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U.S. UTILITY Patent Application

APPL NUM	FILING DATE	CLASS	SUBCLASS	GAU	EXAMINER
10184810	06/28/2002	424	401	1615	CHANNAVAJJALA

**APPLICANTS: Dobson James; Ethier Michael;

**CONTINUING DATA VERIFIED: Verified

THIS APPLICATION IS A CON OF 09/672,348 09/28/2000 PAT 6,423,327

WHICH IS A CON OF 09/179,006 10/26/1998 ABN

Certificate
JUN 22 2010
of Correction

** FOREIGN APPLICATIONS VERIFIED: none

PG-PUB DO NOT PUBLISH ☐ RESCIND ☐

Foreign priority claimed ☐ yes ☑ no

35 USC 119 conditions met ☐ yes ☐ no

Verified and Acknowledged Examiner's Initials

ATTORNEY DOCKET NO 07917-045003

TITLE : Treatment of skin with adenosine or adenosine analog

U.S.DEPT. OF COMM./PAT.& TM-PTO-436L(Rev. 12-94)

10-2-03 Formal Drawings (2 shts) set 1 6-28-02

NOTICE OF ALLOWANCE MAILED		CLAIMS ALLOWED	
4-22-03	Assistant Examiner	Total Claims 10	Print Claim for O.G 1
ISSUE FEE		DRAWING	
Amount Due 690	Date Paid 7-9-03	Sheets Drwg. 2	Figs.Drwg. 4
	Banada LAKSHMI CHANNAVAJJALA ART UNIT 1615 Primary Examiner	Print Fig. 1A & 1B	
☑ TERMINAL DISCLAIMER	PREPARED FOR ISSUE	C Betancourt Application Examiner 4-24-03	

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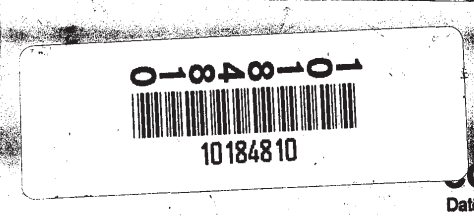
ISSUE FEE IN FILE FILED WITH: ☐ DISK (CRF) ☐ CD-ROM (Attached in pocket on right inside flap)



INITIALS

CONTENTS

Briefed 1600

	Application papers.	Date Received (incl. C. of M.) or Date Mailed			Date Received (incl. C. of M.) or Date Mailed
1.			31.		
2.	Pre amend A	6/28/02	32.		
3.	IDS	6/28/02	33.		
4.	Rejection (3mo)	10.28.02	34.		
5.	Chg of Addr	11-29-02	35.		
6.	Amd B	1-14-03	36.		
7.	Terminal Disc	4-16-03	37.		
8.	Notice of allowance	4.22.03	38.		
9.	LTR. RE: COMMENTS	7-9-03	39.		
10.	Req. for CPC	5-19-2010	40.		
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ISSUE SLIP STAPLE AREA (for additional cross-references)

ISSUING CLASSIFICATION

ORIGINAL		CROSS REFERENCE(S)							
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)						
424	401	424	447	448	449	450			
INTERNATIONAL CLASSIFICATION		514	46						
A61K	7100								
A61K	31/7076								
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INDEX OF CLAIMS

✓ ..... Rejected – (Through numeral) ... Canceled N ..... Non-elected A ..... Appeal
= ..... Allowed + ... Restricted I ..... Interference O ..... Objected

Claim Final	Claim Original	Date
	1	10 23 97 ✓
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If more than 150 claims or 9 actions staple additional sheet here

SEARCH

Class	Sub.	Date	Exmr.
424	401 447 448 449 [redacted]		
514	46	10/23/02	[redacted]
Updated Search		4/18/03	[redacted]

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
424	401 447 448 449		
514	46	4/19/03	[redacted]

SEARCH NOTES

(List databases searched. Attach search strategy inside.)

	Date	Exmr.
Web - EPAB, JPAB, USPAT, PGPUB, DwPI's; Search attached	10/22/02	
Parent Case searched; Invent. name search		[redacted]
STN - Caplus, Medline, biosis, embase	4/8/03	[redacted]
Discussed with TK Page SPE, 1615	4/9/03	[redacted]
STN - Search; Medline, embase, biosis, Caplus; Search attached	4/9/03	[redacted]
Consulted Brian Stanton QAS, regarding obviousness double patenting rejection	4/17/03	[redacted]

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

07/08/2002 WASFAW1 00000013 10184810
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(5/87)

*U.S. Government Printing Office: 2001 — 481-697/59173

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June 28, 2002

Attorney Docket No.: 07917-045003

Box Patent Application
Commissioner for Patents
Washington, DC 20231

Presented for filing is a new continuation patent application of:

Applicant: JAMES G. DOBSON AND MICHAEL F. ETHIER

Title: TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

The prior application is assigned of record to University of Massachusetts, a Massachusetts corporation, by virtue of an assignment submitted to the U.S. Patent and Trademark Office and recorded on January 7, 1999 at 9690/0305.

