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Notice Of Entitlement

I, Joseph H. Handelman, of 26 West 61 Street, New York, New York 10023, UNITED STATES OF AMERICA, being the Applicant/Nominated Person in respect of Application No. 21172/95, state the following:-

The Applicant/Nominated Person has entitlement from the actual inventors as follows:

The Applicant/Nominated Person is the assignee of the actual inventors.

The Applicant/Nominated Person is entitled to rely on the application listed in the Declaration under Article 8 of the PCT as follows:

The Applicant/Nominated Person is the assignee of the basic applicants.

The basic application listed on the Declaration under Article 8 of the PCT is the first application made in a Convention country in respect of the invention.

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INHIBITION OF HAIR GROWTH

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(57) Claim

1. A method of inhibiting mammalian hair growth, comprising

selecting an area of skin from which reduced hair growth is desired; and

applying to said area of skin a composition of an inhibitor of ornithine aminotransferase in an amount effective to reduce hair growth.

11. The new use of an inhibitor of ornithine aminotransferase for reducing hair growth.

12. A composition when used for inhibiting mammalian hair growth, which includes an inhibitor of ornithine aminotransferase in an amount effective to reduce hair growth, and a non-toxic, dermatologically acceptable vehicle or carrier.

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(54) Title: INHIBITION OF HAIR GROWTH

(57) Abstract

Mammalian hair growth is reduced by applying to the skin a composition including an inhibitor of ornithine aminotransferase.

INHIBITION OF HAIR GROWTH

The invention relates to a method of reducing unwanted hair growth in mammals.

A main function of mammalian hair is to provide environmental protection. However, that function has largely been lost in humans, in whom hair is kept or removed from various parts of the body essentially for cosmetic reasons. For example, it is generally preferred to have hair on the scalp but not on the face.

Various procedures have been employed to remove unwanted hair, including shaving, electrolysis, depilatory creams or lotions, waxing, plucking, and other cosmetic procedures, and therapeutic antiandrogens. These conventional procedures generally have drawbacks associated with them. Shaving, for instance, can cause nicks and cuts as well as ingrown hairs resulting in inflammatory lesions, and can also promote the perception of an increase in the rate of hair regrowth. Shaving also can leave stubble. Electrolysis, on the other hand, can keep a treated area free of hair for prolonged periods of time, but can be expensive, painful, and sometimes leaves scarring. Depilatory creams, though very effective, typically are not recommended for frequent use

due to their high irritancy potential. Waxing and plucking can cause pain, discomfort, and poor removal of short hair. Finally, antiandrogens -- which have been used to treat female hirsutism -- can have unwanted side effects.

It has previously been disclosed that the rate and character of hair growth can be altered by applying to the skin inhibitors of certain enzymes. These inhibitors include inhibitors of 5-alpha reductase, ornithine decarboxylase, S-adenosylmethionine decarboxylase, gamma-glutamyl transpeptidase, and transglutaminase. See, for example, Breuer et al., U.S. Pat. No. 4,885,289; Shander, U.S. Pat. No. 4,720,489; Ahluwalia, U.S. Pat. No. 5,095,007; Ahluwalia et al., U.S. Pat. No. 5,096,911; Shander et al., U.S. Pat. No. 5,132,293; and Shander et al., U.S. Pat. No. 5,143,925.

The enzyme ornithine aminotransferase catalyzes the reversible conversion of ornithine and alpha ketoglutarate to delta-1-pyrroline-5-carboxylate and glutamate. Pyrroline-5-carboxylate is an intermediate precursor of proline.

It has now been found that unwanted mammalian (including human) hair growth -- particularly androgen-stimulated hair growth -- can be inhibited by applying to the skin a composition including an ornithine aminotransferase (OAT) inhibitor in an amount effective to reduce hair growth. The unwanted hair growth which is reduced may be normal hair growth which is cosmetically reduced, or hair growth that results from an abnormal or diseased condition.

Among the inhibitors of OAT that can be used are irreversible inhibitors of OAT such as 5-fluoromethylornithine (6-fluoro-2,5-diaminohexanoic acid, 5-FMOrn), (S)-2-amino-4-amino-oxybutyric acid (Canaline), and 3-amino-2,3-dihydrobenzoic acid (Gabaculin). Reversible inhibitors (competitive and non-competitive) can also be used.

The inhibitor of OAT preferably is incorporated in a topical composition or a cosmetic composition, which includes a non-toxic dermatologically acceptable vehicle or carrier which is adapted to be spread upon the skin. Examples of suitable vehicles are acetone, alcohols, or a cream, lotion, or gel which can effectively deliver the active compound. One such vehicle is disclosed in application PCT/US 93/05068. In addition, a penetration enhancer may be added to the vehicle to further enhance the effectiveness of the formulation.

