structures similar to natural PGs. Prostamides and PG esters are two different categories of such synthetic compounds.

23. There are two other medications on the market containing PGs that have been approved by the FDA to lower intraocular eye pressure in people with open-angle glaucoma or ocular hypertension: Xalatan(TM) and Travatan(TM). These products have been approved by the FDA only for the treatment of glaucoma, and both require a physician's prescription before they may be sold.

24. On December 26, 2008, the FDA approved an Allergan product named LATISSE(TM) (bimatoprost ophthalmic solution) 0.03% as a novel treatment for hypotrichosis of the eyelashes. Eyelash hypotrichosis is another name for having inadequate or not enough eyelashes. Other than LATISSE(TM), PGs, PGF esters and prostamides have only been approved by the FDA for use as a prescription medicine to lower intraocular eye pressure in people with open-angle glaucoma or ocular hypertension.

25. Dr. Johnstone filed a patent application claiming the use of PGFs to grow hair, and specifically eyelashes. Application No. 09/366,656 was filed in the United States Patent and Trademark Office on August 3, 1999, claiming the benefit of Provisional Application No. 60/037,237, filed on February 4, 1997.

26. On July 17, 2001, the United States Patent and Trademark Office duly and legally issued United States Patent No. 6,262,105 (the "'105 patent"), entitled "Method of Enhancing Hair Growth" to Dr. Johnstone. A true and correct copy of the '105 patent is attached hereto as Exhibit A. At that time, Dr. Johnstone became the sole and exclusive owner of the '105 patent.

27. On June 29, 2006, Allergan entered into a Patent License Agreement with Dr. Johnstone, which grants to Allergan the exclusive right to make, use, and vend the

patented invention throughout the world. A true and correct copy of the Patent License Agreement is attached hereto as Exhibit B.

28. On January 15, 2003, Patent Application No. 10/345,788 was filed in the United States Patent and Trademark Office, claiming the benefit of Provisional Application No. 60/354,425, filed on February 4, 2002.

29. On April 1, 2008, the United States Patent and Trademark Office duly and legally issued United States Patent No. 7,351,404 (the "'404 patent"). A true and correct copy of the '404 patent is attached hereto as Exhibit C. Allergan is the sole assignee of the '404 patent.

30. On May 26, 2005, Patent Application No. 11/138,097 was filed in the United States Patent and Trademark Office, claiming the benefit of Provisional Application No. 60/193,645, filed on March 31, 2000.

31. On June 17, 2008, the United States Patent and Trademark Office duly and legally issued United States Patent No. 7,388,029 (the "'029 patent"). A true and correct copy of the '029 patent is attached hereto as Exhibit D. Duke University is the sole assignee of the '029 patent.

32. On December 17, 2007, Allergan entered into a Patent License Agreement with Duke University, which grants to Allergan the exclusive right to make, use, and vend the patented invention throughout the world for treating the loss or promoting the growth of eyelashes and/or eyebrows. A true and correct copy of the Patent License Agreement is attached hereto as Exhibit E.

33. Defendants Athena Cosmetics, Stella, PI, Metics, Nutra-Luxe, SRL, Lifetech, Rocasuba, La Canada, Dr. Lin, and PTR have been marketing and selling hair and/or eyelash growth products with prostamides, PGF esters and/or PGFs as the active ingredient. For example, Athena Cosmetics is marketing, promoting and selling products named RevitaLash and Hair by RevitaLash; Stella, PI and Metics are marketing, promoting and selling a product named RenewLash; Nutra-Luxe is marketing, promoting and selling a product named BeautyLash MD; SRL and Lifetech

are marketing, promoting and selling a product named NeuLash; Rocasuba and Lifetech are marketing, promoting and selling a product named Rapidlash Eyelash Renewal Serum; La Canada and Dr. Lin are marketing, promoting and selling a product named MD Lash Factor; and PTR has been marketing, promoting and selling a product called Peter Thomas Roth Lashes To Die For.

34. Plaintiffs are informed and believe that Pharma Tech manufactures and sells the compound that is the active ingredient in Athena Cosmetics' RevitaLash and Hair by RevitaLash products. Plaintiffs are further informed and believe that Pharma Tech promotes the use of this compound in eyelash growth products through marketing.

35. Plaintiffs are informed and believe that DMI manufactures Athena Cosmetics' eyelash and hair growth products, RevitaLash and Hair by RevitaLash. On information and belief, DMI specifically promotes the use of Athena's product for use in a manner that directly infringes the '029 patent.

36. In violation of federal laws regulating the manufacture and sale of prescription medicines, Defendants are manufacturing and selling these products without FDA approval and/or without requiring a prescription.

37. Purchasers of Defendants' products directly infringe the '105, the '404, and/or the '029 patents by using those products in a manner described by the claims of the '105, the '404, and/or the '029 patents.

38. Defendants encourage the direct infringement of the '105, the '404, and/or the '029 patents. Defendants (other than Pharma Tech) develop, market, promote, and sell products for eyelash and hair growth with prostamides, PGF esters, and/or PGFs as an ingredient, and promote their products for use in a manner covered by the claims of the '105, the '404, and/or the '029 patents and provide instructions for use of those products in a manner that directly infringes the '105, the '404, and/or the '029 patents. Defendants (other than Pharma Tech) do so with the knowledge of the existence of the '105, the '404, and/or the '029 patents and with the knowledge and intent that their

products will be used by consumers in a manner that directly infringes the '105, the '404, and/or the '029 patents.

39. Pharma Tech manufactures, markets, promotes, and sells a compound described in the '029 patent to Athena for use in eyelash and hair growth products. Pharma Tech promotes the use of this compound in a manner covered by the claims of the '029 patent. Pharma Tech does so with the knowledge of the existence of the '029 patent and with the knowledge and intent that the products it manufactures and sells will be the active ingredient in products that will be used by consumers in a directly infringing manner.

40. DMI manufactures Athena's products for eyelash and hair growth. DMI manufactures this product with the knowledge of the existence of the '029 patent and with the knowledge and intent that the products it manufactures will be used by consumers in a directly infringing manner.

41. The eyelash growth products manufactured and sold by Defendants (other than Pharma Tech) have no substantial noninfringing use.

42. The compound Pharma Tech sells to Athena is designed especially for Athena and its eyelash and hair growth products. Pharma Tech knows that its compound is used as the active ingredient in Athena's eyelash and hair growth products, and Pharma Tech further knows that the eyelash and hair growth products cannot be used in any substantial way that does not infringe the '029 patent. Plaintiffs are further informed and believe that the compound Pharma Tech sells to Athena has no substantial noninfringing use.

43. Defendants recklessly disregard the '105, the '404 and '029 patents in their development, manufacturing, marketing, promotion, and sale of eyelash and hair growth products with prostamides, PGF esters and/or PGFs as an ingredient (and in the case of Pharma Tech, by supplying others with compounds for use in eyelash and hair growth products and promoting the use of the compounds in such products). Defendants proceed despite an objectively high likelihood that their actions contribute

to and induce infringement of the '105, the '404 and the '029 patents. All Defendants either know or should know that their actions risk infringement of the '105, the '404 and the '029 patents.

FIRST CLAIM FOR RELIEF

(Patent Infringement – United States Patent No. 6,262,105 – Against SRL, Lifetech and Rocasuba)

44. Plaintiffs repeat and incorporate by reference the allegations in paragraphs 1 through 43 above, as if fully set forth herein.

45. In violation of 35 U.S.C. § 271(b), SRL, Lifetech and Rocasuba have actively induced the infringement of one or more claims of the '105 patent.

46. In violation of 35 U.S.C. § 271(c), SRL, Lifetech and Rocasuba have contributed to the infringement of one or more claims of the '105 patent.

47. The infringement of the '105 patent by SRL, Lifetech and Rocasuba has been willful and wanton.

48. Allergan and Dr. Johnstone have suffered and will continue to suffer serious irreparable injury unless SRL's, Lifetech's and Rocasuba's infringement of the '105 patent is enjoined.

SECOND CLAIM FOR RELIEF

(Patent Infringement – United States Patent No. 7,351,404 – Against Defendants Stella, PI, Metics, Nutra-Luxe, La Canada, Dr. Lin and PTR)

49. Plaintiffs repeat and incorporate by reference the allegations in paragraphs 1 through 48 above, as if fully set forth herein.

50. In violation of 35 U.S.C. § 271(b), Stella, PI, Metics, Nutra-Luxe, La Canada, Dr. Lin, and PTR have actively induced the infringement of one or more claims of the '404 patent.

51. In violation of 35 U.S.C. § 271(c), Stella, PI, Metics, Nutra-Luxe, La Canada, Dr. Lin, and PTR have contributed to the infringement of one or more claims of the '404 patent.

52. The infringement of the '404 patent by Stella, PI, Metics, Nutra-Luxe, La Canada, Dr. Lin and PTR has been willful and wanton.

53. Allergan has suffered and will continue to suffer serious irreparable injury unless Stella's, PI's, Metics', Nutra-Luxe's, La Canada's, Dr. Lin's and PTR's infringement of the '404 patent is enjoined.

THIRD CLAIM FOR RELIEF

(Patent Infringement – United States Patent No. 7,388,029 – Against Defendants Stella, PI, Metics, Nutra-Luxe, Athena Cosmetics, Pharma Tech, DMI, La Canada and Dr. Lin)

54. Plaintiffs repeat and incorporate by reference the allegations in paragraphs 1 through 53 above, as if fully set forth herein.

55. In violation of 35 U.S.C. § 271(b), Stella, PI, Metics, Nutra-Luxe, Athena Cosmetics, Pharma Tech, DMI, La Canada and Dr. Lin have actively induced the infringement of one or more claims of the '029 patent.

56. In violation of 35 U.S.C. § 271(c), Stella, PI, Metics, Nutra-Luxe, Athena Cosmetics, Pharma Tech, DMI, La Canada and Dr. Lin have contributed to the infringement of one or more claims of the '029 patent.

57. The infringement of the '029 patent by Stella, PI, Metics, Nutra-Luxe, Athena Cosmetics, Pharma Tech, DMI, La Canada and Dr. Lin has been willful and wanton.

58. Allergan and Duke University have suffered and will continue to suffer serious irreparable injury unless Stella's, PI's, Metics', Nutra-Luxe's, Athena Cosmetics', Pharma Tech's, DMI's, La Canada's and Dr. Lin's infringement of the '029 patent is enjoined.

PRAYER FOR RELIEF

WHEREFORE, Allergan, Dr. Johnstone, and Duke University respectfully requests that this Court enter judgment in their favor and against Defendants and grant the following relief:

A. A judgment that SRL, Lifetech and Rocasuba have induced the infringement of the '105 patent in violation of 35 U.S.C. § 271(b);

B. A judgment that SRL, Lifetech and Rocasuba have contributed to the infringement of the '105 patent in violation of 35 U.S.C. § 271(c);

C. A judgment that Stella, PI, Metics, Nutra-Luxe, La Canada, Dr. Lin, and PTR have induced the infringement of the '404 patent in violation of 35 U.S.C. § 271(b);

D. A judgment that Stella, PI, Metics, Nutra-Luxe, La Canada, Dr. Lin, and PTR have contributed to the infringement of the '404 patent in violation of 35 U.S.C. § 271(c);

E. A judgment that Stella, PI, Metics, Nutra-Luxe, Athena Cosmetics, Pharma Tech, DMI, La Canada and Dr. Lin have induced the infringement of the '029 patent in violation of 35 U.S.C. § 271(b);

F. A judgment that Stella, PI, Metics, Nutra-Luxe, Athena Cosmetics, Pharma Tech, DMI, La Canada and Dr. Lin have contributed to the infringement of the '029 patent in violation of 35 U.S.C. § 271(c);

G. A judgment that SRL's, Lifetech's and Rocasuba's infringement of the '105 patent has been willful and wanton;

H. A judgment that Stella's, PI's, Metics', Nutra-Luxe's, La Canada's, Dr. Lin's, and PTR's infringement of the '404 patent has been willful and wanton;

I. A judgment that Stella's, PI's, Metics', Nutra-Luxe's, Athena Cosmetics', Pharma Tech's, DMI's, La Canada's and Dr. Lin's infringement of the '029 patent has been willful and wanton;

J. A preliminary and permanent injunction, pursuant to 35 U.S.C. § 283, enjoining SRL, Lifetech and Rocasuba, and all persons in active concert or participation with SRL, Lifetech and Rocasuba, from any further acts of infringement, inducement of infringement, or contributory infringement of the '105 patent;

K. A preliminary and permanent injunction, pursuant to 35 U.S.C. § 283, enjoining Stella, PI, Metics, Nutra-Luxe, La Canada, Dr. Lin, and PTR, and all persons in active concert or participation with Stella, PI, Metics, Nutra-Luxe, La Canada, Dr. Lin, and PTR, from any further acts of infringement, inducement of infringement, or contributory infringement of the '404 patent;

L. A preliminary and permanent injunction, pursuant to 35 U.S.C. § 283, enjoining Stella, PI, Metics, Nutra-Luxe, Athena Cosmetics, Pharma Tech, DMI, La Canada, Dr. Lin, and PTI, and all persons in active concert or participation with Stella, PI, Metics, Nutra-Luxe, Athena Cosmetics, Pharma Tech, DMI, La Canada and Dr. Lin, from any further acts of infringement, inducement of infringement, or contributory infringement of the '029 patent;

M. An order, pursuant to 35 U.S.C. § 284, awarding Allergan and Dr. Johnstone damages adequate to compensate Allergan and Dr. Johnstone for SRL's, Lifetech's and Rocasuba's infringement of the '105 patent, in an amount to be determined at trial, but in no event less than a reasonable royalty;

N. An order, pursuant to 35 U.S.C. § 284, awarding Allergan damages adequate to compensate Allergan for Stella's, PI's, Metics', Nutra-Luxe's, La Canada's, Dr. Lin's, and PTR's infringement of the '404 patent, in an amount to be determined at trial, but in no event less than a reasonable royalty;

O. An order, pursuant to 35 U.S.C. § 284, awarding Allergan and Duke University damages adequate to compensate Allergan and Duke University for Stella's, PI's, Metics', Nutra-Luxe's, Athena Cosmetics', Pharma Tech's, DMI's, La Canada's and Dr. Lin's infringement of the '029 patent, in an amount to be determined at trial, but in no event less than a reasonable royalty;

P. An order, pursuant to 35 U.S.C. § 284, and based on SRL's, Lifetech's and Rocasuba's willful and wanton infringement of the '105 patent, trebling all damages awarded to Allergan and Dr. Johnstone under the '105 patent;

Q. An order, pursuant to 35 U.S.C. § 284, and based on Stella's, PI's, Metics', Nutra-Luxe's, La Canada's, Dr. Lin's, and PTR's willful and wanton infringement of the '404 patent, trebling all damages awarded to Allergan under the '404 patent;

R. An order, pursuant to 35 U.S.C. § 284, and based on Stella's, PI's, Metics', Nutra-Luxe's, Athena Cosmetics', Pharma Tech's, DMI's, La Canada's, and Dr. Lin's willful and wanton infringement of the '029 patent, trebling all damages awarded to Allergan and Duke University under the '029 patent;

S. An order, pursuant to 35 U.S.C. § 284, awarding to Allergan, Dr. Johnstone and Duke University interest on the damages and their costs incurred in this action;

T. An order, pursuant to 35 U.S.C. § 285, finding that this is an exceptional case and awarding to Allergan, Dr. Johnstone and Duke University their reasonable attorneys' fees incurred in this action; and

U. Such other and further relief as this Court may deem just and proper.

Dated: March 13, 2009

JEFFREY T. THOMAS
T. KEVIN ROOSEVELT
GIBSON, DUNN & CRUTCHER LLP

By: _____
Jeffrey T. Thomas

Attorneys for Plaintiffs ALLERGAN, INC., MURRAY A. JOHNSTONE, M.D., and DUKE UNIVERSITY

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DEMAND FOR JURY TRIAL

Allergan, Dr. Johnstone and Duke University demand trial by jury on all issues and causes of action properly tried to a jury, pursuant to Federal Rule of Civil Procedure 38.

Dated: March 13, 2009

JEFFREY T. THOMAS
T. KEVIN ROOSEVELT
GIBSON, DUNN & CRUTCHER LLP

By: _____
Jeffrey T. Thomas

Attorneys for Plaintiffs ALLERGAN, INC., MURRAY A. JOHNSTONE, M.D., and DUKE UNIVERSITY

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Exhibit A

US006262105B1

(12) **United States Patent**
Johnstone

(10) **Patent No.: US 6,262,105 B1**
(45) **Date of Patent: Jul. 17, 2001**

(54) **METHOD OF ENHANCING HAIR GROWTH**

(76) Inventor: **Murray A. Johnstone**, 1221 Madison, #1124, Seattle, WA (US) 98104

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/366,656**

(22) Filed: **Aug. 3, 1999**

Related U.S. Application Data

(63) Continuation of application No. PCT/US98/02289, filed on Feb. 3, 1998.
(60) Provisional application No. 60/037,237, filed on Feb. 4, 1997.

(51) **Int. Cl.**[7] **A61K 31/38; A61K 31/215**
(52) **U.S. Cl.** **514/430**; 514/530; 514/880
(58) **Field of Search** 514/430, 530

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(57) **ABSTRACT**

Methods and compositions for stimulating the growth of hair are disclosed containing prostaglandins, derivatives or analogues thereof for use in treating the skin or scalp of a human or non-human animal. Prostaglandins of the A_2, $F_{2\alpha}$ and E_2 types are preferred for this treatment method.

9 Claims, No Drawings

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METHOD OF ENHANCING HAIR GROWTH

This application is a continuation of international application number PCT/US98/02289, filed Feb. 3, 1998, and claims the benefit of provisional application No. 60/037,237, filed Feb. 4, 1997, priority from the filing dates of which is hereby claimed under 35 U.S.C. §§ 119 and 120.

FIELD OF THE INVENTION

This invention relates to a process for stimulating the growth of mammalian hair comprising the application to mammalian skin of prostaglandin compounds, derivatives and analogues and the pharmacologically acceptable acid addition salts thereof, alone or in association with a topical pharmaceutical carrier.

More particularly, the invention is concerned with the use of prostaglandin derivatives of PGA, PGE and PGF for the stimulation of hair growth. The invention relates also to therapeutic compositions, containing an active amount of these prostaglandin derivatives, and the manufacture of such compositions.

BACKGROUND OF THE INVENTION

Dermatologists recognize many different types of hair loss, the most common by far being "alopecia" wherein human males begin losing scalp hair at the temples and on the crown of the head as they get older. While this type of hair loss is largely confined to males, hence its common name "male pattern baldness," it is not unknown in women. Be that as it may, no known cure has yet been found despite continuing attempts to discover one.

Notwithstanding the fact that nothing heretofore has been found which is effective in preventing, yet alone reversing, male pattern baldness, a good deal is known about various types of human hair and its growth patterns on various parts of the body.

For purposes of the present invention, we need consider various types of hair, including, terminal hairs and vellus hairs and modified terminal hairs, such as seen in eye lashes and eye brows. Terminal hairs are coarse, pigmented, long hairs in which the bulb of the hair follicle is seated deep in the dermis. Vellus hairs, on the other hand, are fine, thin, non-pigmented short hairs in which the hair bulb is located superficially in the dermis. As alopecia progresses, a transition takes place in the area of approaching baldness wherein the hairs themselves are changing from the terminal to the vellus type.