Enclosed are the following papers, including those required to receive a filing date under 37 CFR §1.53(b):

	Pages
Specification	20
Claims	7
Abstract	1
Declaration	2
Drawings	2

Enclosures:

— Form PTO-1449, 1 page, listing documents cited in the parent application(s). Please confirm that these have been considered in this

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June 28, 2002
Date of Deposit

Signature

Leroy Jenkins
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application by returning a copy of the Form PTO-1449 with the examiner's initials.
— Preliminary amendment, 3 pages.
— Information Disclosure Statement, 2 pages.
— Postcard.

This application is a continuation (and claims the benefit of priority under 35 USC 120) of U.S. application serial no. 09/672,348, filed on September 28, 2000, pending, which is a continuation of U.S. application serial no. 09/179,006, filed on October 26, 1998, now abandoned. The disclosure of the prior applications are considered part of (and are incorporated by reference in) the disclosure of this application.

Basic filing fee	$370
Total claims in excess of 20 times $9	$0
Independent claims in excess of 3 times $42	$0
Fee for multiple dependent claims	$0
Total filing fee:	$370

A check for the filing fee is enclosed. Please apply any other required fees or any credits to deposit account 06-1050, referencing attorney docket number 07917-045003.

If this application is found to be incomplete, or if a telephone conference would otherwise be helpful, please call the undersigned at (617) 542-5070.

Kindly acknowledge receipt of this application by returning the enclosed postcard.

Please send all correspondence to:

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Boston, Massachusetts 02110-2804

Respectfully submitted,

J. Peter Fasse

J. Peter Fasse, Esq.
Reg. No. 32,983
Enclosures
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TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Abstract of the Disclosure

Methods for enhancing the condition of non-diseased skin by application of compositions containing adenosine or an adenosine analog are disclosed. Also disclosed are methods for increasing DNA synthesis or protein synthesis in dermal cells, and methods for increasing dermal cell size, by application of compositions containing adenosine.

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10184810.062802

Attorney's Docket N. 917-045003 / UMMC 97-32

APPLICATION

FOR

UNITED STATES LETTERS PATENT

TITLE: TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

APPLICANT: JAMES G. DOBSON AND MICHAEL F. ETHIER

CERTIFICATE OF MAILING BY EXPRESS MAIL

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6/28/02
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Leroy Jenkins
Typed or Printed Name of Person Signing Certificate

PATENT
ATTORNEY DOCKET NO: 07917/045002

TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Statement as to Federally Sponsored Research

Work on this invention was supported by funds from the United States government (Public Health Service Grants HL-22828 and AG-11491). The government therefore has certain rights in this invention.

Field of the Invention

This invention relates to dermatology and cell biology.

Background of the Invention

Skin includes a surface layer, known as the epidermis, and a deeper connective tissue layer, known as the dermis. The epidermis undergoes continuous turnover as the outermost cells are exfoliated and replaced by cells that arise from inner dermal layers. The dermis is composed of a variety of cell types, including fibroblasts.

Skin thickness begins to decline in humans after the age of 20 as the dermis becomes thinner and the number of skin fibroblasts declines. As skin ages, or is exposed to UV light and other environmental insults, changes in the underlying dermis can lead to the functional and morphological changes associated with damaged skin. Decreases in the abundance and function of products of the fibroblasts, which include collagen and proteoglycans, are believed to play major roles in wrinkled and damaged skin.

Summary of the Invention

We have discovered that adenosine stimulates DNA synthesis, increases protein synthesis, and increases cell size in cultures of human skin fibroblasts. Based on this discovery, the invention provides methods and compositions for enhancing the condition of skin.

In general, the invention provides a method for enhancing the condition of non-diseased skin of a mammal, e.g., a human. The method includes topically applying a therapeutically effective amount of a composition including adenosine or an adenosine analog to non-diseased skin of the mammal.

The invention also provides a method for promoting healing of broken, non-diseased skin in a mammal by topically administering a composition including a therapeutically effective amount of adenosine or an adenosine analog to the mammal.