The concentration of the inhibitor in the composition may be varied over a wide range up to a saturated solution, preferably from 0.1% to 30% by weight or even more; the reduction of hair growth increases as the amount of inhibitor applied increases per unit area of skin. The maximum amount effectively applied is limited only by the rate at which the inhibitor penetrates the skin. Generally, the effective amounts range from 100 to 3000 micrograms or more per square centimeter of skin.

The composition should be topically applied to a selected area of the body from which it is desired to inhibit hair growth. For example, the composition can be applied to the face, particularly to the beard area of the face, i.e., the cheek, neck, upper lip, and

chin. The composition can also be applied to the legs, arms, torso or armpits. The composition is particularly suitable for reducing the growth of unwanted hair in women suffering from hirsutism or other conditions. In humans, the composition should be applied once or twice a day, or even more frequently, for at least three months to achieve a perceived reduction in hair growth. Reduction in hair growth is demonstrated when the frequency of hair removal (shaving, tweezing, depilatory use, waxing) is reduced, or the subject perceives less hair on the treated site, or quantitatively, when the weight of hair removed by shaving (i.e., hair mass) is reduced. Benefits of reduced hair removal frequency include convenience and less skin irritation.

Male intact Golden Syrian hamsters are considered acceptable models for human beard hair growth in that they display oval shaped flank organs, one on each side, each about 8 mm. in major diameter, which grow thick black and coarse hair similar to human beard hair. These organs produce hair in response to androgens in the hamster. To evaluate the effectiveness of a particular OAT inhibitor, the flank organs of each of a group of hamsters are depilated by applying a thioglycolate based chemical depilatory (Surgex). To one organ of each animal 10-25 μl. of vehicle alone once a day is applied, while to the other organ of each animal an equal amount of vehicle containing an OAT inhibitor is applied. After thirteen applications (one application per day for five days a week), the flank organs are shaved and the amount of recovered hair (hair mass) from each is weighed. Percent-reduction of hair

growth is calculated by subtracting the hair mass (mg) value of the test compound treated side from the hair mass value of the vehicle treated side; the delta value obtained is then divided by the hair mass value of the vehicle treated side, and the resultant number is multiplied by 100.

The above-described assay will be referred to herein as the "Golden Syrian hamster" assay. Preferred compositions provide an inhibition in hair growth of at least about 35%, more preferably at least about 50%, and most preferably at least about 70% when tested in the Golden Syrian hamster assay.

A number of OAT inhibitors were tested in the Golden Syrian hamster assay; the results are presented in Table I. The vehicle used in the compositions tested was 68% deionized water, 16% absolute ethanol, 5% propylene glycol, 5% dipropylene glycol, 4% benzoyl alcohol, and 2% propylene carbonate.

TABLE I
(mean ± SEM)

Treatments	(n)	Treated	Untreated	% Inhibition
5% 5-FMOrn	8	.616 ± .15	1.657 ± .15	66.02 ± 6.30
15% 5-FMOrn	8	.322 ± .07	2.065 ± .17	84.55 ± 2.47
10% Gabaculin	8	1.365 ± .14	2.381 ± .21	43.06 ± 2.72
25% Gabaculin	8	1.266 ± .11	2.556 ± .31	48.08 ± 5.00
2% Canaline		1.553 ± .20	1.996 ± .25	20.99 ± 7.70
10% Canaline		.790 ± .11	1.466 ± .20	44.50 ± 7.40
Control		2.294 ± .18	2.465 ± .25	2.65 ± 8.52

The following assay for OAT activity based on the procedure of O'Donnell et al., Analytical Biochemistry 90, 41-46 (1978) was adapted for OAT measurements in hair follicles, and can be used to evaluate the effectiveness of OAT inhibitors in reducing OAT activity.

The product of OAT activity, pyrroline-5-carboxylic acid (P5C), was measured by reverse-phase HPLC analysis of dihydroquinasolium ion (DHQ). DHQ is a reaction product of P5C and o-aminobenzylaldehyde (OAB). The analysis was performed with a Waters 490 UV detector. The amount of DHQ formed was directly proportional to the concentration of P5C. The sensitivity of the Waters 490 UV detector had been determined to be above 100 picomoles of P5C injected and was reasonably linear.

Initial assays of flank organ follicle OAT activity were conducted employing saturating doses of ornithine (350 mM). The OAT mediated conversion of ornithine to P5C was monitored by measuring in vitro P5C formation, resulting in time and concentration dependent increases in P5C.