Another factor that contributes to the end result is a change in the cycle of hair growth. All hair, both human and animal, passes through a life cycle that includes three phases, namely, (1) the anagen phase (2) the catagen phase and (3) the telogen phase. The anagen phase is the period of active hair growth and, insofar as scalp hair is concerned, this generally lasts from 3–5 years. The catagen phase is a short transitional phase between the anagen and telogen phases which, in the case of scalp hair, lasts only 1–2 weeks. The final phase is the telogen phase which, for all practical purposes, can be denominated a "resting phase" where all growth ceases and the hair eventually is shed preparatory to the follicle commencing to grow a new one. Scalp hair in the telogen phase is also relatively short-lived, some 3–4 months elapsing before the hair is shed and a new one begins to grow.

Under normal hair growth conditions on the scalp, approximately 88% of the hairs are in the anagen phase, only 1% in catagen and the remainder in telogen. With the onset of male pattern baldness, a successively greater proportion of the hairs are in the telogen phase with correspondingly fewer in the active growth anagen phase.

The remaining result associated with alopecia is the severe diminution of hair follicles. A bald human subject will average only about 306 follicles per square centimeter, whereas, a non-bald one in the same age group (30–90 years) will still have an average of 460 follicles per square centimeter. This amounts to a one-third reduction in hair follicles which, when added to the increased proportion of vellus hair follicles and the increased number of hair follicles in telogen, is both significant and noticeable. It is written that approximately 50% of the hairs must be shed to produce visible thinning of scalp hair. It is thus a combination of these factors: (1) transition of hairs from terminal to vellus, (2) increased number of telogen hairs—some of which have been shed, and (3) loss of hair follicles (atrophy) that produces "baldness".

While a good deal is known about the results of male pattern baldness, very little is known about its cause. The cause is generally believed to be genetic and hormonal in origin although, as will be seen presently, the known prior art attempts to control it through hormone adjustment have been singularly unsuccessful.

One known treatment for male pattern alopecia is hair transplantation. Plugs of skin containing hair are transplanted from areas of the scalp where hair is growing to bald areas with reasonable success; however, the procedure is a costly one in addition to being time-consuming and quite painful. Furthermore, the solution is inadequate from the standpoint that it becomes a practical, if not an economic, impossibility to replace but a tiny fraction of the hair present in a normal healthy head of hair.

Other non-drug related approaches to the problem include such things as ultra-violet radiation, massage, psychiatric treatment and exercise therapy. None of these, however, has been generally accepted as being effective. Even such things as revascularization surgery and acupuncture have shown little, if any, promise.

By far, the most common approach to the problem of discovering a remedy for hair loss and male pattern alopecia has been one of drug therapy. Many types of drugs ranging from vitamins to hormones have been tried and only recently has there been any indication whatsoever of even moderate success. For instance, it was felt for a long time that since an androgenic hormone was necessary for the development of male pattern baldness, that either systemic or topical application of an antiandrogenic hormone would provide the necessary inhibiting action to keep the baldness from occurring. The theory was promising but the results were uniformly disappointing.

The androgenic hormone testosterone was known, for example, to stimulate hair growth when applied topically to the deltoid area as well as when injected into the beard and pubic regions. Even oral administration was found to result in an increased hair growth in the beard and pubic areas as well as upon the trunk and extremities. While topical application to the arm causes increased hair growth, it is ineffective on the scalp and some thinning may even result. Heavy doses of testosterone have even been known to cause male pattern alopecia.

Certain therapeutic agents have been known to induce hair growth in extensive areas of the trunk, limbs and even occasionally on the face. Such hair is of intermediate status in that it is coarser than vellus but not as coarse as terminal

hair. The hair is generally quite short with a length of 3 cm. being about maximum. Once the patient ceases taking the drug, the hair reverts to whatever is normal for the particular site after six months to a year has elapsed. An example of such a drug is diphenylhydantoin which is an anticonvulsant drug widely used to control epileptic seizures. Hypertrichosis is frequently observed in epileptic children some two or three months after starting the drug and first becomes noticeable on the extensor aspects of the limbs and later on the trunk and face. The pattern is not unlike that sometimes caused by injury to the head. As for the hair, it is often shed when the drug is discontinued but may, in some circumstances, remain.

Streptomycin is another drug that has been found to produce hypertrichosis in much the same way as diphenylhydantoin when administered to children suffering from tuberculous meningitis. About the same effects were observed and the onset and reversal of the hypertrichosis in relation to the period of treatment with the antibiotic leave little question but that it was the causative agent.

Two treatments have been demonstrated as showing some promise in reversing male pattern alopecia. These treatments include the use of a microemulsion cream containing both estradiol and oxandrolone as its active ingredients and the use of organic silicon.

In addition to the foregoing, it has been reported in U.S. Pat. Nos. 4,139,619 and 4,968,812 that the compound minoxidil is useful for the treatment of male pattern baldness. That compound, among others, has proven to have considerable therapeutic value in the treatment of severe hypertension. It is a so-called "vasodilator" which , as the name implies, functions to dilate the peripheral vascular system. Dermatologists and others have recognized that prolonged vasodilation of certain areas of the human body other than the scalp sometimes result in increased hair growth even in the absence of any vasodilating therapeutic agent. For instance, increased hair growth around surgical scars is not uncommon. Similarly, arteriovenous fistula have been known to result in increased vascularity accompanied by enhanced hair growth. Externally-induced vasodilation of the skin, such as, for example, by repeated biting of the limbs by mental retardates and localized stimulation of the shoulders by water carries has been noted to bring on hypertrichosis in the affected areas. Be that as it may, similar techniques such as continued periodic massage of the scalp have been found totally ineffective as a means for restoring lost hair growth to the scalp. Scar tissue on the scalp inhibits rather than promotes hair growth.

The use of prostaglandins in the treatment of glaucoma has also recently been reported. Glaucoma treatments can be given by means of drugs, laser or surgery. In drug treatment, the purpose is to lower either the flow (F) or the resistance (R) which will result in a reduced intraocular pressure (IOP); alternatively to increase the flow via the uveoscleral route which also gives a reduced pressure. Cholinergic agonists, for instance pilocarpine, reduce the intraocular pressure mainly by increasing the outflow through Schlemm's canal.

Prostaglandins, which recently have met an increasing interest as IOP-lowering substances may be active in that they will cause an increase in the uveoscleral outflow. They do not appear, however to have any effect on the formation of aqueous humor or on the conventional outflow through Schlemm's canal.

The use of prostaglandins and their derivatives is described for instance in U.S. Pat. Nos. 4.599,353 (Bito), U.S. Pat. No. 4,883,819 (Bito), U.S. Pat. No. 4,952,581 (Bito), International Application Publication No. WO89/03384 (Stjernschantz), European Patent Nos. 170258 (Cooper), 253094 (Gob, Yasumasa), 308135 (Ueno, Ryuzo), and by Alm, A., *Surv. Ophthalmol.* 41(Suppl. 2): 5105–5110 (1997); Bito, L. Z. et al., *Invest. Ophthalmol. Vis. Sci.* 24(3): 312–319 (1983); Camras, C. B. et al., *Current Eye Res.* 1(40): 205–209 (1981); Camras, C. B. et al., *Invest. Ophthalmol. Vis. Sci.* 28(3): 463–469 (1987); Camras, C. B. et al., *Invest. Ophthalmol. Vis. Sci.* 28(6): 921–926 (1987); Camras, C. B. et al., *Invest. Ophthalmol. Vis. Sci.* 29(9): 1428–1436 (1988); Camras, C. B. et al., Ophthalmology 103(1): 138–147 (1996); Camras, C. B. et al., *Ophthalmology* 103(11): 1916–1924 (1996); Giuffre, G., *Graefes. Arch. Clin. Exp. Ophthalmol.* 222(3): 139–141 (1985); Kaufman, P. L., *Exp. Eye Res.* 43(5): 819–827 (1986); Kerstetter, J. R. et al., *Am. J. Ophthalmol.* 105(1): 30–34 (1988); Lee, P. -Y. et al., *Invest. Ophihalmol. Vis. Sci.* 29(10): 1474–1477 (1988); Villumsen, J. et al., *Br. J. Ophthalmol.* 73(12): 975–979 (1989); and Mishima, H. K. et al., *Arch. Ophthalmol.* 114(8): 929–932 (1996).

U.S. Pat. Nos. 5,321,128 (Stjernschantz et al.), U.S. Pat. No. 5,422,368 (Stjernschantz et al.), U.S. Pat. No. 5,422,369 (Stjernschantz et al.), and U.S. Pat. No. 5,578,618 (Stjernschantz et al.) disclose the use of certain derivatives of prostaglandins A, E and F, in which the omega chain has been modified with the common feature of containing a ring structure, for the treatment of glaucoma or ocular hypertension. A representative prostaglandin derivative from this group, 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester, also known as latanoprost or Xalatan (trade name, Pharmacia & Upjohn Company, Kalamazoo, Mich., U.S.A.), has recently been introduced into clinical use for the treatment of glaucoma. Introduction of the agent represents the culmination of years of effort by Laslo Bito and others who noted that prostaglandins may lower intraocular pressure. They continued to work with the medication prostaglandin F2 alpha ($PGF_2\alpha$) to optimize efficacy while minimizing side effects. The isopropyl ester had increased efficacy with reduced side effects thought to be partially a result of the lower dose required. Because of the troublesome persistent side effect of eye redness, or hyperemia associated with vasodilation a phenyl-substituted compound was developed. This phenyl-substituted compound was found to be effective in elimination of the troublesome clinical problem of hyperemia or vasodilation. Finally resolution of the epimeric mixture was found to be an even more potent ocular hypotensive agent. Prostaglandins represent a novel new class of drugs for the treatment of glaucoma. The agents have previously been in use in limited clinical trials to establish efficacy and safety data for FDA approval. FDA approval followed by distribution for clinical use has occurred only within the past year. Accordingly, there has not been a large clinical experience with this medication and as with other new medications unrecognized side affects are not unlikely.

U.S. Pat. No. 4,311,707 (Bernbaum et al.), U.S. Pat. No. 5,288,754 (Woodward et al.) and U.S. Pat. No. 5,532,708 (Woodward et al.) describe prostaglandin derivatives having vasodilation properties.

Finally, International Publication No. WO95/11003 (Stjernschantz et al.) discloses compositions containing prostaglandins, and derivatives and analogues thereof, particularly derivatives and analogues of prostaglandin F2α and prostaglandin E2, for increasing pigmentation of tissues or modified tissues, e.g., hair.

The foregoing notwithstanding, the literature is devoid of any suggestion that prostaglandin derivatives may be useful

in the stimulation of hair growth despite extensive detailed studies of numerous patients from three disparate regions of the world (Camras, C. B. (1996a), supra; Mishima, H. K., supra; and Alm, A. and Stjernschantz, J., *Ophthalmology* 102:1243–1252 (1995)).

It is, therefore, a principal object of the present invention to provide a novel and effective treatment for the stimulation of hair growth and the treatment of male pattern baldness.

Another object of the invention forming the subject matter hereof is to provide a method of stimulating hair growth in humans and non-human animals that is compatible with various types of therapeutic agents or carriers and, therefore, would appear to be combinable with those which, by themselves, demonstrate some therapeutic activity such as, for example, microemulsion creams or topical compositions containing estradiol and oxandrolone, minoxidil or agents that block the conversion of testosterone to dihydrotesterone (Procipia).

Still another objective is the provision of a treatment for the stimulation of hair growth which, while effective for its intended purpose, is apparently non-toxic and relatively free of unwanted side effects.

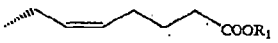
An additional object of the invention herein disclosed and claimed is to provide a method for treating hair loss in men or women which can be applied by the patient under medical supervision no more stringent than that demanded for other topically-administered therapeutic agents.

Other objects of the invention are to provide a treatment for male pattern alopecia which is safe, simple, painless, cosmetic in the sense of being invisible, easy to apply and quite inexpensive when compared with hair transplants and the like.

SUMMARY OF THE INVENTION

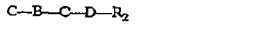
This invention provides pharmaceutical compositions for topical application comprising a prostaglandin compound, in free form or a pharmaceutically acceptable salt thereof, in association with a pharmaceutical carrier adapted for topical application to mammalian skin. Preferably, the prostaglandin compound is a $PGF_2\alpha$ derivative, such as 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ or a pharmaceutically acceptable salt thereof.

Another aspect of the invention provides methods for stimulating the rate of hair growth and for stimulating the conversion of vellus hair or intermediate hair to growth as terminal hair in a human or non-human animal by administering to the skin of the animal an effective amount of a prostaglandin PGA, PBE or PGF compound wherein the alpha chain of the compound has the formula:



in which R_1 is H or an alkyl group having 1–10 carbon atoms, especially 1–6 atoms, for instance methyl, ethyl, propyl, isopropyl, butyl, isobutyl, neopentyl or benzyl or a derivative giving the final substance equivalent properties as a hair growth stimulating agent; and

the omega chain of the compound has the formula:



wherein C is a carbon atom or loweralkyl chain, optionally substituted with one or more —OH groups;

B is a single bond, a double bond or a triple bond;

D is a chain with 1–10 carbon atoms, optionally substituted with one or more —OH groups; and

R_2 is H or a phenyl group which is unsubstituted or has one or more substituents selected from the group consisting of C_1–C_5 alkyl groups, C_1–C_4 alkoxy groups, trifluoromethyl groups, C_1–C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl groups; or an aromatic heterocyclic group having 5–6 ring atoms, like thiazol, imidazole, pyrrolidine, thiopene and oxazole; or a cycloalkane or a cycloalkene with 3–7 carbon atoms in the ring, optionally substituted with lower alkyl groups with 1–5 carbon atoms;

and the pharmacologically acceptable acid addition salts thereof, in association with a topical pharmaceutical carrier.

These and other aspects of the invention will become apparent from the description of the invention which follows below.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Alopecia (baldness) a deficiency of either normal or abnormal hair, is primarily a cosmetic problem in humans. It is a deficiency of terminal hair, the broad diameter, colored hair that is readily seen. However, in the so-called bald person although there is a noticeable absence of terminal hair, the skin does contain vellus hair which is a fine colorless hair which may require microscopic examination to determine its presence. This vellus hair is a precursor to terminal hair. In accordance with the invention as described herein, prostaglandin derivatives and analogues can be used to stimulate, such as stimulating the conversion of vellus hair to growth as terminal hair as well as increasing the rate of growth of terminal hair.

In the course of treating patients having glaucoma, treatment may only be appropriate in one eye. Within the course of daily practice it was discovered that a patient who had taken a representative prostaglandin derivative, latanoprost, for 17 weeks has lashes that were longer, thicker and fuller in the treated eye than in the non-treated eye. On examination the difference was found to be very striking. The lashes were about 30% longer and had a more full dense appearance in the treated eye. The lash appearance on the lids of the treated eye would have appeared quite attractive if it represented a bilateral phenomenon. Because of its asymmetric nature, the long lashes on one side could be construed as disturbing from a cosmetic standpoint. Because of the very unusual appearance a systematic examination of other patients who were taking latanoprost in only one eye was made. It soon became apparent that this altered appearance was not an isolated finding. Comparison of the lids of patients who were taking latanoprost in only one eye following 5–6 weeks of use revealed subtle changes in the lashes and adjacent hairs of the latanoprost-treated side in several patients. Definite differences could be identified to varying degrees in the lashes and adjacent hairs of all patients who were taking the drug on a unilateral basis for longer than 3 months.

These findings were totally unexpected and surprising. Minoxidil is thought to stimulate hair growth by its ability to cause vasodilation suggesting that agents with such a capability may be uniquely effective in stimulating hair growth. The finding that prostaglandin derivatives, such as latanoprost, stimulate hair growth is especially surprising and unexpected since latanoprost was specifically tailored to eliminate clinical hyperemia and vasodilation.

The changes in the lashes were apparent on gross inspection in several patients once attention was focused on the issue. In those with light colored hair and lashes, the differences were only seen easily with the aid of the high magnification and lighting capabilities of the slit lamp biomicroscope. In the course of a glaucoma follow up examination, attention is generally immediately focused on the eye itself. Because of the high power magnification needed only one eye is seen at a time and the eye is seen at a high enough power that the lashes are not in focus. At these higher powers, any lash asymmetry between the two eyes is not likely to be noticed except by careful systematic comparison of the lashes and adjacent hairs of the eyelids of the two eyes.

Observed parameters leading to the conclusion that more robust hair growth occurred in the treated area following administration of latanoprost were multiple. They included increased length of lashes, increased numbers of lashes along the normal lash line, increased thickness and luster of lashes, increased auxiliary lash-like terminal hair in transitional areas adjacent to areas of normal lash growth, increased lash-like terminal hairs at the medial and lateral canthal area, increased pigmentation of the lashes, increased numbers, increased length, as well as increased luster, and thickness of fine hair on the skin of the adjacent lid, and finally increased perpendicular angulation of lashes and lash-like terminal hairs. The conclusion that hair growth is stimulated by latanoprost is thus supported not by evidence of a difference in a single parameter but is based on multiple parameters of hair appearance in treated vs. control areas in 43 subjects. This finding is entirely unexpected and represents a previously unrecognized effect of prostaglandins on stimulation of hair follicles. Increased pigmentation of the iris, primarily those with hazel and light brown eyes is, however, a known side effect of latanoprost and was reported to the FDA during clinical trials because of a concern that some patients might find a change in iris color unacceptable, especially if unilateral. The change in pigmentation of the iris is thought to result from stimulation of melanin production, rather than proliferation of melanocytes. Another manifestation of the ability of the drug latanoprost to alter melanin production appears to be an analogous stimulation of melanin production in the hair follicles. The increased pigmentation observed may not be limited to selective stimulation of melanin production. In view of all the other evidence of increased activity of the hair follicles described in this patent it seems likely that the increased pigmentation is a manifestation of a much broader robust stimulation of all the components involved in growth and development of the hair within the hair follicle. Thus, described herein is the stimulation of growth of hairs of different types in different areas, the lashes, transitional auxiliary hairs adjacent to the lashes and fine microscopic hair on the skin. The modified hairs of the lashes normally turn over slowly and are in their resting phase longer than hair on, for example, the scalp. The ability to cause differences in appearance of lashes, the ability to stimulate conversion of vellus or intermediate hair to terminal hairs in transitional areas and the ability to stimulate growth of vellus hair on the skin indicates that the agent is a diversely effective and efficacious agent for the stimulation of hair growth. Thus, the present invention provides a treatment by prostaglandins of hair of the scalp, eyebrows, beard and other areas that contain hair that results in increased hair growth in the corresponding areas.

Patients that are treated in or around the eye with compounds of the invention, such as latanoprost regularly develop hypertrichosis including altered differentiation, numbers, length, thickness, curvature and pigmentation in the region of treatment. The phases of the hair cycle require coordinated control of cellular proliferation, differentiation, migration, angiogenesis, involution and apoptosis. Numerous cellular interactions occur and require simultaneous participation of epithelial cells, dermal papilla fibroblasts, nerve fibers, melanocytes, and vascular endothelial cells.

Although practice of the invention is not limited to any particular mechanism of operation, a review of properties characterized through laboratory studies provide several possible mechanisms that may individually or in concert explain the altered growth pattern of hair follicles observed in the current clinical study. Hair follicles have a rich vasculature in the region of the base of the hair bulb. PGF2 alpha analogs can cause a vasodilation effect and through that mechanism may provide enhanced perfusion to the region of the hair bulb and thus stimulate increased trophic activity in the hair follicles.