Also included in the invention is a method for increasing DNA synthesis in a dermal cell of non-diseased skin of a mammal. The method includes topically administering a therapeutically effective amount of adenosine or an adenosine analog to a region of non-diseased skin of the mammal containing dermal cell. The adenosine is added so that it does not cause proliferation of the dermal cell.

The invention also features a method of increasing protein synthesis in a dermal cell of non-diseased skin of a mammal. The method includes topically administering a composition including a therapeutically effective amount of adenosine or an adenosine analog to a region of skin of the mammal containing the dermal cell. The adenosine or adenosine analog does not cause proliferation of the dermal cell.

Also provided in the invention is a method of increasing cell size in a dermal cell in non-diseased skin of a mammal, e.g., a human. The method includes topically administering a composition including a therapeutically effective amount of adenosine to a region of skin of the mammal containing the dermal cell, wherein addition of the adenosine does not cause proliferation of the dermal cell, wherein addition of the adenosine does not cause proliferation of the dermal cell.

The invention also includes a method for enhancing skin condition in a mammal, e.g., a human. The method includes providing fibroblasts from the mammal *ex vivo*, culturing the fibroblasts in the presence of adenosine, and reintroducing the fibroblasts into the mammal.

The therapeutically effective amount of adenosine used in the above-described methods is preferably 10^{-3} M to 10^{-7} M, more preferably 10^{-4} M to 10^{-6} M, and most preferably about 10^{-4} M.

The composition used in the above-described methods can include a second agent in addition to adenosine. The second agent can be, e.g. an agent that promotes binding of adenosine or an adenosine analog to an adenosine receptor, an angiogenic factor such as vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (BFGF), an agent that itself enhances skin condition, such as tretoinin or another known conditioning agent such as an emollient, a humectant, or an occlusive agent.

In preferred embodiments of the invention, the adenosine or an adenosine analog does not promote skin cell proliferation.

The invention also provides a composition including about 10^{-3} M to about 10^{-7} M adenosine and a therapeutically effective amount of an angiogenesis factor. In some

embodiments, the composition of the adenosine is about 10^{-4} M.

As used herein, "enhancement of skin condition" means a noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling in skin.

As used herein, a "therapeutically effective amount" of adenosine or an adenosine analog means an amount that enhances skin condition when applied to skin.

As used herein, "non-diseased skin" means skin free of any proliferative disorder observable by visual inspection.

The present invention advantageously allows for enhancement of skin condition. This results in skin that shows a less wrinkled, rough, or dry complexion. For example, the invention provides for enhancing the condition of skin damaged due to exposure to the sun or skin whose condition has deteriorated due to normal aging.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of this invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Brief Description of the Drawings

Figs. 1A and 1B are histograms showing the effect of adenosine on [^{3}H]thymidine incorporation in cultures of normal human skin (Fig. 1A) and lung fibroblasts (Fig. 1B). After incubation in serum-free medium for 24 hours, cells were exposed to 10^{-4} M adenosine for 18 hours. Medium was replaced with serum-free medium without adenosine, and [^{3}H]thymidine was added. Results are expressed as percent [^{3}H]thymidine incorporation compared to control cultures without adenosine and are means ± SEM for 4-5 experiments. "*" denotes value was significantly different from control value without adenosine.

Figs. 2A and 2B are histograms showing concentration responses of adenosine-stimulated protein synthesis in human skin fibroblasts from a young (Fig. 2A) and aged (Fig. 2B) donor. Cells were grown to 75% confluence. Medium was then replaced with serum-free medium with or without adenosine. After 48 hours, [^{3}H]phenylalanine incorporation was determined as described. Results are expressed as % [^{3}H]phenylalanine incorporation compared to control cultures without adenosine and are means ±SEM for 6-25 experiments. "*" denotes value was significantly different from control value without adenosine.

Detailed Description

The invention is suitable for treating skin of a mammal, e.g., a human, for which promotion of fibroblast-associated dermal functions is desired. For example,

promotion of fibroblast-associated functions is desirable in enhancing the condition of aged skin, which is associated with a decrease in dermal cell function and is characterized by increased dryness or roughness, or both. The method can also be used on subjects having otherwise damaged skin, *e.g.*, wrinkled skin and skin with a non-proliferative disorder. The method can may further be used prophylactically on a subject to minimize deterioration of skin condition associated with aging or environmental factors, such as photodamage.