Assays (including the initial assays) were conducted utilizing excised hamster flank organ follicles. The excised hamster follicles were diluted in assay buffer (2 follicles/300 μl) and then were minced with scissors and homogenized with a sonicator. The resultant homogenate was centrifuged to obtain a cytosolic supernatant which was assayed for OAT. Samples were incubated for one hour with either Gabaculin, L-Canaline, or 5-FMOrn at 1mM, 100 μM, 10 μM, and 1 μM concentrations. The concentration of P5C was then assayed. The results are provided in Table II. Gabaculin the most potent inhibitor and completely inhibited

OAT at a concentration of 100 μM; 75% inhibition was observed at a concentration of 10 μM, and no inhibition was seen at a concentration of 1 μM. L-Canaline inhibited OAT completely at a concentration of 1mM, 25% inhibition was seen at a concentration of 100 μM, and no inhibition was shown at a concentration of 10 and 1 μM concentrations. 5-FMOrn demonstrated 83% OAT inhibition at a concentration of 1mM. No OAT inhibition was exhibited by 5-FMOrn at concentrations of 100 μM, 10 μM and 1 μM.

TABLE II

Compound	Final Concentration		Percent Inhibition	nm P5C formed/fol/1hr
Gabaculin	1 mM	pH=4.5	100	n.d.
	100 μM	(pH=7.5)	100	n.d.
	10 μM		74.268	5.057
	1 μM		0.089	19.637
L-Canaline	1 mM	pH=7.5	100	n.d.
	100 μM		25.653	14.612
	10 μM		none	24.096
	1 μM		none	29.859
5-FMOrn	1 mM	pH=7.5	83.036	3.334
	100 μM		0.471	19.562
	10 μM		none	29.327
	1 μM		none	31.419
	Control		0.000	19.654

n.d. = not detectable

It will be appreciated by those skilled in the art that the invention can be performed within a wide range of equivalent parameters of composition and conditions without departing from the spirit or scope of the invention or of any embodiment thereof.

The claims defining the invention are as follows:

1. A method of inhibiting mammalian hair growth, comprising

selecting an area of skin from which reduced hair growth is desired; and

applying to said area of skin a composition of an inhibitor of ornithine aminotransferase in an amount effective to reduce hair growth.

2. The method of claim 1, wherein said inhibitor is 6-fluoro-2,5-diaminohexanoic acid, (S)-2-amino-4-amino-oxybutyric acid or 3-amino-2, 3-dihydrobenzoic acid.

3. The method of claim 1, wherein said inhibitor is an irreversible inhibitor.

4. The method of claim 1, wherein the concentration of said inhibitor in said composition is between 1% and 30%.

5. The method of claim 1, wherein the composition is applied to the skin in an amount of from 100 to 3000 micrograms of said inhibitor per square centimeter of skin.

6. The method of claim 1, wherein the composition is applied to the skin on the face of said mammal.

7. The method of claim 1, wherein the composition provides a reduction in hair growth of at least 30%, when tested in the Golden Syrian hamster assay.

8. The method of claim 7, wherein the composition provides a reduction in hair growth of at least 50%, when tested in the Golden Syrian hamster assay.

9. The method of claim 7, wherein the composition provides a reduction in hair growth of at least 70%, when tested in the Golden Syrian hamster assay.

10. A method according to any one of claims 1 to 9, wherein said applying of said inhibitor has a cosmetic effect.

11. The new use of an inhibitor of ornithine aminotransferase for reducing hair growth.

12. A composition when used for inhibiting mammalian hair growth, which includes an inhibitor of ornithine aminotransferase in an amount effective to reduce hair growth, and a non-toxic, dermatologically acceptable vehicle or carrier.

13. A composition according to claim 12, wherein said inhibitor is as defined in any one of claims 2 to 9.

14. A composition according to claim 12 or claim 13 which is a cosmetic composition.

Dated 14 July, 1998
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AUSTRALIAN PATENT OFFICE

INTERNATIONAL SEARCH REPORT

Inte[illegible]nal Application No
PCT/US 95/02915

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,86 02269 (HANDELMAN, JOSEPH, H) 24 April 1986 cited in the application *Complete docment*	1-16
P,A	WO,A,94 21216 (HANDELMAN,JOSEPH,H) 29 September 1994 *Document*	1-16
P,A	WO,A,94 21217 (HANDELMAN,JOSEPH,H) 29 September 1994 *Document*	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 July 1995	18. 07. 95
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INTERNATIONAL SEARCH REPORT

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