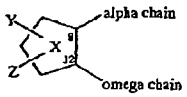
PGF2 alpha analogues stimulate cell surface receptors linked by a G protein to phosphoralase C, an enzyme with the principle property of triggering the activation of a family of protein kinases. The protein kinases produce a varied array of responses that play a key role in trophic metabolic activity and are of fundamental importance in cell growth (Darnell, J. et al., *Molecular Cell Biology* (Darnell, J., Lidish, H., Baltimore, D., Eds.), W. H. Freeman and Company, New York, N.Y., pp. 738–743 (1990)).

Modulation of the extracellular matrix environment and integrins, another well characterized property of PGF2 alpha analogues alters tensegrity. Tensegrity represents an architectual system in which structures stabilize themselves by balancing the counteracting forces of compression and tension to give shape and structure to natural and artificial forms. The cytoskeleton of the living cell is a framework composed of compressive "girders" inside the cell that are represented either by microtubules or large bundles of cross-linked microfilaments with the cytoskeleton. A third component of the cytoskeleton, the intermediate filaments, are the integrators connecting microtubules and contratile microfilaments to one another as well as to the cell surface membrane and to the cell's nucleus. The intermediate filaments act as guy wires, stiffening the central nucleus and securing it in place. By modifying the shape of the cell as occurs with alterations in the extracellular matrix researchers can switch the cells between different genetic programs. For example, by altering the extracellular environment they can cause the cells to divide, to differentiate, to remain in steady state, or to involute or to activate a death program known as apoptosis. Alterations in the extracellular matrix can thus evoke responses such as gene expression, cell division and prevention of apoptosis (Darnell, J. et al., supra), and prolong the hair cycle. By increasing the duration of the cell cycle, the interval in the anagen phase may be increased permitting hypertrophy of the follicles with longer and thicker hairs as observed. PGF2 alpha is capable of direct induction of DNA replication and stimulates cell division and growth in a number of tissues in vitro (Fagot, D. et al., *Endocrinology* 132:1724–1734 (1993).

Latanoprost, an analogue of PGF2 alpha, retains the well-characterized functional groups that confer the ability to act as a mitogen or growth factor (Jimenez de Asua, L. et al., *Journal of Biological Chemistry* 256:8774–8780 (1983).

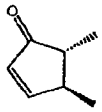
Properties characterized through laboratory studies thus provide several possible mechanisms that may individually or in concert explain the altered growth pattern of hair follicles observed in the current clinical study.

Prostaglandin derivatives have the general structure:

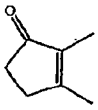


wherein X represents the alicyclic ring C_8–C_{12} which may contain one or more double bonds, Y and Z represent substituents in the 9, 10 and/or 11 positions that may be hydrogen, hydroxyl or oxo—in either stereochemical configuration, and the bonds between the ring and the side chains represent the various isomers. The prostaglandins PGA, PGB, PGC, PGD, PGE, PGF and PGJ X have the following ring X structural formulas:

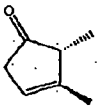
PGA



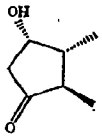
PGB



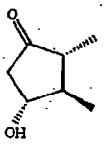
PGC



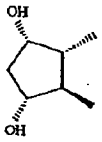
PGD



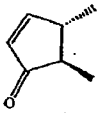
PGE



PGF

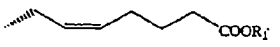


PGJ



Particularly useful in the practice of the present invention are derivatives of the prostaglandins characterized by presence or lack of modifications to their omega chain and the presence or lack of various modifications of the alpha chain.

The alpha chain can typically be the naturally occurring alpha chain, which is esterified to the structure:



in which R_1 is H or an alkyl group, preferably with from 1 to 10 carbon atoms, especially 1 to 6 atoms, for instance methyl, ethyl, propyl, isopropyl, butyl, isobutyl, neopentyl or benzyl or a derivative giving the final substance equivalent properties as a hair growth stimulating agent. The chain could preferably be a C_6–C_{10} chain which can be saturated or unsaturated, having one or more double bonds, and allenes or a triple bond. In addition, the chain can contain one or more substituents such as alkyl groups, alicyclic rings, or aromatic rings with or without hetero atoms.

The omega chain is defined by the following formula:

wherein C is a carbon atom or loweralkyl chain, optionally substituted with one or more —OH groups;

B is a single bond, a double bond or a triple bond;

D is a chain with from 1 to 10 carbon atoms, preferably more than 2 and less than 8 atoms, and especially less than 5 atoms, optionally substituted with one or more —OH groups. Presently preferred derivatives have a chain with 3 atoms. The chain is optionally interrupted by preferably not more than two hetero atoms (O, S, or N), and may optionally be substituted with the substituents on each carbon atom of the chain being H, alkyl groups, preferably lower alkyl groups with 1–5 carbon atoms, a carbonyl group, or a hydroxyl group, whereby the substituent on C_{15} preferably being a carbonyl group, or (R)—OH or (S)—OH, each chain D containing preferably not more than three hydroxyl groups or more than three carbonyl groups;

R_2 is H or a ring structure such as a phenyl group which is unsubstituted or has one or more substituents selected from C_1–C_5 alkyl groups, C_1–C_5 haloalkyl groups such as trifluoromethyl groups, C_1–C_4 alkoxy groups, C_1–C_4 haloalkoxy groups such as trifluoromethoxy groups, C_1–C_3 aliphatic acylamino groups, nitro groups, halogen atoms such as fluoro or chloro, and an phenyl group; or an aromatic heterocyclic group having 5–6 ring atoms, like thiazol, imidazole, pyrrolidine, thiopene and oxazole; or a cycloalkane or a cycloalkene with 3–7 carbon atoms in the ring, optionally substituted with lower alkyl groups withal-5 carbon atoms.

Some examples of representative derivatives useful in the practice of the invention having a phenyl substituent on the omega chain include the compounds shown in Table 1:

TABLE 1

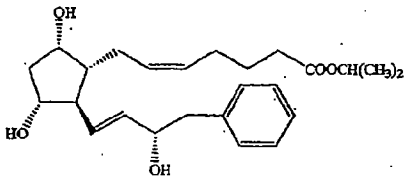
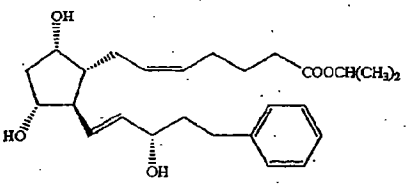
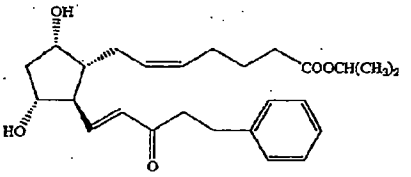
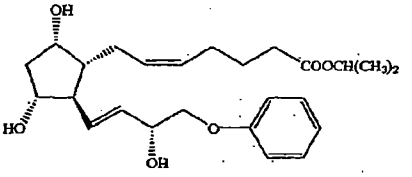
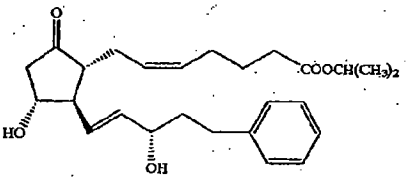
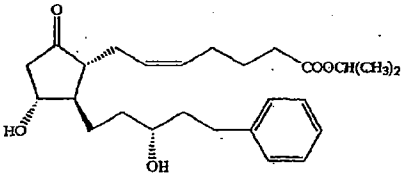
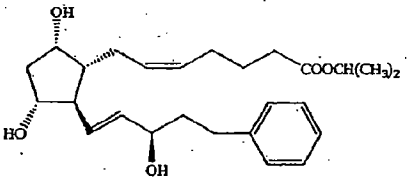
1	
2	
3	
4	
5	
6	
7	

TABLE 1-continued

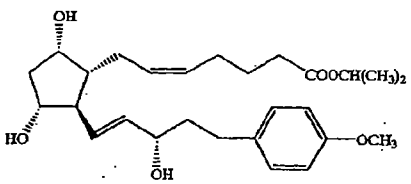
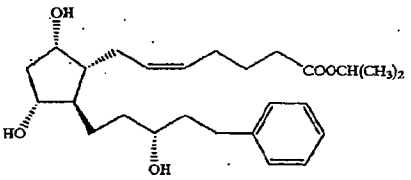
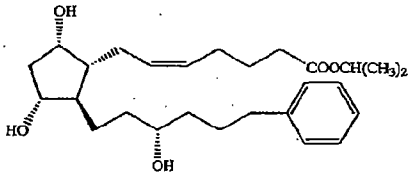
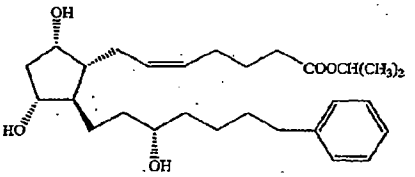
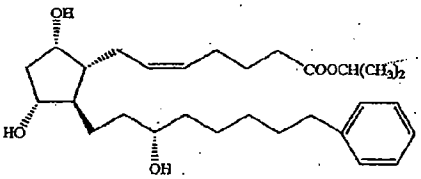
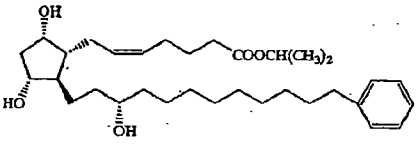
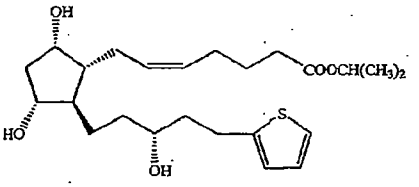
8	
9	
10	
20	
112	
113	
114	

TABLE 1-continued

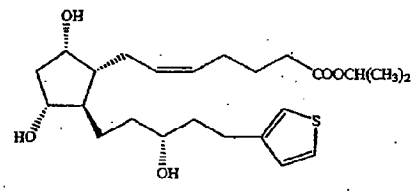
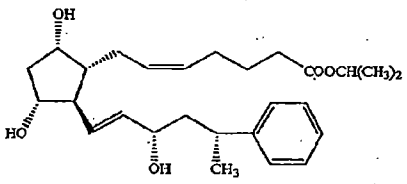
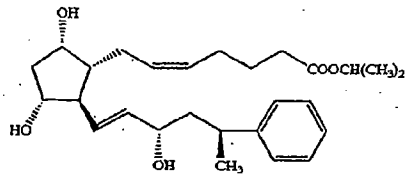
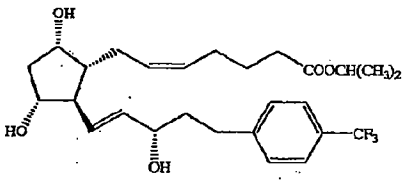
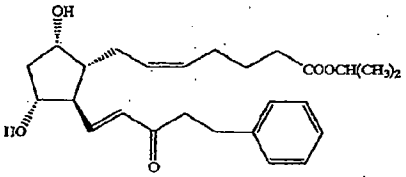
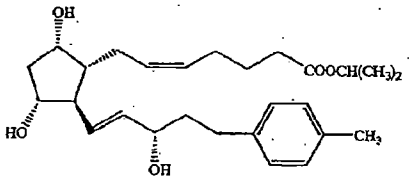
115 	
116 	
117 	
118 	
119 	
120 	

TABLE 1-continued

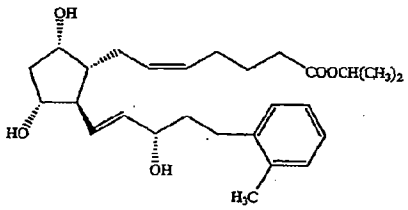
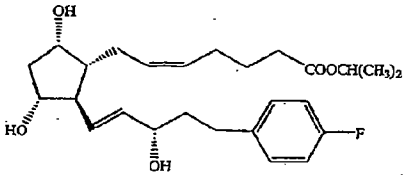
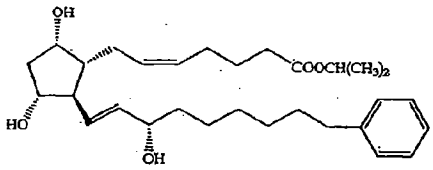
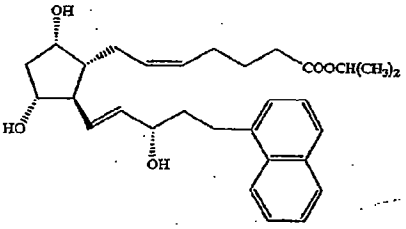
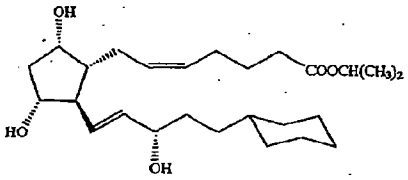
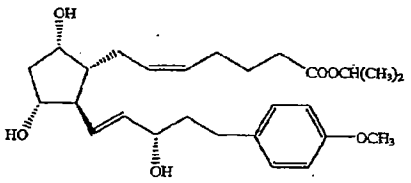
121 	
122 	
123 	
124 	
125 	
126 	

TABLE 1-continued

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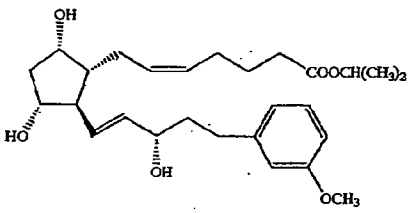

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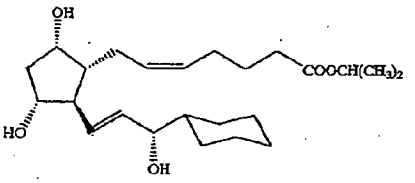

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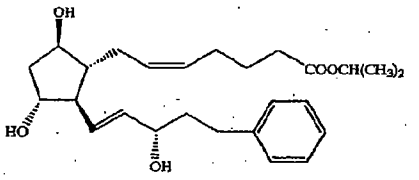

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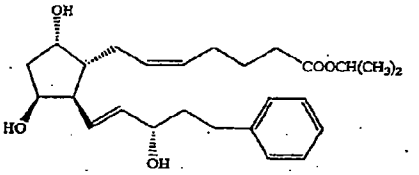


In Table 1, the structures have the following nomenclature, as used herein:

(1) 16-phenyl-17,18,19,20-tetranor-$PGF_2\alpha$-isopropyl ester

(2) 17-phenyl-18,19,20-trinor-$GF_2\alpha$-isopropyl ester

(3) 15-dehydro-17-phenyl-t8,19,20-$PGF_2\alpha$-isopropyl ester

(4) 16-phenoxy-17,18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(5) 17-phenyl-18,19,20-trinor-$PGE_2\alpha$-isopropyl ester

(6) 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGA_2\alpha$-isopropyl ester

(7) 15-(R)-17-phenyl-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(8) 16-[4-methoxyphenyl]-17,18,19,20-tetranor-$PGF_2\alpha$-isopropyl ester

(9) 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(10) 18-Phenyl-19,20-dinor-$PGF_2\alpha$-isopropyl ester

(20) 19-phenyl-20-nor-$PGF_2\alpha$-isopropyl ester

(112) 20-phenyl-$PGF_2\alpha$-isopropyl ester

(113) 20-(4-phenylbutyl)-$PGF_2\alpha$-isopropyl ester

(114) 17-(2-thiophene)-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(115) 17-(3-thiophene)-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(116 and 117) 17-R,S-methyl-17-phenyl-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(118) 17-(4-trifluoromethyl phenyl)-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(119) 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(120) 17-(4-methylphenyl)-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(121) 17-(2-methylphenyl)-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(122) 17-(4-fluorophenyl)-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(123) 20-(methylenephenyl)-$PGF_2\alpha$-isopropyl ester

(124) 17-naphthyl-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(125) 17-cyclohexyl-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(126) 17-(4-methoxyphenyl)-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(127) 17-(3-methoxyphenyl)-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester

(128) 15-cyclohexyl-16,17,18,19,20-pentanor-$PGF_2\alpha$-isopropylester

The synthesis of the isopropyl esters described above has been disclosed in U.S. Pat. Nos. 5,321,128, 5,422,368, 5,422,369, and 5,578,618, but any alkyl ester of the prostaglandin derivatives, preferably with 1–10 carbon atoms and especially with 1–6 atoms, for instance methyl, ethyl, propyl, isopropyl, butyl, isobutyl, neopentyl or benzyl esters, may be used in the practice of the invention.

Also preferred prostaglandin derivatives at present are those in which the omega chain of the prostaglandin has the 18,19,20-trinor form and especially the 17-phenyl analogues, such as the 15-(R)-, 15-dehydro and 13,14-dihydro-17-phenyl-18,19,20-trinor forms, and the carboxylic acid esters thereof. Such derivatives are represented by (3), (6), (7) and (9) in the formulas given in Table 1.

Also preferred derivatives include those in which the omega chain has not been substituted with a phenyl ring structure, such as those compounds described in U.S. Pat. Nos. 4,311,707, 5,288,754 and 5,352,708.

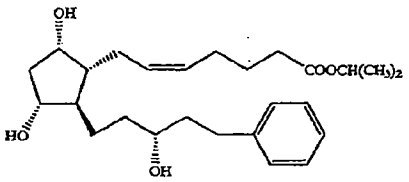
In the formula given above the presently preferred prostaglandin derivatives are obtained when the prostaglandin is a derivative of PGA_2, PGE_2, and $PGF_2\alpha$, where:

B is a single bond or a double bond,

D is a carbon chain with 2–5, especially 3 atoms; C_{15} having a carbonyl or (S)—OH substituent and C_{16}–C_{19} having lower alkyl substituents, or preferably H,

R_2 is H or a phenyl ring, optionally having substituents selected among alkyl and alkyoxy groups.

One presently preferred compound for use in the practice of the present invention is 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ isopropyl ester, also known as latanoprost and sold under the name Xalatan by Pharmacia & Upjohn Company, Kalamazoo, Mich., U.S.A. This compound has the following structure:



The invention thus relates to the use of certain derivatives of PGA_2, PGE_2 and $PGF_2\alpha$, or prodrugs of the active compounds, for treatment for the stimulation of hair growth. As used herein, hair growth includes hair associated with the scalp, eyebrows, eyelids, beard, and other areas of the skin of animals. Among the derivatives defined above, some may be irritating or otherwise not optimal, and in certain cases not even useful due to adverse effects and these are excluded in that the group of prostaglandin derivatives defined above is limited to therapeutically effective, that is hair growth stimulating, and physiologically acceptable derivatives. So, for instance, while compound (1) above (16-phenyl-17,18, 19,20-tetranor-$PGF_2\alpha$-isopropyl ester, Table 1) may be irritating, the irritation may be reduced or eliminated by substituting the phenyl ring with a methoxy group giving compound (8), Table 1, which represents a therapeutically more useful compound. On the other hand, other preferred groups are not substituted with a ring structure, which creates a greater degree of hyperemia (vasodilation) of the treated tissues.

In accordance with one aspect of the invention, the prostaglandin derivative is mixed with a dermatologically compatible vehicle or carrier known per se. The vehicle which may be employed for preparing compositions of this invention may comprise, for example, aqueous solutions such as e.g., physiological salines, oil solutions or ointments. The vehicle furthermore may contain dermatologically compatible preservatives such as e.g., benzalkonium chloride, surfactants like e.g., polysorbate 80, liposomes or polymers, for example, methyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid; these may be used for increasing the viscosity. Furthermore, it is also possible to use soluble or insoluble drug inserts when the drug is to be administered.

The invention is also related to dermatological compositions for topical treatment for the stimulation of hair growth which comprise an effective hair growth stimulating amount of one or more prostaglandin derivatives as defined above and a dermatologically compatible carrier. Effective amounts of the active derivatives will vary depending on the derivative employed, frequency of application and desired result, but will generally range from about 0.0000001 to about 50% by weight of the dermatological composition. Representative compositions may thus comprise from about 0.001 to about 50 μg of the derivatives in about 1 to about 100 μg of total dermatological composition, more preferably from about 0.1 to about 30 μg in about 10 to about 50 μg of the composition.