Adenosine and suitable adenosine analogs are suitable for use in enhancing skin condition. Adenosine analogs such as adenosine agonists, adenosine receptor agonists, and compounds that increase intracellular or extracellular adenosine levels are suitable for use in the invention.

Agonists of adenosine include 2'-deoxyadenosine; 2',3'-isopropoylidene adenosine; toyocamycin; 1-methyladenosine; N-6-methyladenosine; adenosine N-oxide; 6-methylmercaptopurine riboside; 6-chloropurine riboside, 5'-adenosine monophosphate, 5'-adenosine diphosphate, or 5'-adenosine triphosphate. Adenosine receptor agonists include phenylisopropyl-adenosine ("PIA"), 1-Methylisoguanosine, ENBA (S(-), N^6-Cyclohexyladenosine (CHA), N^6-Cyclopentyladenosine (CPA), 2-Chloro-N_6-cyclopentyladenosine, 2-chloroadenosine, and adenosine amine congener (ADAC), all of which are agonists for the adenosine A_1 receptor. Other receptor agonists include 2-p-(2-carboxy-ethyl) phenethyl-amino-5'-N-ethylcarboxamido-adenosine (CGS-21680), N-ethylcarboxamido-adenosine (NECA) and napthyl-substituted aralkoxyadenosine (SHA-082), 5'(N-Cyclopropyl)-carboxamidoadenosine, DPMA (PD 129,944), Metrifudil, which are agonists for the adenosine A_2

receptor. Other adenosine receptor agonists include those which preferentially bind the A_1 receptor relative to the A_2 receptor, such as 2-Chloroadenosine, N^6-Phenyladenosine, and N^6-Phenylethyladenosine; and those which preferentially bind the A_2 receptor relative to the A_1 receptor, such as 2-Phenylaminoadenosine and MECA.

Also suitable for use are compounds that increase intracellular adenosine concentration by inhibiting the cellular uptake of adenosine or the breakdown of adenosine. One pathway of adenosine metabolism is the conversion of adenosine to inosine by adenosine deaminase. An example of an adenosine deaminase inhibitor is erythro-9-(2-hydroxy-3-nonyl) adenine ("EHNA"). Adenosine kinase inhibitors can also be used. Adenosine kinase converts adenosine to adenosine monophosphate by adenosine kinase. An example of an adenosine kinase inhibitor is iodotubercidin. Other suitable compounds include those that inhibit the dipyridamole-sensitive nucleoside transporter, which exports adenosine from the cytoplasm, and agents that promote the activity of a 5'-nucleotidase, e.g., the ATP-activated 5'-nucleotidase, which forms adenosine. Compounds that increase tissue adenosine and ATP levels include acadesine (AICA-riboside), which is described in Gruber et al., Circulation 80:1400-1411 (1989).

Adenosine can be also be administered with a second compound. The second compound can enhance the action of adenosine or the adenosine analog, e.g., by enhancing binding of adenosine or an adenosine analog to an adenosine receptor. An example of such a compound is PD 81,728, which is described in Kollias-Baker et al. J. Pharmacol. Exp. Ther. 281:761-68. Alternatively, the second agent can itself act to enhance skin condition. Examples of these types of agents include tretinoin, a recognized skin

conditioning agent (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 37:217-26, 1997), an angiogenic factor such as vascular endothelial cell growth factor (VEGF) or basic fibroblast growth factor (BFGF), or a conditioning agent.

The second compound can also be a conditioning agent such as an emollient, humectant, or occlusive agent. Numerous examples of particular conditioning agents are provided in the CTFA Cosmetic Ingredient Handbook (Cosmetic Toiletries and Fragrances Association, Washington, D.D., 1988). Emollients help to maintain the soft, smooth, and pliable appearance of skin and function by remaining on the skin surface or in the stratum corneum to act as lubricants, to reduce flaking, and to improve the skin's appearance. Examples of emollients include acetyl trioctyl citrate, cetyl alcohol, butyl myristate, cetyl alcohol, and mineral oil.

Humectants act to increase the water content of the top layers of the skin. Humectants include, *e.g.*, acetamide MEA, fructose, and xylitol. Occlusive agents inhibit the evaporation of water from skin, thereby increasing the water contend of the skin. Acetylated castor oil, mineral oil, and lauryl stearate are examples of occlusive agents.

A subject can be treated by applying adenosine or an adenosine analog in a pharmaceutical composition in an effective amount and for a period of time sufficient to improve the condition of the skin.