The present invention finds application in all mammalian species, including both humans and animals. In humans, the compounds of the subject invention can be applied for example, to the scalp, face, beard, head, pubic area, upper lip, eyebrows, and eyelids. In animals raised for their pelts, e.g., mink, the compounds can be applied over the entire surface of the body to improve the overall pelt for commercial reasons. The process can also be used for cosmetic reasons in animals, e.g., applied to the skin of dogs and cats having bald patches due to mange or other diseases causing a degree of alopecia.

The pharmaceutical compositions contemplated by this invention include pharmaceutical compositions suited for topical and local action.

The term "topical" as employed herein relates to the use of a prostaglandin compound, derivative or analogue as described herein, incorporated in a suitable pharmaceutical carrier, and applied at the site of thinning hair or baldness for exertion of local action. Accordingly, such topical compositions including those pharmaceutical forms in which the compound is applied externally by direct contact with the skin surface to be treated. Conventional pharmaceutical forms for this purpose include ointments, liniments, creams, shampoos, lotions, pastes, jellies, sprays, aerosols, and the like, and may be applied in patches or impregnated dressings depending on the part of the body to be treated. The term "ointment" embraces formulations (including creams) having oleaginous, absorption, water-soluble and emulsion-type bases, e.g., petrolatum, lanolin, polyethylene glycols, as well as mixtures of these.

Although the invention is not limited to any particular mechanism or theory of action, various physiological considerations are relevant to the concepts disclosed herein. When hair follicles initially form embryologically, they do so by means of a stimulus sent from a group of specialized fibroblast cells in the dermis which will become the dermal papilla. These dermal papilla cells induce cells of the epidermis to migrate downward and ultimately form the hair follcile. At each hair cycle, the epithelial elements and dermal papilla migrate upward within the skin to an area close to the surface and undergo a programmed involution or dedifferentiation. Throughout life each new hair cycle recapitulates the embryologic event by repeatedly transitioning from the resting telogen or involutional stage beneath the surface of the skin to the anagen phase with associated proliferation, differentiation and migration of epithelial elements in response to induction by stimulus factors in the dermal papilla.

The prostaglandin derivatives of the invention, such as PGF2 alpha analogs, are local hormones or paracrine agents that induce local effects in cells in their immediate area. The cells are also capable of autocrine signalling, thus, they can also send signals to themselves by binding back to their own receptors. During development, for example, once a cell has been directed into a particular path of differentiation, it may begin to secrete autocrine signals that reinforce this developmental decision.

Because autocrine signaling is most effective when carried out simultaneously by neighboring cells of the same type, it may be used to encourage groups of identical cells to make the same developmental decisons. For this reason, autocrine signalling is thought to be one possible mechanism underlying the "community effect" observed in early development, where a group of identical cells can respond to a differentiation inducing signal but a single isolated cell of the same type cannot. These signalling mechanisms provide a reinforcing or amplifying effect. Paracrine and autocrine signalling are not confined to development, however, and the eiconsanoids are signalling molecules that regularly act on mature systems.

The unique observations described herein indicate that PGF2 alpha analogs may be able to initiate hair growth in response to very low total dosages and very short dosage durations. In view of the recapitulation of embryologic behavior at the initiation of the hair cycle it might be anticipated that very small dosages at a critical time in the

resting or telogen stage may be able to initiate the anagen phase of growth by inducing follicles to trigger the anagen phase and then sending autocrine signals that reinforce and amplify that developmental decision to differentiate into a mature follicle. PFG2 alpha analogues, rather than reaching a level where increased dosage will simply not cause an increased effect may, rather, cause a decrease in the effectiveness of the agent. For example, this has been shown to be true of the prostaglandin derivative latanoprost in relation to its effect on intraocular pressure where higher dosages may not provide as effective a pressure lowering response.

For the reasons mentioned above, one presently preferred embodiment of the invention comprises treating a human or non-human animal with relatively low doses of a prostaglandin of the invention that will deliver a dosage found in the Examples or as little as 0.1 nanograms (ng), depending on the analogue and mode of application.

Typically, the prostaglandins are applied repeatedly for a sustained period of time topically on the part of the body to be treated, for example, the eyelids, eyebrows, skin or scalp. The preferred dosage regimen will generally involve regular, such as daily, administration for a period of treatment of at least one month, more preferably at least three months, and most preferably at least six months.

Alternatively, the prostaglandins may be applied intermittently, or in a pulsed manner. For example, in the studies described in Example 1, supra, in each of the patients who took the drug for a duration of 5 days, effects were present that persisted for as long as 14 months. In contrast, several patients who used the drug for 4 months or more on a sustained chronic basis had a loss of the effect within 4 months of stopping the drug. Accordingly, it is a presently preferred alternative embodiment of the invention to apply the prostaglandins on an intermittent or pulsed dosage schedule. For example, the prostaglandins of the invention may be used for two or more days, stopped, then restarted again at a time from between 2 weeks to 3 months later in the case of eyelashes, and at even more long-spaced intervals in the case of the scalp.

This pulsed delivery approach may be used by itself or with other agents that may set the stage for initiation and perpetuation of the anagen phase of hair growth. For example, agents such as estrogen creams may at times make the follicle more responsive to the inductive and differentiating influences of eiconsonoids. Alternatively, the pulsed approach may be used with agents such as the alpha reductase drugs, such as, for example, proscar or Procipia. An additional alternative is the use in a pulsed fashion with minoxidil.

For topical use on the eyelids or eyebrows, the active prostaglandins as well as their derivatives and analogues, including esters and salts, can be formulated in aqueous solutions, creams, ointments or oils exhibiting physiologically acceptable osmolarity by addition of pharmacologically acceptable buffers and salts. Such formulations may or may not, depending on the dispenser, contain preservatives such as benzalkonium chloride, chlorhexidine, chlorobutanol, parahydroxybenzoic acids and phenylmercuric salts such as nitrate, chloride, acetate, and borate, or antioxidants, as well as additives like EDTA, sorbitol, boric acid etc. as additives. Furthermore, particularly aqueous solutions may contain viscosity increasing agents such as polysaccharides, e.g., methylcellulose, mucopolysaccharides, e.g., hyaluronic acid and chondroitin sulfate, or polyalcohol, e.g., polyvinylalcohol. Various slow releasing gels and matrices may also be employed as well as soluble and insoluble ocular inserts, for instance, based on substances forming in-situ gels. Depending on the actual formulation and prostaglandin analogue to be used, various amounts of the drug and different dose regimens may be employed. Typically, the daily amount of prostaglandin for treatment of the eyelid may be about 0.1 ng to about 100 mg per eyelid, more preferably about 1 ng to about 100 μg per eyelid.

For topical use on the skin and the scalp, the prostaglandin can be advantageously formulated using ointments, creams, liniments or patches as a carrier of the active ingredient. Also, these formulations may or may not contain preservatives, depending on the dispenser and nature of use. Such preservatives include those mentioned above, and methyl-, propyl-, or butyl-parahydroxybenzoic acid, betain, chlorhexidine, benzalkonium chloride, and the like. Various matrices for slow release delivery may also be used. Typically, the dose to be applied on the scalp is in the range of about 0.1 ng to about 100 mg per day, more preferably about 1 ng to about 10 mg per day, and most preferably about 10 ng to about 1 mg per day depending on the prostaglandin and the formulation. To achieve the daily amount of medication depending on the formulation, the prostaglandin may be administered once or several times daily with or without antioxidants.

Several different prostaglandins may be employed to achieve the therapeutic effect on stimulation of hair growth in the types of tissues discussed above, e.g., the eyelid, eyebrow, scalp and skin. Particularly preferred prostaglandins are those of the A, F and E types. To minimize side effects, such as irritation and redness of the skin, it may be advantageous to use prostaglandin derivatives or analogues which have been found to exert less side effects, such as phenyl- and other ring-substituted prostaglandin derivatives. On the other hand, increased hyperemia experienced with other substituents may be more beneficial in causing increased vasodilation, resulting in hair growth. Prostaglandin derivatives that exhibit high pharmacological activity and no or only very small side effects, such as 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ and its carboxylic acid esters, are also presently particularly preferred, especially in use in large areas of the skin or scalp.

EXAMPLES

Example 1

In Vivo Treatment

A study was initiated to systematically evaluate the appearance of lashes and hair around the eyes of patients who were administering latanoprost in only one eye. The study involved 10 Caucasian subjects, 5 male, 5 female, average age 71±13 years, (ranging from 48–94 years). All patients had glaucoma. Each subject was treated daily by the topical application of one drop of 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$-isopropyl ester (latanoprost) at a dosage of 1.5 μg/ml/eye/day (0.005% ophthalmic solution, sold under the name Xalatan by Pharmacia & Upjohn Company, Kalamazoo, Mich., U.S.A.) to the region of one eye by instilling the drop onto the surface of the eye. The region of the fellow control eye was not treated with latanoprost and served as a control.

In the course of treatment with eye drops, there is typically spontaneous tearing, and excess fluid from the drops and associated tears gathers at the lid margins. In the course of wiping the drug containing fluid from the lid margins and adjacent lid, a thin film of the fluid is routinely spread to contact the adjacent skin of the lid area. This widespread

exposure of the skin around the lid to the effect of drops is regularly demonstrated in patients who develop a contact dermatitis. Typically the entire area of the upper and lower lid are involved with induration, erythema and edema demonstrating the regular extensive exposure of the ocular adnexa to the influence of topically applied drugs.

The study was limited to subjects who had administered latanoprost to one eye for more than 3 months. The mean duration of exposure to latanoprost prior to assessing the parameter of lash growth between the control and study eye was 129 days (range 90–254 days). Observations were made under high magnification at the slit lamp biomicroscope. Documentation of differences between the control and treatment areas was accomplished using a camera specially adapted for use with the slit lamp biomicroscope. Photographs are on file documenting each of the observations described below.

The results of the observations are as follows:

Length of lashes: Increased length of eyelashes was regularly observed on the side treated with latanoprost. The difference in length varied from approximately 10% to as much as 30%.

Number of lashes: Increased numbers of lashes were observed in the treated eye of each patient. In areas where there were a large number of lashes in the control eye, the increased number of lashes in the latanoprost-treated eye gave the lashes on the treated side a more thickly matted overall appearance. The difference in lash numbers was most easily appreciated in the area of the lower lid. Lashes of the lower lid were typically relatively sparse in the control eye. The lower lid of the treated eye consistently had more lashes. Portions of the lateral part of the lower lid in some patients had either extremely sparse or absent lashes in the control eye, the same lid area of the treated eye generally had an apparent full complement of lashes creating an appearance of a lash distribution and density more like that seen in the central portion of the lower lid.

Pigmentation: Lash pigmentation was increased in the treated eye of most patients. The difference was subtle in eyes of patients with gray or blonde colored hair. Increased pigmentation was more prominent in lashes and adjacent hairs of patients who had brown or black hair.

Increased luster, brilliance and sheen: The lashes of the treated eye had the appearance of an increased luster, which may be variously described as increased sheen, brilliance, gloss, glow, polish, shine or patina compared to the control eye. This difference in appearance was present in patients ranging from those with light blond hair to those with black hair. This increased luster, sheen or brilliance was in addition to, and appeared to be independent of, the appearance of increased pigmentation that was observed in some patients with darker hair and lashes.

Auxiliary lash-like hair growth: Several patients had an apparent increase in lash-like hair in transitional areas adjacent to areas of normal lash distribution. These prominent robust appearing lash-like hairs appeared to be of comparable length to the actual lashes. These long, thick lash-like hairs were present in the central portion of the lids of several patients in a linear arrangement just above the lash line. Hairs were present at similar locations in the control eyes but were by contrast thinner or more fine in appearance, had less luster and pigment and were more flat against the skin of the lid typical of vellus or intermediate hairs. In several patients, lash-like terminal hairs were growing luxuriantly in the medial canthal area in the treated eye. In the corresponding control eye, vellus hairs were seen at the same location. Lash-like hairs were also present in the lateral canthal area of the treated eye but not the control eye in several subjects. Large lashes are not normally present at the lateral canthus and the area is generally free of all but a few occasional very fine lashes or vellus hairs. Growth of lashes directly from the lateral canthus can create a medical problem. Because of the anatomic arrangement, dense lash growth directly from the lateral canthus can result in lashes growing directly toward the eye, causing an irritation of the eye tissue.

Increased growth of vellus hair on lids: Fine microscopic vellus hair is present on the skin of the lids and is easily seen with the slit lamp biomicroscope. This vellus hair is typically denser adjacent to and below the lateral portion of the lower lids. While remaining microscopic, vellus hairs were increased in number, appeared more robust and were much longer and thicker in treated than in control eyes in the areas below and lateral to the lower lid.

Perpendicular angulation of hairs: In areas where there were lash-like hairs above the lash line and in the medial and lateral canthal areas, the hairs were much longer, thicker and heavier. They also left the surface of the skin at a more acute angle, as though they were stiffer or held in a more erect position by more robust follicles. This greater incline, pitch, rise or perpendicular angulation from the skin surface gave the appearance of greater density of the hairs.

The foregoing observations clearly establish that an autocoid, more specifically, a prostaglandin derivative (latanoprost) can be used to increase the growth of hair in man. This conclusion is based on the regular and consistent finding of manifestations of increased hair growth in treated vs. control areas in human subjects. The conclusion that the drug latanoprost is capable of inducing increased robust growth of hair is based not on a single parameter, i.e., length, but is based on multiple lines of evidence as described in the results. Detailed examination and description of multiple parameters of differences in hair was greatly facilitated by the ability to examine the hairs at high magnification under stable conditions of fixed focal length and subject position utilizing the capabilities of the slitlamp biomicroscope.

The foregoing study was expanded to include 43 patients who had administered unilateral topical latanoprost for greater than 10 weeks and who would be available for additional follow-up. Each patient of the 43 patients in the study had glaucoma and treatment consisted of one unilateral drop of latanoprost daily. Mean treatment duration was 19.8±6.1 weeks, range (11–40). No consistent pattern of other topical or systemic medication use was identified. Evidence of hypertrichosis was observed in the region of the treated eye in each of the subjects; 38 Caucasian, 3 African-American, 1 Asian, 1 Hispanic; 13 male, 30 female; average age 65±13, range (36–84). Slitlamp photographs were made of the region of the control eye and treated eye in each patient.

Increased numbers of lashes were present in preexisting lash rows and in some patients additional rows of lashes were seen in the upper and lower lid of the latanoprost treated eye. Increased lash size involving both length and thickness was also apparent in both the upper and lower lids of the treated eye. Several patients had a striking curling of the lashes of the treated compared with the untreated control eye.

The lower lids generally had fewer rows of lashes and the lashes were also less curled than in the upper lids making comparative measurements of the lashes of the lower lid

lashes feasible. Accordingly, calipers were used to measure the length of longest lashes of the lower lids in 30 patients. Mean lower lid lash length was 5.83±76 mm in the control eye versus 6.95±91 mm in the treated eye ($p<0.0001$), (unpaired t-test, Statview statistics program). This represents a 19.5% increased lash length in the treated eye, range (0–36%). Two patients who had no measurable lash length change exhibited increased numbers of lashes.

In the treated eye, lash-like hair growth was observed in several patients in areas adjacent to the region of normal lash distribution. Hairs in the control eye were a mixture of vellus and intermediate-type in the areas of transition between the terminal lashes along the lash line and the vellus hair of the skin. Hairs in the same location in the treated eye had a more robust appearance, were longer, thicker, more pigmented and arose at a more acute angle from the skin than in the control eye, imparting the appearance of a partial new row of terminal lashes.

In the medial and lateral canthal area where vellus and intermediate hairs were present in the control eye, a number of patients had a greater abundance of thicker, longer more pigmented terminal hairs in the same area of the treated eye. Although not grossly visible, with slitlamp examination the vellus hair of the skin of the lateral portion of the lower lid was generally more abundant, longer, thicker and darker in the treated eye. Pigmentation of the lashes and associated hairs was regularly greater in the treated eye than in the control eye and was more obvious in patients who had brown or black hair. (Patients who exhibited hypertrichosis with latanoprost were removed from further drug administration.)

Example 2

Length of Treatment

Eighty-nine subjects were treated as generally described in Example 1 by topical application of latanoprost at a dosage of 1.5 μg/ml/eye/day. Five of the subjects (2 male, 3 female, average age 72 years, all Caucasian) received treatment for a total period of less than 21 days (2, 3, 5, 12 and 17 days, respectively). Follow-up evaluation occurred in ascending order of treatment duration at 13, 14, 5, 6 and 4 months, respectively. The results were compared with the remainder of the subjects who received treatment for greater than 21 days.

In the 5 patients treated briefly, increased number, length, thickness, and pigmentation of lashes occurred and was similar to findings following unilateral sustained treatment. There was no obvious correlation between appearance and duration of treatment except in 3 patients who took latanoprost for <5 days. Each had marked curling of lashes, which was non-uniform in direction and degree, in contrast to the occasional more modest uniform curling seen with sustained treatment. In each patient treated briefly, lash changes persisted to some degree throughout the duration of the follow-up interval.

Brief (less than 21 days), low total dosage (3–25.5 μg) topical latanoprost treatment appears to cause increased lash numbers and altered differentiation involving hypertrophy and hyperpigmentation. Marked irregular curling was observed with <5 days treatment and may result from non-uniform penetration into the hair follicle. Residual evidence of unilateral lash changes following brief treatment may persist for up to 14 months, suggesting a prolongation of the hair cycle (normally about 5 months) or an effect that lasts from one hair cycle to the next.

Example 3

Topical Cream

A topical cream is prepared as follows: Tegacid and spermaceti are melted together at a temperature of 70–80° C. Methylparaben is dissolved in about 500 gm of water and propylene glycol, polysorbate 80, and 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ isopropyl ester are added in turn, maintaining a temperature of 75–80° C. The methylparaben mixture is added slowly to the Tegacid and spermaceti melt, with constant stirring. The addition is continued for at least 30 minutes with additional stirring until the temperature has dropped to 40–45° C. Finally, sufficient water is added to bring the final weight to 1000 gm and the preparation stirred to maintain homogeneity until cooled and congealed.

The composition is applied to bald human scalp three times a day to stimulate the growth of hair.

Example 4

Topical Cream

A topical cream is prepared as follows: Tegacid and spermaceti are melted together at a temperature of 70–80° C. Methylparaben is dissolved in water and propylene glycol, polysorbate 80, and 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ isopropyl ester are added in turn, maintaining a temperature of 75–80° C. The methylparaben mixture is added slowly to the Tegacid and spermaceti melt, with constant stirring. The addition is continued for at least 30 minutes with additional stirring until the temperature has dropped to 40–45° C. Finally, sufficient water is added to bring the final weight to 1000 gm and the preparation stirred to maintain homogeneity until cooled and congealed.

The composition is applied to bald human scalp once daily to stimulate the growth of hair.

Example 5

Topical Ointment

An ointment containing 2% by weight 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ is prepared as follows:

White petrolatum and wool fat are melted, strained and liquid petrolatum is added thereto. The 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ isopropyl ester, zinc oxide, and calamine are added to the remaining liquid petrolatum and the mixture milled until the powders are finely divided and uniformly dispersed. The mixture is stirred into the white petrolatum, melted and cooled with stirring until the ointment congeals.

The foregoing ointment can be applied topically to mammalian skin for increased rate of hair growth, and can be prepared by omitting the zinc oxide and calamine.

Example 6

Ointment

A dermatological ophthalmic ointment containing 10% by weight 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ isopropyl ester is prepared by adding the active compound to light liquid petrolatum. White petrolatum is melted together with wool fat, strained, and the temperature adjusted to 45–50° C. The liquid petrolatum slurry is added and the ointment stirred until congealed. Suitably the ointment is packaged in 30 gm tubes.

The foregoing ointment can be applied to the eyelid to enhance the growth of eyelashes. Similarly the composition can be applied to the brow for eyebrow growth.

Example 7

Solution

An aqueous solution containing 5% by weight 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ iso-

propyl ester is prepared as follows. The ingredient is dissolved in water and the resulting solution is sterilized by filtration. The solution is aseptically filled into sterile containers.

The composition so prepared can be used in the topical treatment of baldness by application to the scalp daily.

Example 8

Lotion

A sample of 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ isopropyl ester is dissolved in the vehicle of N-methyl pyrrolidone and propylene glycol. The composition can be used for application to dogs or cats having hair loss due to mange or alopecia of other causes.

Example 9

Aerosol

An aerosol containing approximately 0.1% by weight 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ isopropyl ester is prepared by dissolving the 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ in absolute alcohol. The resulting solution filtered to remove particles and lint. This solution is chilled to about minus 30° C. To the solution is added a chilled mixture of dichlorodifluoromethane and dichlorotetrafluoroethane. Thirteen ml plastic-coated amber bottles are cold filled with 11.5 gm each of the resulting solution and capped.

The composition can be sprayed on the scalp daily to stimulate the growth of hair.

Example 10

Dusting Powder

A powder of the compound 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ isopropyl ester is prepared by mixing in dry form with talcum powder at a weight/weight ratio of 1:10. The powdered mixture is dusted on the fur of minks or other commercially valuable fur bearing animals and show animals for increased rate of hair growth.

Example 11

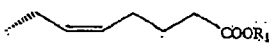
Related Compounds

Following the procedure of the preceding Examples, compositions are similarly prepared substituting an equimolar amount of a compound of Table 1 for the 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ isopropyl ester disclosed in the preceding Examples. Similar results are obtained.

While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

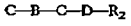
The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method for stimulating hair growth in a mammalian species comprising the application to mammalian skin of an effective amount of a prostaglandin PGF compound wherein the alpha chain of the compound has the formula:



in which R_1 is H or an alkyl group having from 1 to 10 carbon atoms; and

the omega chain of the compound has the formula:



wherein C is a carbon atom or lower alkyl chain, optionally substituted with one or more —OH groups;

B is a single bond, a double bond or a triple bond;

D is a chain having from 1 to 10 carbon atoms, optionally substituted with one or more —OH groups; and

R_2 is H; a phenyl group having none, one or more substituents selected from the group consisting of C_1–C_5 alkyl groups, C_1–C_5 haloalkyl groups, C_1–C_4 alkoxy groups, C_1–C_4 haloalkoxy groups, trifluoromethyl groups, C_1–C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl groups; an aromatic heterocyclic group having 5–6 ring atoms; or a cycloalkane or a cycloalkene with 3–7 carbon atoms in the ring, optionally substituted with lower alkyl groups with 1–5 carbon atoms;

or a pharmacologically acceptable acid addition salt thereof.

2. The method of claim 1 wherein the concentration of the compound applied is from about 0.0000001% to about 50% by weight of the composition.

3. The method of claim 1 wherein the compound is a $PGF_2\alpha$ derivative.

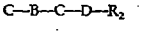
4. The method of claim 3 wherein the compound is 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ isopropyl ester or a pharmaceutically acceptable salt thereof.

5. A method for the conversion of vellus hair or intermediate hair to growth as terminal hair comprising the application to mammalian skin at the locale of vellus hair of an effective amount of a prostaglandin PGF compound wherein the alpha chain of the compound has the formula:



in which R_1 is H or an alkyl group having 1 to 10 carbon atoms, especially 1 to 6 atoms, for instance methyl, ethyl, propyl, isopropyl, butyl, isobutyl, neopentyl or benzyl or a derivative giving the final substance equivalent properties as a hair growth stimulating agent; and

the omega chain of the compound has the formula:



wherein C is a carbon atom or lower alkyl chain, optionally substituted with one or more —OH groups;

B is a single bond, a double bond or a triple bond;

D is a chain having from 1 to 10 carbon atoms, optionally substituted with one or more —OH groups; and

R_2 is H; a phenyl group having none, one or more substituents selected from the group consisting of C_1–C_5 alkyl groups, C_1–C_5 haloalkyl groups, C_1–C_4 alkoxy groups, C_1–C_4 haloalkoxy groups, trifluoromethyl groups, C_1–C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl groups; an aromatic

heterocyclic group having 5–6 ring atoms; or a cycloalkane or a cycloalkene with 3–7 carbon atoms in the ring, optionally substituted with lower alkyl groups with 1–5 carbon atoms;

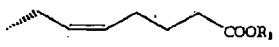
or a pharmacologically acceptable acid addition salt thereof.

6. The method of claim 5 wherein the concentration of the compound applied is from about 0.0000001% to about 50% by weight of the composition.

7. The method of claim 5 wherein the compound is a $PGF_2\alpha$ derivative.

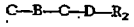
8. The method of claim 7 wherein the compound applied is 13,14-dihydro-15-dehydro-17-phenyl-18,19,20-trinor-$PGF_2\alpha$ isopropyl ester in the form of the free base or acid addition salts thereof.

9. A method for stimulating hair follicles to increase hair growth and one or more properties selected from the group consisting of luster, sheen, brilliance, gloss, glow, shine or patina of hair associated with the follicles, comprising the application to mammalian skin at the locale of the follicles of an effective amount of a prostaglandin PGF compound wherein the alpha chain of the compound has the formula:



in which R_1 is H or an alkyl group having 1 to 10 carbon atoms, especially 1 to 6 atoms, for instance methyl, ethyl, propyl, isopropyl, butyl, isobutyl, neopentyl or benzyl or a derivative giving the final substance equivalent properties as a hair growth stimulating agent; and

the omega chain of the compound has the formula:



wherein C is a carbon atom or lower alkyl chain, optionally substituted with one or more —OH groups;

B is a single bond, a double bond or a triple bond;

D is a chain having from 1 to 10 carbon atoms, optionally substituted with one or more —OH groups; and

R_2 is H; a phenyl group having none, one or more substituents selected from the group consisting of C_1–C_5 alkyl groups, C_1–C_5 haloalkyl groups, C_1–C_4 alkoxy groups, C_1–C_4 haloalkoxy groups, trifluoromethyl groups, C_1–C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl groups; an aromatic heterocyclic group having 5–6 ring atoms; or a cycloalkane or a cycloalkene with 3–7 carbon atoms in the ring, optionally substituted with lower alkyl groups with 1–5 carbon atoms;

or a pharmacologically acceptable acid addition salt thereof.

* * * * *

Exhibit B

PATENT LICENSE AGREEMENT

This AGREEMENT (as herein defined), made and effective as of this 29th day of June 2006 (hereinafter referred to as the "Effective Date"), by and between Murray A. Johnstone, an individual, (hereinafter referred to as "JOHNSTONE") having a residence at 1221 Madison #1124, Seattle, WA 98104 and Allergan, Inc., a Delaware Corporation having a place of business at 2525 Dupont Drive, Irvine, California 92612 and Allergan Sales LLC, a Delaware Liability Company having a place of business at 2525 Dupont Drive, Irvine, California 92612 (hereinafter collectively referred to as "ALLERGAN")

WITNESSETH THAT:

WHEREAS, JOHNSTONE has "Patent Rights" (as hereinafter defined) relating to the use of a prostaglandin compounds or certain derivatives of said prostaglandin compounds for stimulating hair growth, e.g. enhancing eyelashes, in a mammal; and

WHEREAS, ALLERGAN desires to develop one or more pharmaceutical compositions containing a prostaglandin compound or a derivative of a prostaglandin compound for stimulating hair growth, e.g. enhancing eyelashes, in a mammal; and

WHEREAS, ALLERGAN is engaged in the business of, and has the facilities for, developing, registering, manufacturing and marketing pharmaceutical products in the "Territory" (as hereinafter defined); and

WHEREAS, ALLERGAN desires to obtain from JOHNSTONE and JOHNSTONE is willing to grant to ALLERGAN an exclusive license in the Territory relating to the Patent Rights in respect of the Products (as herein defined).

NOW, THEREFORE, in consideration of the foregoing and the mutual covenants and considerations set forth herein, the parties hereto mutually agree as follows:

ARTICLE I - DEFINITIONS:

The following terms shall have the meanings set forth in this Article I:

1.1 "Affiliate" shall mean all corporations or business entities which, directly or indirectly, are controlled by, control, or are under common control with ALLERGAN. For this purpose, the meaning of the word "control" shall mean the ownership of fifty percent (50%) or more of the voting shares or interest of such corporation or business entity or any corporation or business entity in which ALLERGAN can demonstrate, even though the extent of ownership of such shares or interest in such corporation or business entity is less than fifty percent (50%), that the operation and management of such corporation or business entity is carried out in conformity with ALLERGAN standing policy; such corporation or business entity to be deemed an Affiliate only so long as such ownership of voting shares or interest or adherence to such standing policy continues.

1.2 "Major Market Country" shall mean one of the following countries; France, Germany, Italy, Japan, Spain, United Kingdom or the United States of America.

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1.3 "Net Sales" means, with regard to any Product, the amount of gross sales by ALLERGAN, or its Affiliate or sublicensee, to a third party which is not an Affiliate or sublicensee of ALLERGAN for sales of such Product, less the following items:

(a) credits or allowances actually granted for damaged products, returns or rejections of product, price adjustments and billing errors;

(b) governmental and other rebates (or equivalents thereof) granted to managed health care organizations, pharmacy benefit managers (or equivalents thereof), federal, state/provincial, local and other governments, their agencies and purchasers and reimbursers or to trade customers;

(c) normal and customary trade, cash and quantity discounts, allowances and credits actually allowed or paid;

(d) commissions allowed or paid to third party distributors, brokers or agents other than sales personnel, sales representatives and sales agents employed by ALLERGAN;

(e) transportation costs, including insurance, for outbound freight related to delivery of the product to the extent included in the gross amount invoiced;

(f) sales taxes, VAT taxes and other taxes directly linked to the sales of Product to the extent included in the gross amount invoiced; and

(g) any other items that reduce gross sales amounts as required by United States Generally Accepted Accounting Principles applied on a consistent basis.

1.4 "Patent Rights" shall mean the patents and patent applications included in Exhibit A attached hereto and made a part hereof, together with any and all patents that may issue or may have issued therefrom, including any and all divisions, continuations, continuations-in-part, extensions, additions or reissues of or to any of the aforesaid patents and patent applications.

1.5 "Product" shall mean a pharmaceutical composition containing a prostaglandin compound or a derivative thereof for enhancing hair growth.

1.6 "Territory" shall mean the world.

1.7 "Third Party" shall mean any party other than JOHNSTONE, ALLERGAN, and its Affiliates.

1.8 "Valid Claim" shall mean a claim of an unexpired patent included within the Patent Rights, which has not been held unenforceable, unpatentable or invalid by a decision of a court or other governmental agency of competent jurisdiction and which has not been admitted to be invalid or unenforceable through reexamination, reissue or disclaimer or otherwise.

ARTICLE II - WARRANTIES:

JOHNSTONE warrants that he is exclusive owner of all right, title and interest in and to the Patent Rights. JOHNSTONE MAKES NO REPRESENTATION OR WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, NOR IS THERE ANY OTHER EXPRESSED OR IMPLIED REPRESENTATION OR WARRANTIES WITH RESPECT TO THE PATENT RIGHTS OR THE PRODUCT. Without limitation of the generality of the preceding sentence, JOHNSTONE makes no representation or warranty as to the use of the Product for ALLERGAN's purposes, the likelihood of success of ALLERGAN's development or commercialization of the Product, or the validity or enforceability of Patent Rights.

ARTICLE III - LICENSE GRANT:

JOHNSTONE hereby grants to ALLERGAN and its Affiliates an exclusive license (with the right to grant sublicenses) to make, have made, export, use, offer for sale and sell the Product in the Territory, under the Patent Rights.

ARTICLE IV - ROYALTIES:

ALLERGAN shall directly pay to JOHNSTONE royalties as follows:

4.1 One percent (1%) of the Net Sales of Product sold by ALLERGAN, or its Affiliates or sublicensees.

4.2 Notwithstanding the above, ALLERGAN is not obligated to pay royalties in excess of $200,000 in any calendar year.

4.3 Beginning with the first commercial sale of the Product, in each calendar year, ALLERGAN shall achieve annual minimum Net Sales sufficient to provide JOHNSTONE with a minimum royalty ("Minimum Royalty") of $50,000, or pay to JOHNSTONE the difference between the actual royalties due on Net Sales and $50,000. The obligation to pay said Minimum Royalty for any period that is less than a calendar year shall be prorated.

ARTICLE V - PAYMENT OF ROYALTIES:

5.1 Royalties accruing hereunder shall be reported and shall be due and payable on the sixtieth (60th) day following the close of each fiscal quarter, payable in U.S. dollars. For purposes hereof, a "fiscal quarter" shall be each of the quarterly periods utilized by ALLERAGN in reporting its financial results, which currently are the quarterly periods ending on the last Friday of each of March, June and September and the last day of December. Together with each royalty payment, ALLERGAN shall provide to JOHNSTONE a written report detailing the basis for computations of royalties due on a country-by-country basis for the reported period.

5.2 Upon payment of all applicable royalties, fees and milestones which may be due under ARTICLES IV and VII, ALLERGAN's licenses hereunder shall be paid-up, perpetual and irrevocable.

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ARTICLE VI - ROYALTY REPORTS:

6.1 ALLERGAN shall maintain and keep for a period of at least three (3) years complete and accurate records in sufficient detail to enable any royalties which shall have accrued hereunder to be determined.

6.2 Upon the request of JOHNSTONE, but not exceeding once in any one (1) year period, ALLERGAN shall permit an independent certified accountant, selected by JOHNSTONE and acceptable to ALLERGAN which acceptance shall not be unreasonably withheld, to have access to such records of ALLERGAN as may be necessary to verify the accuracy of the royalty reports and payments submitted to JOHNSTONE hereunder. Said independent certified accountant shall verify to JOHNSTONE only the amount of royalty due hereunder and disclose no other information revealed in its audit. Any such audit of records shall be at JOHNSTONE's expense. In the event such examination discloses a variance of more than five percent (5%) between the amount of royalties due and the amount of royalties paid to JOHNSTONE, ALLERGAN shall pay the expense of such audit. Any deficiency shall be paid promptly to JOHNSTONE, plus interest at the commercial prime lending rate of the Bank of America (or equivalent banking institution) until the date paid.

ARTICLE VII - FEES AND MILESTONES:

7.1 In consideration of the license granted to ALLERGAN by JOHNSTONE, hereunder, ALLERGAN shall pay the following amounts in U.S. Dollars to JOHNSTONE as a non refundable fee and upon the achievement (prior to the expiration or termination of this Agreement) of the noted milestone:

(1) Fee

$250,000 promptly upon the execution of this AGREEMENT

(2) Milestone	Payment
First receipt of written approval of the right to market Product by the FDA, or other drug regulatory agency, respectively, with claims to enhancing hair growth, such as the growth of eyelashes, in a Major Market Country. This milestone payment will be made once and only once.	$250,000

7.2 All payments to be made by ALLERGAN to JOHNSTONE pursuant to ARTICLES IV and VII shall be made in United States dollars. ALLERGAN shall promptly notify JOHNSTONE in writing of the occurrence of the milestone set forth above. Within fifteen (15) business days after the date of such notice, ALLERGAN shall pay to JOHNSTONE by certified or bank check, wire transfer or other means acceptable to JOHNSTONE, the milestone payment set forth above.

ARTICLE VIII - DEVELOPMENT AND REGISTRATION:

ALLERGAN shall be responsible for the development of Product(s) at its sole cost. ALLERGAN shall exclusively own all rights to, and bear the cost and expense of, any submissions required to obtain premarketing government approvals or any other approvals necessary to commercialize the Product in each country of the Territory. ALLERGAN shall use commercially reasonable efforts to develop, register, manufacture, market, and sell the Product(s). Upon request of JOHNSTONE, ALLERGAN will provide JOHNSTONE with a detailed written report, no less frequently than once every 6 months, setting forth ALLERGAN's activities and progress toward product development and obtaining government approval for marketing Products. In the event that ALLERGAN has not made substantial progress toward obtaining governmental approval in a Major Market Country within five (5) years of the Effective Date, the AGREEMENT maybe terminated under Section 9.1 hereof. Notwithstanding the above, ALLERGAN shall not be obligated to obtain the approval of more than one Product nor shall ALLERGAN be required to obtain the approval to market any Product in a country other than the Major Market Countries.

ARTICLE IX - TERMINATION:

9.1 Upon the failure of either party hereto to comply with any of their respective obligations and conditions contained herein, (including ALLERGAN's failure to pay minimum royalties under Section 4.3, above,) the other party shall be entitled, without prejudice to any other rights conferred on it herein, to terminate this AGREEMENT upon not less than three (3) months notice of such default, provided that the party in default has failed to cure such default within such three (3) months period.

9.2 ALLERGAN shall have the right to terminate this Agreement in its entirety or with regards to any license(s) granted herein as to any Product in any country(ies) of the Territory at any time upon three (3) months prior written notice to JOHNSTONE.

9.3 In the event of any early termination of the license granted herein as to the Product, ALLERGAN shall promptly make an accounting to JOHNSTONE of the inventory of all Product which it and its agents and distributors have on hand, if any, as of the date of such termination and said parties shall thereafter have the right for a period of six (6) months after said termination to sell such inventory of Product provided that the Net Sales thereof shall be subject to the royalty provisions of ARTICLE IV and so payable to JOHNSTONE.

9.4 Termination of this AGREEMENT, either in whole or in part, for any reason, shall be without prejudice to:

(1) JOHNSTONE's right to receive all royalties, fees and/or milestones accrued to it and unpaid on the effective date of such termination or thereafter in accordance with ARTICLES IV, VII, and subparagraph 9.3 of this ARTICLE IX;

(2) the rights and obligations of the parties provided in ARTICLES VI and XIV of this AGREEMENT; and

(3) any other rights or remedies then or thereafter available to either party under this AGREEMENT or otherwise.

9.5 The rights granted either party to terminate this AGREEMENT, either in whole or in part, prior to the expiration of its term, shall not be affected in any way by that party's waiver of or failure to take action with respect to any previous default hereunder.

ARTICLE X - INFORMATION TRANSFER; COOPERATION:

Promptly following execution of this Agreement, JOHNSTONE shall provide to ALLERGAN copies of all patents, patent applications and related files included in the Patent Rights, and, throughout the term of this AGREEMENT, shall continue to furnish ALLERGAN with copies of such files. Upon request of ALLERGAN, JOHNSTONE shall provide reasonable assistance and cooperation in all patent-related matters relevant to this AGREEMENT.

ARTICLE XI - INFRINGEMENT:

11.1 JOHNSTONE and ALLERGAN shall each give to the other prompt written notice of any claim or action made against either of them alleging that the manufacture, use or sale of the Product in any country(ies) of the Territory infringe the rights of a Third Party. JOHNSTONE and ALLERGAN agree to cooperate and collaborate with each other in undertaking a full investigation of the situation and in taking such action as they shall agree is appropriate in the circumstances.

11.2 Should JOHNSTONE or ALLERGAN become aware of any infringement or alleged infringement of or by any Third Party of the Patent Rights, the party made aware shall immediately notify the other party in writing of the name and address of the alleged infringer, the alleged acts and dates of infringement, and any available evidence of infringement. JOHNSTONE and ALLERGAN agree to work jointly (on a reasonable efforts basis and at ALLERGAN's expense) to prevent any infringement and defend the Patent Rights, and to prosecute alleged infringers. ALLERGAN shall have the first right to prosecute the alleged infringer, and JOHNSONE shall have the secondary right, and in such event the prosecuting Party (whether JOHNSTONE or ALLERGAN) shall bear all costs, fees and expenses of legal proceedings and actions regarding infringement and shall be entitled to all awards, damages recovered in settlement or other proceeds paid. Both parties shall fully cooperate with one another in all such matters.

ARTICLE XII - MAINTENANCE OF PATENT RIGHTS:

Subsequent to the Effective Date, ALLERGAN shall be solely responsible for and bear the cost of the prosecution and maintenance of the Patent Rights. ALLERGAN shall give JOHNSTONE three (3) months advance written notice of any decision not to maintain any patent or patent application included in the Patent Rights and JOHNSTONE may assume the responsibility at his own cost to continue to maintain any such patent or patent application.

ARTICLE XIII - TRANSFER OF RIGHTS AND OBLIGATIONS:

This Agreement, in whole or in part, shall not be assignable by either party hereto to any Third Party without the prior written consent of the other party hereto that ALLERGAN may assign this AGREEMENT to the successor or assignee of that portion of its business to which this AGREEMENT relates. It is expressly understood and agreed by the parties hereto that the assignor of any rights hereunder shall remain bound by its duties and liable for its obligations hereunder. Any assignment or attempt at same, except as provided for herein, shall be void and of no effect.

ARTICLE XIV - INDEMNIFICATION:

14.1 ALLERGAN agrees to defend, indemnify and hold harmless JOHNSTONE, against claims for loss, liability, damage and costs for personal injury or recall attributable to the negligence or willful misconduct of ALLERGAN, its Affiliates, agents or employees, in connection with the development, manufacture, marketing, use or sale of the Product.

14.2 As to any claim or lawsuit with respect to which JOHNSTONE seeks indemnification hereunder, JOHNSTONE shall provide prompt notice, thereof to ALLERGAN and assist in the defense of such claim or lawsuit at ALLERGAN's expense. ALLERGAN shall have the right to control the defense of said lawsuit, including the selection of attorneys, and any settlement thereof.

ARTICLE XV - TERM OF AGREEMENT:

This AGREEMENT, unless sooner terminated as elsewhere provided in this AGREEMENT, shall continue in full force and effect for the time commencing with the Effective Date and continuing (a) with regard to the patent licenses granted herein, until expiration of the last to expire patent (including any modification, extension or reissue thereof) within the applicable Patent Rights.

ARTICLE XVI - DISCLOSURE:

Any announcement, news release, or any other disclosure regarding the existence of this AGREEMENT, or the terms thereof, may be made by either party hereto only with the prior written consent of the other party.

ARTICLE XVIII – NOTICES:

Any notice or report required or permitted to be given or made under this AGREEMENT by either party to the other shall be in writing, sent by hand or by registered or express mail or courier, postage prepaid, addressed to such other party "Attention: General Counsel" in the case of ALLERGAN and to JOHNSTONE, at his address indicated at the beginning of this AGREEMENT, or to such other address as the addressee shall have last furnished in writing to the addressor, and shall be effective upon receipt by the addressee.

ARTICLE XIX - GOVERNING LAW:

This Agreement shall be governed by the laws of the State of California, excluding its choice of laws rules. In case of dispute, venue shall be in Orange County, California.

ARTICLE XX - SEVERABILITY:

Whenever possible, each provision of this AGREEMENT shall be interpreted in such manner as to be effective and valid under applicable law, but if any provision of this AGREEMENT should be prohibited or invalid under applicable law, such provision shall be ineffective to the extent of such invalidity without invalidating the remainder of such provision or the remaining provisions of this AGREEMENT.

ARTICLE XXI - PARAGRAPH HEADINGS:

The subject headings of the Articles of this AGREEMENT are included for the purposes of convenience only, and shall not affect the construction or interpretation of any of its provisions.

ARTICLE XXII - ENTIRE AGREEMENT; AMENDMENT:

This AGREEMENT contains the entire understanding of the parties with respect to the matters contained herein and supersedes any previous agreements and may be altered or amended only by a written instrument duly executed by both parties hereto.

WITNESS WHEREOF, the parties here executed this Agreement this 29th day of June 2006.

JOHNSTONE	ALLERGAN, INC.
By: Murray A. Johnstone	By:
Name: Patent Right Holder	Name: Jeffrey L. Edwards
Title:	Title: EVP, CFO
Date: 6-29-06	Date: 6/29/06

Approved Law Department

ALLERGAN SALES, LLC.
By:
Name: David Lawrence
Title: Senior Vice President, ~~Business~~ Development CORPORATE
Date: 6/29/06

Approved Law Department

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Exhibit A

JOHNSTONE Patent Portfolio

Country	Application No.	Filing Date	Patent No.	Grant Date	Status
Australia	62709/98	02/03/98	750039	10/24/02	Issued
Canada	2,279,967	02/03/98			Issue fee due 10/12/06
France	EP98904968.9	02/03/98	EP1021179	05/12/04	Issued
Germany	EP98904968.9	02/03/98	EP1021179	05/12/04	Issued
Italy	EP98904968.9	02/03/98	EP1021179	05/12/04	Issued
Japan	1998-533248	02/03/98			Pending
United Kingdom	EP98904968.9	02/03/98	EP1021179	05/12/04	Issued
United States	09/366,656	08/03/99	6,262,105	07/17/01	Issued
International	PCT/US98/02289	02/03/98			Entered National Phase

Exhibit C

US007351404B2

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

(10) **Patent No.: US 7,351,404 B2**
(45) **Date of Patent: *Apr. 1, 2008**

(54) **METHOD OF ENHANCING HAIR GROWTH**

(75) Inventors: **David F. Woodward**, Lake Forest, CA (US); **Amanda M. VanDenburgh**, Huntington Beach, CA (US)

(73) Assignee: **Allergan, Inc.**, Irvine, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 496 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/345,788**

(22) Filed: **Jan. 15, 2003**

(65) **Prior Publication Data**

US 2003/0147823 A1 Aug. 7, 2003

Related U.S. Application Data

(60) Provisional application No. 60/354,425, filed on Feb. 4, 2002.

(51) **Int. Cl.**
A61K 8/00 (2006.01)

(52) **U.S. Cl.** **424/70.1**; 424/400

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

(56) **References Cited**

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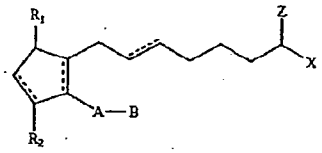
(Continued)

Primary Examiner—Michael P. Woodward
Assistant Examiner—Eric E. Silverman
(74) *Attorney, Agent, or Firm*—Martin Voet; Brent Johnson

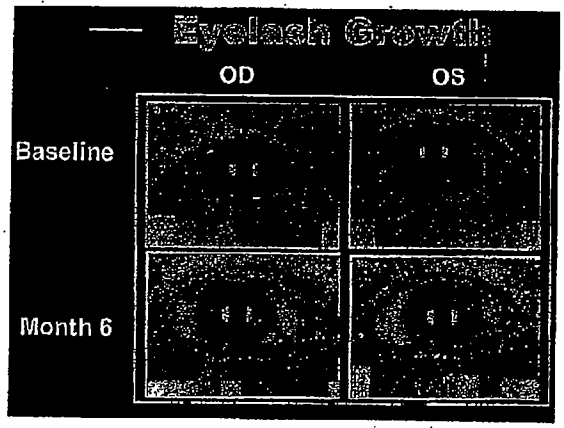
(57) **ABSTRACT**

Methods and compositions for stimulating the growth of hair are disclosed wherein said compositions include a cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compound represented by the formula I



wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A, B, Z, X, R_1 and R_2 are as defined in the specification. Such compositions are used in treating the skin or scalp of a human or non-human animal. Bimatoprost is preferred for this treatment.

16 Claims, 1 Drawing Sheet



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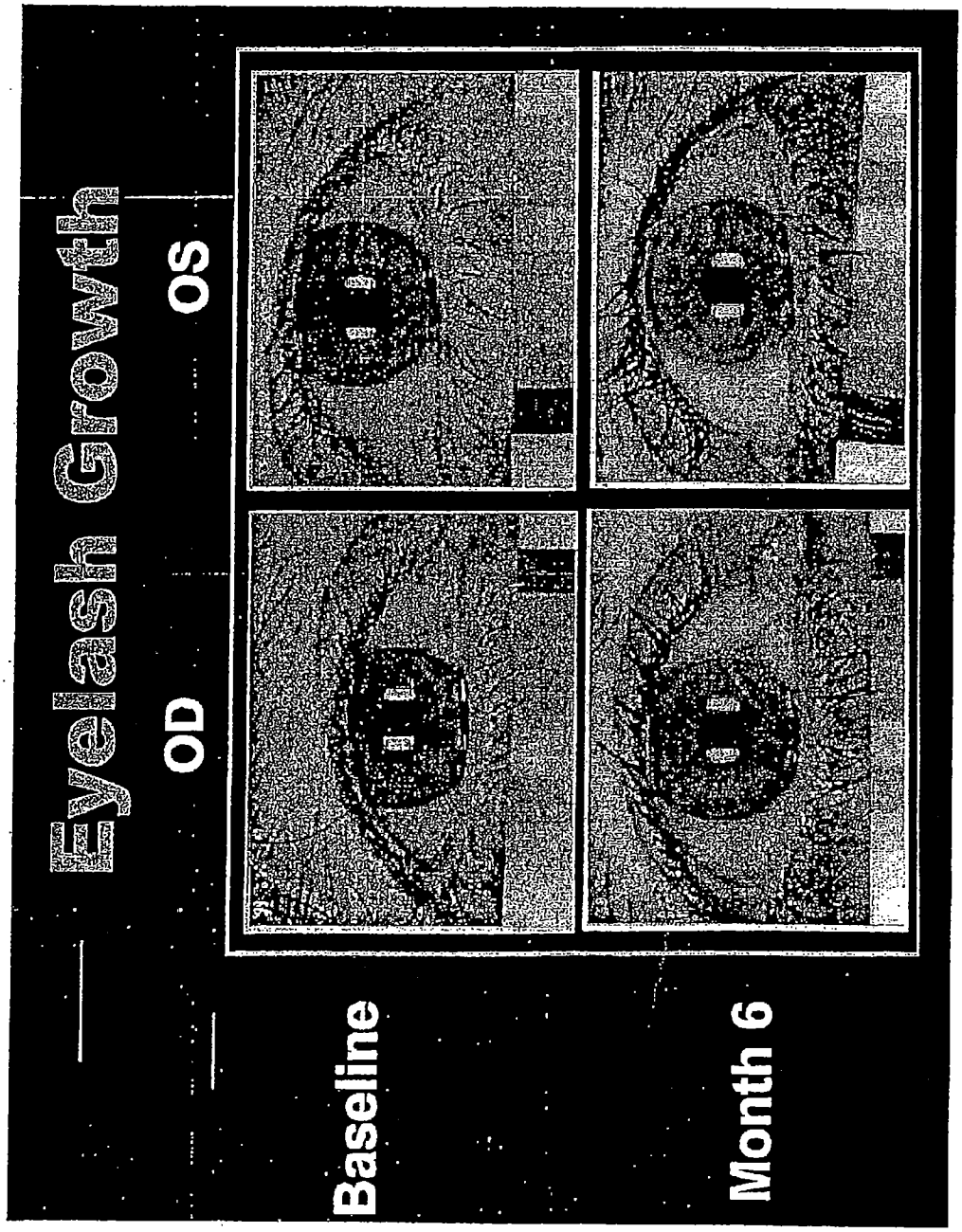

Eyelash Growth
OD
OS
Baseline
Month 6

METHOD OF ENHANCING HAIR GROWTH

RELATED APPLICATIONS

This application is based on, and claims the benefit of, U.S. Provisional Application No. 60/354,425, filed Feb. 4, 2002 and which is incorporated herein by reference.

FIELD OF THE INVENTION

This invention relates to a method for stimulating the growth of mammalian hair comprising the application to mammalian skin of a cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl derivative or a pharmacologically acceptable acid addition salt thereof, alone, or in association with a topical pharmaceutical carrier.

BACKGROUND OF THE INVENTION

Dermatologists recognize many different types of hair loss, the most common by far being "alopecia" wherein human males begin losing scalp hair at the temples and on the crown of the head as they get older. While this type of hair loss is largely confined to males, hence its common name "male pattern baldness," it is not unknown in women. No known cure has yet been found despite continuing attempts to discover one.

A good deal is known about various types of human hair and its growth patterns on various parts of the body.

For purposes of the present invention, it is necessary to consider various types of hair, including, terminal hairs and vellus hairs and modified terminal hairs, such as seen in eye lashes and eye brows. Terminal hairs are coarse, pigmented, long hairs in which the bulb of the hair follicle is seated deep in the dermis. Vellus hairs, on the other hand, are fine, thin, non-pigmented short hairs in which the hair bulb is located superficially in the dermis. As alopecia progresses, a transition takes place in the area of approaching baldness wherein the hairs themselves are changing from the terminal to the vellus type.

Another factor that contributes to the end result is a change in the cycle of hair growth. All hair, both human and animal, passes through a life cycle that includes three phases, namely, the anagen phase, the catagen phase and the telogen phase. The anagen phase is the period of active hair growth and, insofar as scalp hair is concerned, this generally lasts from 3-5 years. The catagen phase is a short transitional phase between the anagen and telogen phases which, in the case of scalp hair, lasts only 1-2 weeks. The final phase is the telogen phase which, for all practical purposes, can be denominated a "resting phase" where all growth ceases and the hair eventually is shed preparatory to the follicle commencing to grow a new one. Scalp hair in the telogen phase is also relatively short-lived, some 3-4 months elapsing before the hair is shed and a new one begins to grow.

Under normal hair growth conditions on the scalp, approximately 88% of the hairs are in the anagen phase, only 1% in catagen and the remainder in telogen. With the onset of male pattern baldness, a successively greater proportion of the hairs are in the telogen phase with correspondingly fewer in the active growth anagen phase.

Alopecia is associated with the severe diminution of hair follicles. A bald human subject will average only about 306 follicles per square centimeter, whereas, a non-bald human

in the same age group will have an average of 460 follicles per square centimeter. This amounts to a one-third reduction in hair follicles which, when added to the increased proportion of vellus hair follicles and the increased number of hair follicles in the telogen phase, is both significant and noticeable. Approximately 50% of the hairs must be shed to produce visible thinning of scalp hair. It is thus a combination of these factors: transition of hairs from terminal to vellus, increased number of telogen hairs—some of which have been shed, and loss of hair follicles that produces "baldness".

While a good deal is known about the results of male pattern baldness, very little is known about its cause. The cause is generally believed to be genetic and hormonal in origin although, the known prior art attempts to control it through hormone adjustment have been singularly unsuccessful.

One known treatment for male pattern alopecia is hair transplantation. Plugs of skin containing hair are transplanted from areas of the scalp where hair is growing to bald areas with reasonable success; however, the procedure is a costly one in addition to being time-consuming and quite painful. Furthermore, the solution is inadequate from the standpoint that it becomes a practical, if not an economic, impossibility to replace but a tiny fraction of the hair present in a normal healthy head of hair.

Other non-drug related approaches to the problem include such things as ultra-violet radiation, massage, psychiatric treatment and exercise therapy. None of these, however, has been generally accepted as being effective. Even such things as revascularization surgery and acupuncture have shown little, if any, promise.

By far, the most common approach to the problem of discovering a remedy for hair loss and male pattern alopecia has been one of drug therapy. Many types of drugs ranging from vitamins to hormones have been tried and only recently has there been any indication whatsoever of even moderate success. For instance, it was felt for a long time that since an androgenic hormone was necessary for the development of male pattern baldness, that either systemic or topical application of an antiandrogenic hormone would provide the necessary inhibiting action to keep the baldness from occurring. The theory was promising but the results were uniformly disappointing.

The androgenic hormone testosterone was known, for example, to stimulate hair growth when applied topically to the deltoid area as well as when injected into the beard and pubic regions. Even oral administration was found to result in an increased hair growth in the beard and pubic areas as well as upon the trunk and extremities. While topical application to the arm causes increased hair growth, it is ineffective on the scalp and some thinning may even result. Heavy doses of testosterone have even been known to cause male pattern alopecia.

Certain therapeutic agents have been known to induce hair growth in extensive areas of the trunk, limbs and even occasionally on the face. Such hair is of intermediate status in that it is coarser than vellus but not as coarse as terminal hair. The hair is generally quite short with a length of 3 cm. being about maximum. Once the patient ceases taking the drug, the hair reverts to whatever is normal for the particular site after six months to a year has elapsed. An example of such a drug is diphenylhydantoin which is an anticonvulsant

drug widely used to control epileptic seizures. Hypertrichosis is frequently observed in epileptic children some two or three months after starting the drug and first becomes noticeable on the extensor aspects of the limbs and later on the trunk and face. (The same pattern of hypertrichosis is sometimes caused by injury to the head.) As for the hair, it is often shed when the drug is discontinued but may, in some circumstances, remain.

Streptomycin is another drug that has been found to produce hypertrichosis, in much the same way as diphenylhydantoin, when administered to children suffering from tuberculous meningitis. About the same effects were observed and the onset and reversal of the hypertrichosis in relation to the period of treatment with the antibiotic leave little question but that it was the causative agent.

Two treatments have been demonstrated as showing some promise in reversing male pattern alopecia. These treatments include the use of a microemulsion cream containing both estradiol and oxandrolone as its active ingredients and the use of organic silicon.

In addition to the foregoing, it has been reported in U.S. Pat. Nos. 4,139,619 and 4,968,812 that the compound minoxidil is useful for the treatment of male pattern baldness. That compound, among others, has proven to have considerable therapeutic value in the treatment of severe hypertension. It is a so-called "vasodilator" which, as the name implies, functions to dilate the peripheral vascular system. Dermatologists and others have recognized that prolonged vasodilation of certain areas of the human body other than the scalp sometimes result in increased hair growth even in the absence of any vasodilating therapeutic agent. For instance, increased hair growth around surgical scars is not uncommon. Similarly, arteriovenous fistula have been known to result in increased vascularity accompanied by enhanced hair growth. Externally-induced vasodilation of the skin, such as, for example, by repeated biting of the limbs by the mentally retarded and localized stimulation of the shoulders by water carries has been known to bring on hypertrichosis in the affected areas. Be that as it may, similar techniques such as continued periodic massage of the scalp have been found to be totally ineffective as a means for restoring lost hair growth to the scalp. Scar tissue on the scalp inhibits rather than promotes hair growth.

U.S. Pat. No. 6,262,105 to Johnstone suggests that prostaglandins and derivatives thereof are useful in a method of enhancing hair growth.

Bimatoprost, which is sold by Allergan, Inc. of Irvine, Calif., U.S.A. as Lumigan® ophthalmic solution, for treating glaucoma now has been found as being effective to increase the growth of eyelashes when applied in the FDA approved manner.

It is, therefore, a principal object of the present invention to provide a novel and effective treatment for the stimulation of hair growth and the treatment of male pattern baldness.

Another object of the invention is to provide a method of stimulating hair growth in humans and non-human animals that is compatible with various types of therapeutic agents or carriers and, therefore, would appear to be combinable with those which, by themselves, demonstrate some therapeutic activity such as, for example, microemulsion creams or topical compositions containing estradiol and oxandrolone, minoxidil or agents that block the conversion of testosterone to dihydrotesterone (Procipia).

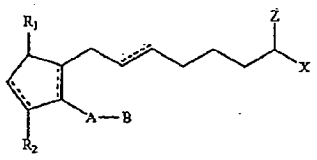
Still another objective is the provision of a treatment for the stimulation of hair growth which, while effective for its intended purpose, is apparently non-toxic and relatively free of unwanted side effects.

An additional object of the invention herein disclosed and claimed is to provide a method for treating hair loss in men or women which can be applied by the patient under medical supervision no more stringent than that demanded for other topically-administered therapeutic agents.

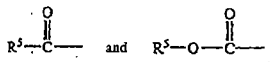
Other objects of the invention are to provide a treatment for male pattern alopecia which is safe, simple, painless, cosmetic in the sense of being invisible, easy to apply and quite inexpensive when compared with hair transplants and the like.

SUMMARY OF THE INVENTION

This invention provides pharmaceutical compositions for topical application to enhance hair growth comprising an effective amount of a cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compound represented by the formula I

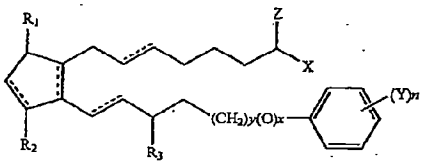


wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxa radicals and substituted with one or more hydroxy, oxo, alkyloxy or akylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrogen, a lower alkyl radical having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is $—N(R^4)_2$ wherein R^4 is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six carbon atoms,



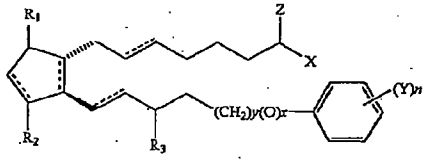
wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O; one of R_1 and R_2 is =O, —OH or a —O(CO)R_6 group, and the other one is —OH or —O(CO)R_6, or R_1 is =O and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or $—(CH_2)mR_7$, wherein m is 0 or an integer of from 1 to 10; and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above in free form or a pharmaceutically acceptable salt thereof, in association with a pharmaceutical carrier adapted for topical application to mammalian skin.

Preferably, the compound is a cyclopentane heptanoic acid, 2-(phenyl alkyl or phenyloxyalkyl) represented by the formula II



wherein y is 0 or 1, x is 0 or 1 and x and y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, e.g. fluoro, chloro, etc., nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy, halo substituted alkyl wherein said alkyl radical comprises from one to six carbon atoms, etc. and n is 0 or an integer of from 1 to 3 and R_3 is =O, —OH or —O(CO)R_6 wherein R_6 is as defined above or a pharmaceutically acceptable salt thereof.

More preferably the compound is a compound of formula III.

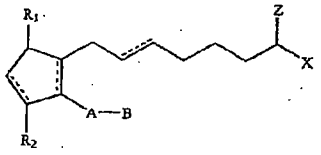


wherein hatched lines indicate α configuration, solid triangles are used to indicate β configuration.

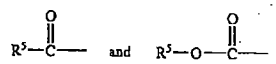
More preferably y is 1 and x is 0 and R_1, R_2 and R_3 are hydroxy.

Most preferably the compound is cyclopentane N-ethyl heptanamide-5-cis -2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1_α,2^β,3_α,5_α], also known as bimatoprost.

Another aspect of the invention provides methods for stimulating the rate of hair growth and for stimulating the conversion of vallus hair of intermediate hair to growth as terminal hair is in a human of non-human animal by administering to the skin of the animal an effective amount of a compound wherein the compound has the formula:



Wherein the dashed bonds represent a single or double bond which can be in the cis of trans configuration, A is and alkelene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxa radicals and substituted with one or more hydroxy, oxo, alkyloxy of alylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group cosisting of nitrogen, oxygen and sulfur atoms; X is —$N(R^4)_2$ wherein R_4 is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six carbon atoms,



wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O; one of R_1 and R_2 is =O, —OH or a —O(CO)R_6 group, and the other one is —OH or —O(CO)R_6, or R_1 is =O and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or —(CH_2)mR_7, wherein m is 0 or an integer of from 1 to 10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above in free form or a pharmaceutically acceptable salt thereof.

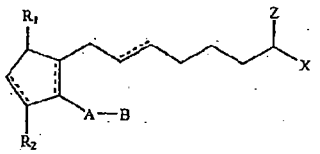
These and other aspects of the invention will become apparent from the description of the invention which follows below.

BRIEF DESCRIPTION OF THE DRAWING FIGURE

The FIGURE shows the effect on the eyelashes of one patient treated for glaucoma with Lumigan® bimatoprost for six months.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Alopecia (baldness) a deficiency of either normal or abnormal hair, is primarily a cosmetic problem in humans. It is a deficiency of terminal hair, the broad diameter, colored hair that is readily seen. However, in the so-called bald person although there is a noticeable absence of terminal hair, the skin does contain vellus hair which is a fine colorless hair which may require microscopic examination to determine its presence. This vellus hair is a precursor to terminal hair. In accordance with the invention as described herein, compounds represented by



wherein R_1, R_2, A, B, Z and X are defined above, can be used to stimulate, such as stimulating the conversion of vellus hair to growth as terminal hair as well as increasing the rate of growth of terminal hair.

The present invention was discovered as follows:

In the course of treating patients having glaucoma, treatment may only be appropriate in one eye. Within the course

of daily practice it was discovered that a patient who been treated with bimatoprost has lashes that were longer, thicker and fuller in the treated eye than in the non-treated eye. On examination the difference was found to be very striking. The lashes were longer and had a more full dense appearance in the treated eye. The lash appearance on the lids of the treated eye would have appeared quite attractive if it represented a bilateral phenomenon. Because of its asymmetric nature, the long lashes on one side could be construed as disturbing from a cosmetic standpoint. Because of the very unusual appearance a systematic examination of other patients who were taking bimatoprost in only one eye was made. It soon became apparent that this altered appearance was not an isolated finding. Comparison of the lids of patients who were taking bimatoprost in only one eye revealed subtle changes in the lashes and adjacent hairs of the bimatoprost-treated side in several patients. Definite differences could be identified to varying degrees in the lashes and adjacent hairs of all patients who were taking the drug on a unilateral basis for longer than 6 months.

These findings were totally unexpected and surprising. Minoxidil is thought to stimulate hair growth by its ability to cause vasodilation suggesting that agents with such a capability may be uniquely effective in stimulating hair growth. The finding that bimatoprost, which, as explained below, is not a prostaglandin derivative, such as latanoprost stimulates hair growth is especially surprising and unexpected.

The changes in the lashes were apparent on gross inspection in several patients once attention was focused on the issue. In those with light colored hair and lashes, the differences were only seen easily with the aid of the high magnification and lighting capabilities of the slit lamp biomicroscope. In the course of a glaucoma follow up examination, attention is generally immediately focused on the eye itself. Because of the high power magnification needed only one eye is seen at a time and the eye is seen at a high enough power that the lashes are not in focus. At these higher powers, any lash asymmetry between the two eyes is not likely to be noticed except by careful systematic comparison of the lashes and adjacent hairs of the eyelids of the two eyes.

Observed parameters leading to the conclusion that more robust hair growth occurred in the treated area following administration of bimatroprost were multiple. They included increased length of lashes, increased numbers of lashes along the normal lash line, increased thickness and luster of lashes, increased auxiliary lash-like terminal hair in transitional areas adjacent to areas of normal lash growth, increased lash-like terminal hairs at the medial and lateral canthal area, increased pigmentation of the lashes, increased numbers, increased length, as well as increased luster, and thickness of fine hair on the skin of the adjacent lid, and finally increased perpendicular angulation of lashes and lash-like terminal hairs. The conclusion that hair growth is stimulated by bimatoprost is thus supported not by evidence of a difference in a single parameter but is based on multiple parameters of hair appearance in treated vs. control areas in many subjects. This finding is entirely unexpected and represents a previously unrecognized effect of bimatoprost on stimulation of hair follicles. The modified hairs of the lashes normally turn over slowly and are in their resting phase longer than hair on, for example, the scalp. The ability to cause differences in appearance of lashes, the ability to stimulate conversion of vellus or intermediate hair to terminal hairs in transitional areas and the ability to stimulate growth of vellus hair on the skin indicates that bimatoprost is a diversely effective and efficacious agent for the stimulation of hair growth. Thus, the present invention provides a treatment by bimatoprost of hair of the scalp, eyebrows, beard and other areas that contain hair that results in increased hair growth in the corresponding areas.

Patients that are treated in or around the eye with compounds of the invention, such as bimatoprost, regularly develop hypertrichosis including altered differentiation, numbers, length, thickness, curvature and pigmentation in the region of treatment.

Some examples of representative compounds useful in the practice of the present invention include the compounds shown in Table 1:

TABLE 1

cyclopentane heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1_α,2_β,3_ω,$5_6\alpha$]

cyclopentane N,N-dimethylheptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [$1_\omega$$2_\beta$,$3_\omega$,$5_\alpha$]

cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-metachlorophenoxy-1-trans-pentenyl)-3,5-dihydroxy, [$1_\omega$$2_\beta$,$3_\omega$,$5_\alpha$]

cyclopentane heptenylamide-5-cis-2-(3α-hydroxy-4-trifluoromethylphenoxy-1-trans-pentenyl)-3,5-dihydroxy, [$1_\omega$$2_\beta$,$3_\omega$,$5_\alpha$]

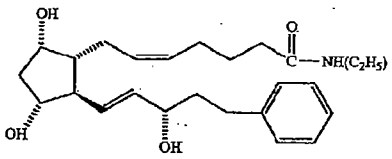
cyclopentane N-isopropyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [$1_\omega$$2_\beta$,$3_\omega$,$5_\alpha$]

cyclopentane N-ethyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1_α,2_β,3_α,5_α]

cyclopentane N-methyl heptenamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1_α,2_β,3_α,5_α]

cyclopentane heptenamide-5-cis-2-(3α-hydroxy-4-metachlorophenoxy-1-trans-butenyl)-3,5-dihydroxy, [1_ω,2_β,3_ω,5_α]

One presently preferred compound for use in the practice of the present invention is cyclopentane N-ethyl heptanamide-5-cis-2-(3α-hydroxy-5-phenyl-1-trans-pentenyl)-3,5-dihydroxy, [1_ω,2_β,3_ω,5_α], also known as bimatoprost and sold under the name of Lumigan® by Allergan, Inc., California, USA. This compound has the following structure:



The synthesis of the above compounds described above has been disclosed in U.S. Pat. No. 5,607,978. This patent also shows, particularly in Examples 1, 2, 5 and 7 that these compounds are not prostaglandins, in that they do not behave as prostaglandins in art-recognized assays for prostaglandin activity. The invention thus relates to the use of the above compounds, or prodrugs of the active compounds, for treatment for the stimulation of hair growth. As used herein, hair growth includes hair associated with the scalp, eyebrows, eyelids, beard, and other areas of the skin of animals.

In accordance with one aspect of the invention, the compound is mixed with a dermatologically compatible vehicle or carrier. The vehicle which may be employed for

preparing compositions of this invention may comprise, for example, aqueous solutions such as e.g., physiological salines, oil, solutions or ointments. The vehicle furthermore may contain dermatologically compatible preservatives such as e.g., benzalkonium chloride, surfactants like e.g., polysorbate 80, liposomes or polymers, for example, methyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid; these may be used for increasing the viscosity. Furthermore, it is also possible to use soluble or insoluble drug inserts when the drug is to be administered.

The invention is also related to dermatological compositions for topical treatment for the stimulation of hair growth which comprise an effective hair growth stimulating amount of one or more compounds as defined above and a dermatologically compatible carrier. Effective amounts of the active compounds may be determined by one of ordinary skill in the art but will vary depending on the compound employed, frequency of application and desired result, and the compound will generally range from about 0.0000001 to about 50%, by weight, of the dermatological composition, preferably from about 0.001 to about 50%, by weight, of total dermatological composition, more preferably from about 0.1 to about 30%, by weight of the composition.

The present invention finds application in all mammalian species, including both humans and animals. In humans, the compounds of the subject invention can be applied for example, to the scalp, face, beard, head, pubic area, upper lip, eyebrows, and eyelids. In animals raised for their pelts, e.g., mink, the compounds can be applied over the entire surface of the body to improve the overall pelt for commercial reasons. The process can also be used for cosmetic reasons in animals, e.g., applied to the skin of dogs and cats having bald patches due to mange or other diseases causing a degree of alopecia.

The pharmaceutical compositions contemplated by this invention include pharmaceutical compositions suited for topical and local action.

The term "topical" as employed herein relates to the use of a compound, as described herein, incorporated in a suitable pharmaceutical carrier, and applied at the site of thinning hair or baldness for exertion of local action. Accordingly, such topical compositions include those pharmaceutical forms in which the compound is applied externally by direct contact with the skin surface to be treated. Conventional pharmaceutical forms for this purpose include ointments, liniments, creams, shampoos, lotions, pastes, jellies, sprays, aerosols, and the like, and may be applied in patches or impregnated dressings depending on the part of the body to be treated. The term "ointment" embraces formulations (including creams) having oleaginous, water-soluble and emulsion-type bases, e.g., petrolatum, lanolin, polyethylene glycols, as well as mixtures of these.

Typically, the compounds are applied repeatedly for a sustained period of time topically on the part of the body to be treated, for example, the eyelids, eyebrows, skin or scalp. The preferred dosage regimen will generally involve regular, such as daily, administration for a period of treatment of at least one month, more preferably at least three months, and most preferably at least six months.

For topical use on the eyelids or eyebrows, the active compounds can be formulated in aqueous solutions, creams, ointments or oils exhibiting physiologically acceptable osmolarity by addition of pharmacologically acceptable buffers and salts. Such formulations may or may not, depending on the dispenser, contain preservatives such as benzalkonium chloride, chlorhexidine, chlorobutanol, parahydroxybenzoic acids and phenylmercuric salts such as nitrate, chloride, acetate, and borate, or antioxidants, as well as additives like EDTA, sorbitol, boric acid etc. as additives. Furthermore, particularly aqueous solutions may contain viscosity increasing agents such as polysaccharides, e.g., methylcellulose, mucopolysaccharides, e.g., hyaluronic acid and chondroitin sulfate, or polyalcohol, e.g., polyvinylalcohol. Various slow releasing gels and matrices may also be employed as well as soluble and insoluble ocular inserts, for instance, based on substances forming in-situ gels. Depending on the actual formulation and compound to be used, various amounts of the drug and different dose regimens may be employed. Typically, the daily amount of compound for treatment of the eyelid may be about 0.1 ng to about 100 mg per eyelid.

For topical use on the skin and the scalp, the compound can be advantageously formulated using ointments, creams, liniments or patches as a carrier of the active ingredient. Also, these formulations may or may not contain preservatives, depending on the dispenser and nature of use. Such preservatives include those mentioned above, and methyl-, propyl-, or butyl-parahydroxybenzoic acid, betain, chlorhexidine, benzalkonium chloride, and the like. Various matrices for slow release delivery may also be used. Typically, the dose to be applied on the scalp is in the range of about 0.1 ng to about 100 mg per day, more preferably about 1 ng to about 10 mg per day, and most preferably about 10 ng to about 1 mg per day depending on the compound and the formulation. To achieve the daily amount of medication depending on the formulation, the compound may be administered once or several times daily with or without antioxidants.

The invention is further illustrated by the following non-limiting examples:

EXAMPLE 1

In Vivo Treatment

A study is initiated to systematically evaluate the appearance of lashes and hair around the eyes of patients who are administering bimatoprost in only one eye. The study involves 10 subjects, 5 male, 5 female, average age 70 years, (ranging from 50-94 years). All patients have glaucoma. Each subject is treated daily by the topical application of one drop of bimatoprost at a dosage of 1.5 .mu.g/ml/eye/day (0.03%, by weight, ophthalmic solution, sold under the name Lumigan® by Allergan, Irvine, Calif., U.S.A.) to the region of one eye by instilling the drop onto the surface of the eye. The region of the fellow control eye is not treated with bimatoprost and served as a control.

In the course of treatment with eye drops, there is typically spontaneous tearing, and excess fluid from the drops and associated tears gathers at the lid margins. In the course of wiping the drug containing fluid from the lid margins and adjacent lid, a thin film of the fluid is routinely spread to contact the adjacent skin of the lid area. This widespread exposure of the skin around the lid to the effect of drops is regularly demonstrated in patients who develop a contact dermatitis. Typically the entire area of the upper and lower lid are involved with induration, erythema and edema demonstrating the regular extensive exposure of the ocular adnexa to the influence of topically applied drugs.

The study is limited to subjects who have administered bimatoprost to one eye for more than 3 months. The mean duration of exposure to bimatoprost prior to assessing the parameter of lash growth between the control and study eye is 129 days (range 90-254 days). Observations are made

under high magnification at the slit lamp biomicroscope. Documentation of differences between the control and treatment areas is accomplished using a camera specially adapted for use with the slit lamp biomicroscope.

The Results of the Observations are as Follows:

Length of lashes: Increased length of eyelashes is regularly observed on the side treated with bimatoprost. The difference in length varies from approximately 10% to as much as 30%.

Number of lashes: Increased numbers of lashes are observed in the treated eye of each patient. In areas where there are a large number of lashes in the control eye, the increased number of lashes in the bimatoprost-treated eye gave the lashes on the treated side a more thickly matted overall appearance.

Auxiliary lash-like hair growth: Several patients have an apparent increase in lash-like hair in transitional areas adjacent to areas of normal lash distribution. These prominent robust appear lash-like hairs appeared to be of comparable length to the actual lashes. These long, thick lash-like hairs were present in the central portion of the lids of several patients in a linear arrangement just above the lash line. Hairs are present at similar locations in the control eyes but are by contrast thinner or more fine in appearance, have less luster and pigment and are more flat against the skin of the lid typical of vellus or intermediate hairs. In several patients, lash-like terminal hairs grow luxuriantly in the medial canthal area in the treated eye. In the corresponding control eye, vellus hairs are seen at the same location. Lash-like hairs are also present in the lateral canthal area of the treated eye but not the control eye in several subjects. Large lashes are not normally present at the lateral canthus and the area is generally free of all but a few occasional very fine lashes or vellus hairs.

Increased growth of vellus hair on lids: Fine microscopic vellus hair is present on the skin of the lids and is easily seen with the slit lamp biomicroscope. This vellus hair is typically denser adjacent to and below the lateral portion of the lower lids. While remaining microscopic, vellus hairs are increased in number, appear more robust and are much longer and thicker in treated than in control eyes in the areas below and lateral to the lower lid.

Perpendicular angulation of hairs: In areas where there are lash-like hairs above the lash line and in the medial and lateral canthal areas, the hairs are much longer, thicker and heavier. They also leave the surface of the skin at a more acute angle, as though they are stiffer or held in a more erect position by more robust follicles. This greater incline, pitch, rise or perpendicular angulation from the skin surface gives the appearance of greater density of the hairs.

The foregoing observations clearly establish that bimatoprost can be used to increase the growth of hair in man. This conclusion is based on the regular and consistent finding of manifestations of increased hair growth in treated vs. control areas in human subjects. The conclusion that the drug bimatoprost is capable of inducing increased robust growth of hair is based not on a single parameter, i.e., length, but is based on multiple lines of evidence as described in the results.

Detailed examination and description of multiple parameters of differences in hair is greatly facilitated by the ability to examine the hairs at high magnification under stable conditions of fixed focal length and subject position utilizing the capabilities of the slitlamp biomicroscope.

The FIGURE shows the actual results on the eyelashes of a patient treated for glaucoma with Lumigan® bimatoprost for 6 months..

EXAMPLE 2

Topical Cream

A topical cream is prepared as follows: Tegacid and spermaceti are melted together at a temperature of 70-80° C. Methylparaben is dissolved in about 500 gm of water and propylene glycol, polysorbate 80, and bimatoprost are added in turn, maintaining a temperature of 75-80° C. The methylparaben mixture is added slowly to the Tegacid and spermaceti melt, with constant stirring. The addition is continued for at least 30 minutes with additional stirring until the temperature has dropped to 40-45° C. Finally, sufficient water is added to bring the final weight to 1000 gm and the preparation stirred to maintain homogeneity until cooled and congealed.

EXAMPLE 3

Topical Cream

A topical cream is prepared as follows: Tegacid and spermaceti are melted together at a temperature of 70-80° C. Methylparaben is dissolved in water and propylene glycol, polysorbate 80, and bimatoprost are added in turn, maintaining a temperature of 75-80° C. The methylparaben mixture is added slowly to the Tegacid and spermaceti melt, with constant stirring. The addition is continued for at least 30 minutes with additional stirring until the temperature has dropped to 40-45° C. Finally, sufficient water is added to bring the final weight to 1000 gm and the preparation stirred to maintain homogeneity until cooled and congealed.

The composition is applied to bald human scalp once daily to stimulate the growth of hair.

EXAMPLE 4

Topical Ointment

An Ointment Containing 2% by Weight Bimatoprost is Prepared as Follows:

White petrolatum and wool fat are melted, strained and liquid petrolatum is added thereto. The bimatoprost, zinc oxide, and calamine are added to the remaining liquid petrolatum and the mixture milled until the powders are finely divided and uniformly dispersed. The mixture is stirred into the white petrolatum, melted and cooled with stirring until the ointment congeals.

The foregoing ointment can be applied topically to mammalian skin for increased rate of hair growth, and can be prepared by omitting the zinc oxide and calamine.

EXAMPLE 5

Ointment

A dermatological ophthalmic ointment containing 10% by weight bimatoprost is prepared by adding the active compound to light liquid petrolatum. White petrolatum is melted together with wool fat, strained, and the temperature adjusted to 45-50° C. The liquid petrolatum slurry is added and the ointment stirred until congealed. Suitably the ointment is packaged in 30 gm tubes.

The foregoing ointment can be applied to the eyelid to enhance the growth of eyelashes. Similarly the composition can be applied to the brow for eyebrow growth.

EXAMPLE 6

Solution

An aqueous solution containing 5%, by weight, bimatoprost is prepared as follows. Bimatoprost is dissolved in water and the resulting solution is sterilized by filtration. The solution is aseptically filled into sterile containers.

The composition so prepared can be used in the topical treatment of baldness by application to the scalp daily.

EXAMPLE 7

Lotion

A sample of bimatoprost is dissolved in the vehicle of N-methyl pyrrolidone and propylene glycol. The composition can be used for application to dogs or cats having hair loss due to mange or alopecia of other causes.

EXAMPLE 8

Aerosol

An aerosol containing approximately 0.1% by weight bimatoprost is prepared by dissolving the bimatoprost in absolute alcohol. The resulting solution filtered to remove particles and lint. This solution is chilled to about minus 30° C. To the solution is added a chilled mixture of dichlorodifluoromethane and dichlorotetrafluoroethane.

Thirteen ml plastic-coated amber bottles are cold filled with 11.5 gm each of the resulting solution and capped..

The composition can be sprayed on the scalp daily to stimulate the growth of hair.

EXAMPLE 9

Dusting Powder

A powder of the compound bimatoprost is prepared by mixing in dry form with talcum powder at a weight/weight ratio of 1:10. The powdered mixture is dusted on the fur of minks or other commercially valuable fur bearing animals and show animals for increased rate of hair growth.

EXAMPLE 10

Related Compounds

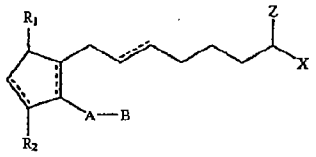
Following the procedure of the preceding Examples, compositions are similarly prepared substituting an equimolar amount of a compound of Table 1 for the bimatoprost disclosed in the preceding Examples. Similar results are obtained.

While the preferred embodiment of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

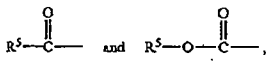
The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

What is claimed is:

1. A method for stimulating hair growth in a mammalian species comprising the application to mammalian skin of an effective amount of a cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compound represented by the formula I



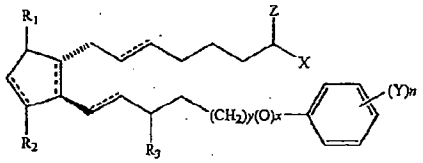
wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxa radicals and substituted with one or more hydroxy, oxo, alkyloxy or akylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is —N(R^4)2 wherein R^4 is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six carbon atoms,



wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O; one of R_1 and R_2 is =O, —OH or a —O(CO)R_6 group, and the other one is —OH or —O(CO)R_6, or R_1 is =O and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or —(CH_2)mR_7, wherein m is 0 or an integer of from 1 to 10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above or a pharmacologically acceptable acid addition salt thereof.

2. The method of claim 1 wherein the concentration of the compound applied is from about 0.0000001% to about 50% by weight of the composition.

3. The method of claim 1 wherein the compound is a compound of formula (III).

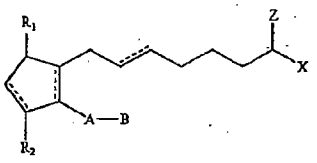


wherein y is 0 or 1, x is 0 or 1 and x and y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy, halo substituted alkyl wherein said alkyl radical comprises from one to six carbon atoms, n is 0 or an integer of from 1 to about 3 and R_3 is =O, —OH or —O(CO)R_6 wherein

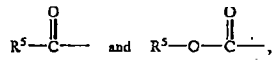
R_6, hatched lines indicate α a configuration and solid triangles are used to indicate β configuration.

4. The method of claim 3 wherein the compound is bimatoprost or a pharmaceutically acceptable salt thereof.

5. A method for the conversion of vellus hair or intermediate hair to growth as terminal hair comprising the application to mammalian skin at the locale of vellus hair of an effective amount of a cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compound represented by the formula I



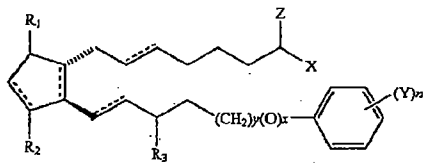
wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxa radicals and substituted with one or more hydroxy, oxo, alkyloxy or akylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical,selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is $—N(R_4)_2$ wherein R^4 is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six carbon atoms,



wherein R^5 is a lower alkyl radical having from one to six carbon atoms; Z is =O; one of R_1 and R_2 is =O, —OH or a $—O(CO)R_6$ group, and the other one is —OH or $—O(CO)R_6$, or R_1 is =O and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or $—(CH_2)mR_7$ wherein m is 0 or an integer of from 1 to 10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above or a pharmacologically acceptable acid addition salt thereof.

6. The method of claim 5 wherein the concentration of the compound applied is from about 0.0000001% to about 50% by weight of the composition.

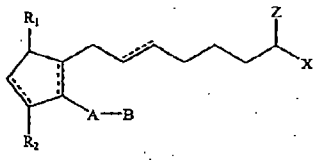
7. The method of claim 5 wherein the compound is a compound of formula (III).



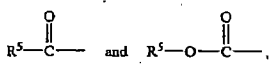
wherein y is 0 or 1, x is 0 or 1 and x and y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy, halo substituted alkyl wherein said alkyl radical comprises from one to six carbon atoms, n is 0 or an integer of from 1 to about 3 and R_3 is =O, —OH or $—O(CO)R_6$, hatched lines indicate α configuration and solid triangles are used to indicate β configuration.

8. The method of claim 7 wherein the compound applied is bimatoprost in the form of the free base or acid addition salts thereof.

9. A method for stimulating hair follicles to increase hair growth and one or more properties selected from the group consisting of luster, sheen, brilliance, gloss, glow, shine or patina of hair associated with the follicles, comprising the application to mammalian skin at the locale of the follicles of an effective amount of a cyclopentane heptanoic acid, 2-cycloalkyl or arylalkyl compound represented by the formula I



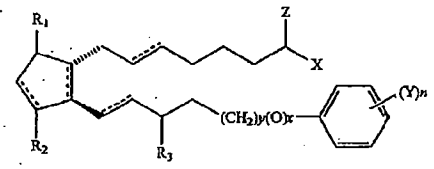
wherein the dashed bonds represent a single or double bond which can be in the cis or trans configuration, A is an alkylene or alkenylene radical having from two to six carbon atoms, which radical may be interrupted by one or more oxide radicals and substituted with one or more hydroxy, oxo, alkyloxy or akylcarboxy groups wherein said alkyl radical comprises from one to six carbon atoms; B is a cycloalkyl radical having from three to seven carbon atoms, or an aryl radical, selected from the group consisting of hydrocarbyl aryl and heteroaryl radicals having from four to ten carbon atoms wherein the heteroatom is selected from the group consisting of nitrogen, oxygen and sulfur atoms; X is $—N(R^4)_2$ wherein R^4 is selected from the group consisting of hydrogen, a lower alkyl radical having from one to six carbon atoms,



wherein R^5 is a lower alkyl radical having from one to six carbon atoms; z is =O; one of R_1 and R_2 is =O, —OH or a $—O(CO)R_6$ group, and the other one is —OH or $—O(CO)R_6$, or R_1 is =O and R_2 is H, wherein R_6 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or $—(CH_2)mR_7$ wherein m is 0 or an integer of from 1 to 10, and R_7 is cycloalkyl radical, having from three to seven carbon atoms, or a hydrocarbyl aryl or heteroaryl radical, as defined above or a pharmacologically acceptable acid addition salt thereof.

10. The method of claim 1 wherein the concentration of the compound applied is from about 0.0000001% to about 50% by weight of the composition.

11. The method of claim 10 wherein the compound is a compound of formula (III)



wherein y is 0 or 1, x is 0 or 1 and x and y are not both 1, Y is a radical selected from the group consisting of alkyl, halo, nitro, amino, thiol, hydroxy, alkyloxy, alkylcarboxy, halo substituted alkyl wherein said alkyl radical comprises from one to six carbon atoms, n is 0 or an integer of from 1 to about 3 and R_3 is =O, —OH or —O(CO)R_6 wherein R_6, hatched lines indicate α configuration and solid triangles are used to indicate β configuration.

12. The method of claim 11 wherein the compound is bimatoprost or a pharmaceutically acceptable salt.

13. The method of claim 1 wherein hair growth is eye lashes.

14. The method of claim 13 wherein said compound is bimatoprost.

15. A method of stimulating eyelash growth comprising administering an effective amount of bimatoprost to a person.

16. The method of claim 15 wherein a liquid composition containing about 0.03% by weight of bimatoprost is administered to the person.

* * * * *

Exhibit D

US007388029B2

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

(10) **Patent No.: US 7,388,029 B2**
(45) **Date of Patent: Jun. 17, 2008**

(54) **COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS**

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(73) Assignee: **Duke University**, Durham, NC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 355 days.

(21) Appl. No.: **11/138,097**

(22) Filed: **May 26, 2005**

(65) **Prior Publication Data**

US 2005/0222232 A1 Oct. 6, 2005

Related U.S. Application Data

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(60) Provisional application No. 60/193,645, filed on Mar. 31, 2000.

(51) **Int. Cl.**
A61K 31/215 (2006.01)
A61K 31/33 (2006.01)
A61K 31/41 (2006.01)
A61K 31/38 (2006.01)

(52) **U.S. Cl.** **514/530**; 514/183; 514/222.2; 514/359; 514/360; 514/367; 514/438; 514/439; 514/506; 514/531; 514/613; 514/617; 514/621

(58) **Field of Classification Search** 514/183, 514/222.2, 359, 360, 367, 438, 439, 506, 514/530, 531, 613, 617, 621
See application file for complete search history.

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(74) *Attorney, Agent, or Firm*—Michael Best & Friedrich LLP

(57) **ABSTRACT**

A method for treating hair loss in mammals uses compositions containing prostaglandin F analogs. The compositions can be applied topically to the skin. The compositions can arrest hair loss, reverse hair loss, and promote hair growth.

20 Claims, No Drawings

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COMPOSITIONS AND METHODS FOR TREATING HAIR LOSS USING NON-NATURALLY OCCURRING PROSTAGLANDINS

This application is a divisional of and claims priority to U.S. patent application Ser. No. 09/774,557 filed on Jan. 31, 2001, now abandoned, which claims priority, under 35 U.S.C. §119, of provisional application no. 60/193,645 filed on Mar. 31, 2000. This application claims the priority of each of these applications, and fully incorporates the subject matter thereof.

FIELD OF THE INVENTION

This invention relates to compositions and methods for treating hair loss in mammals. More particularly, this invention relates to compositions and methods for arresting or reversing hair loss, or both, and promoting hair growth.

BACKGROUND OF THE INVENTION

Hair loss is a common problem which is, for example, naturally occurring or chemically promoted through the use of certain therapeutic drugs designed to alleviate conditions such as cancer. Often such hair loss is accompanied by lack of hair re-growth which causes partial or full baldness.

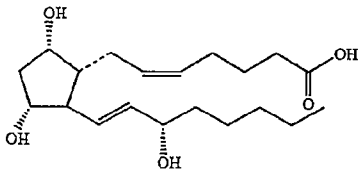
Hair growth on the scalp does not occur continuously, but rather occurs by a cycle of activity involving alternating periods of growth and rest. This cycle is divided into three main stages; anagen, catagen, and telogen. Anagen is the growth phase of the cycle and is characterized by penetration of the hair follicle deep into the dermis with rapid proliferation of cells which are differentiating to form hair. The next phase is catagen, which is a transitional stage marked by the cessation of cell division, and during which the hair follicle regresses through the dermis and hair growth ceases. The next phase, telogen, is characterized as the resting stage during which the regressed follicle contains a germ with tightly packed dermal papilla cells. At telogen, the initiation of a new anagen phase is caused by rapid cell proliferation in the germ, expansion of the dermal papilla, and elaboration of basement membrane components. When hair growth ceases, most of the hair follicles reside in telogen and anagen is not engaged, thus causing the onset of full or partial baldness.

Attempts to invoke the re-growth of hair have been made by, for example, the promotion or prolongation of anagen. Currently, there are two drugs approved by the United States Food and Drug Administration for the treatment of male pattern baldness: topical minoxidil (marketed as ROGAINE® by Pharmacia & Upjohn), and oral finasteride (marketed as PROPECIA® by Merck & Co., Inc.). However, the search for efficacious hair growth inducers is ongoing due to factors including safety concerns and limited efficacy.

The thyroid hormone thyroxine ("T4") converts to thyronine ("T3") in human skin by deiodinase I, a selenoprotein. Selenium deficiency causes a decrease in T3 levels due to a decrease in deiodinase I activity; this reduction in T3 levels is strongly associated with hair loss. Consistent with this observation, hair growth is a reported side effect of administration of T4. See, e.g., Berman, "Peripheral Effects of L-Thyroxine on Hair Growth and Coloration in Cattle", *Journal of Endocrinology*, Vol. 20, pp. 282-292 (1960); and Gunaratnam, "The Effects of Thyroxine on Hair Growth in the Dog", *J. Small Anim. Pract.*, Vol. 27, pp. 17-29 (1986). Furthermore, T3 and T4 have been the subject of several patent publications relating to treatment of hair loss. See, e.g., Fischer et al., DE 1,617,477, published Jan. 8, 1970; Mortimer, GB 2,138,286, published Oct. 24, 1984; and Lindenbaum, WO 96/25943, assigned to Life Medical Sciences, Inc., published Aug. 29, 1996.

Unfortunately, however, administration of T3 or T4, or both, to treat hair loss is often not practicable because these thyroid hormones can induce significant cardiotoxicity. See, e.g., Walker et al., U.S. Pat. No. 5,284,971, assigned to Syntex, issued Feb. 8, 1994 and Emmett et al., U.S. Pat. No. 5,061,798, assigned to Smith Kline & French Laboratories, issued Oct. 29, 1991.

In an alternative approach, prostaglandins have been proposed to promote hair growth because prostaglandins may have a similar benefit to thyroid hormones, i.e., increasing hair length and changing pigmentation. Naturally occurring prostaglandins (e.g., PGA_2, PGB_2, PGE_1, $PGF_{2\alpha}$, and PGI_2) are C-20 unsaturated fatty acids. $PGF_{2\alpha}$, the naturally occurring Prostaglandin F analog in humans, is characterized by hydroxyl groups at the C9 and C11 positions on the alicyclic ring, a cis-double bond between C5 and C6, and a trans-double bond between C13 and C14. $PGF_{2\alpha}$ has the formula:



Analogs of naturally occurring Prostaglandin F are known in the art. For example, see U.S. Pat. No. 4,024,179 issued to Bindra and Johnson on May 17, 1977; German Pat. No. DT-002,460,990 issued to Beck, Lerch, Seeger, and Teufel published on Jul. 1, 1976; U.S. Pat. No. 4,128,720 issued to Hayashi, Kori, and Miyake on Dec. 5, 1978; U.S. Pat. No. 4,011,262 issued to Hess, Johnson, Bindra, and Schaaf on Mar. 8, 1977; U.S. Pat. No. 3,776,938 issued to Bergstrom and Sjovall on Dec. 4, 1973; P. W. Collins and S. W. Djuric, "Synthesis of Therapeutically Useful Prostaglandin and Prostacyclin Analogs", *Chem. Rev., Vol.* 93, pp. 1533-1564 (1993); G. L. Bundy and F. H. Lincoln, "Synthesis of 17-Phenyl-18,19,20-Trinorprostaglandins: I. The PG_1 Series", *Prostaglandin*, Vol. 9 No. 1, pp. 1-4 (1975); W. Bartman, G. Beck, U. Lerch, H. Teufel, and B. Scholkens, "Luteolytic Prostaglandin: Synthesis and Biological Activity", *Prostaglandin*, Vol. 17 No. 2, pp. 301-311 (1979); C. Iiljebris, G. Selen, B. Resul, J. Sternschantz, and U. Hacksell, "Derivatives of 17-Phenyl-18, 19,20-trinorprostaglandin $F_2\alpha$. Isopropyl Ester: Potential Antiglaucoma Agents", *Journal of Medicinal Chemistry*, Vol. 38, No. 2, pp. 289-304 (1995).

Prostaglandins in general have a wide range of biological activities. For example, PGE_2 has the following properties: a) regulator of cell proliferation, b) regulator of cytokine synthesis, c) regulator of immune responses and d) inducer of vasodilatation. Vasodilatation is thought to be one of the mechanisms of how minoxidil provides a hair growth benefit. In vitro results in the literature also indicate some anti-inflammatory properties of the prostaglandins. c.f.; Tanaka, H. *Br J. Pharm.*, 116, 2298, (1995).

However, previous attempts at using prostaglandins to promote hair growth have been unsuccessful. Different prostaglandin analogs can bind to multiple receptors at various concentrations with a biphasic effect. Furthermore, administration of naturally occurring prostaglandins can