The pharmaceutical composition may be formulated using conventional methods to prepare pharmaceutically useful compositions. Such compositions preferably include at least one pharmaceutically acceptable carrier, such as those described in Remington's Pharmaceutical Sciences (E.W. Martin). In addition, the compositions preferably include a pharmaceutically acceptable buffer, preferably phosphate

buffered saline, together with a pharmaceutically acceptable compound for adjusting isotonic pressure, such as, for example, sodium chloride, mannitol, or sorbitol.

Adenosine or an adenosine agonist can also be provided in carriers and adjuvants such as ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances, such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances and polyethylene glycol. Adjuvants for topical or gel base forms of adenosine or adenosine analogs may, for example, be selected from the group consisting of sodium carboxymethylcellulose, polyacrylates, polyoxythylene-polyoxypropylene-block polymers, polyethylene glycol and wood wax alcohols. For all administrations, conventional depot forms may be used.

The adenosine or adenosine analog-containing compositions may be in any pharmaceutically acceptable dosage form. They are preferably applied by topical routes to exert local therapeutic effects. For topical application, the penetration of the adenosine into skin tissue may be enhanced by a variety of methods known to those of ordinary skill in the art. For example, adenosine may be applied directly and mechanically rubbed into the skin. Alternatively, adenosine or adenosine analogs may be incorporated into a transdermal patch that is applied to the skin. Preferably, the penetration resulting from these methods is enhanced with a chemical transdermal delivery agent such as dimethyl sulfoxide (DMSO) or the nonionic

surfactant, n-decylmethyl sulfoxide (NDMS), as described in Choi et al., Pharmaceutical Res., 7(11):1099, 1990.

Other modes of administration include, e.g., oral, subdermal, intradermal, or intravenous. When oral administration is used, it is critical that the adenosine or adenosine analog be delivered to that it is not degraded prior to exiting the digestive system.

The most effective mode of administration and dosage regimen of adenosine or the adenosine analog will depend upon the skin condition, previous therapy, the subject's health status, response to the adenosine, the judgment of the treating physician and the mode in which the adenosine is applied. For example, dosages for a therapeutically effective amount for topical application would be in the range of 100 ng to 10 mg per treated surface area per day. The adenosine may be administered to the patient at one time or over a series of treatments. When adenosine or the adenosine analog is administered in conjunction with a second agent, they can be administered either concurrently or sequentially, and can be administered in the same mode or a different mode, e.g., topical or oral.

Adenosine or an adenosine analog enhances skin condition when there is a noticeable decrease in noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling of the treated skin. Methods of measuring improvements in skin condition are well known in the art (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 26:215-24, 1992), and can include subjective evaluations by the patient or a second party, e.g., a treating physician. Objective methods can include skin topography measurements, such as those described in Grove et al., J. Amer. Acad. Dermatol. 21:631-37 (1989). In skin topography measurements, silicone rubber replicas are made

of a small area of skin, e.g., a 1 cm diameter circular area. The silicone rubber replicas capture fine lines and wrinkles on the skin. These specimens are then analyzed using computerized digital image processing to provide an objective measurement of the skin's topography. Skin topography measurements generated following digital-image processing can be measured using the values R_a and R_z as described in Olsen et al., J. Amer. Acad. Dermatol. 37:217-26, 1997, where R_a represents the area of deviation of skin surface features above and below an average central line, and R_z represents the difference between the maximum and minimum heights in five equal segments of the skin surface profile. A statistically significant decline (e.g., $P < 0.05$) in R_a and R_z values in skin treated with adenosine or an adenosine analog compared to untreated skin indicates an enhancement of skin condition.

Fibroblasts treated with adenosine or adenosine analogs can also be incorporated into a matrix and implanted in the body, e.g., as part of a skin graft. In addition, fibroblasts can be genetically engineered ex vivo to increase the amount of intracellular adenosine levels and then re-introduced into a human patient. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959, each of which is incorporated by reference herein in its entirety).

Experimental Information

Cell Culture

Human skin fibroblasts and human lung fibroblasts were supplied by the N.I.A. Aging Culture Repository Center (Camden, NJ). For skin fibroblasts, primary cultures had been initiated from explants obtained from a 3 mm punch biopsy of the mesial aspect of the upper left arm. Human

lung fibroblasts (IMR-90) were established from a 16-week normal female fetus. All cells displayed a normal diploid karyotype and all cells tested negative for bacteria, fungi and mycoplasma contamination.

Cells were grown in Eagle's minimal essential medium (MEM) supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 mg/ml streptomycin in a 37°C, 5% CO_2/95% air environment. After reaching confluence, cells were subcultivated with 0.25% trypsin in MEM with no added Ca^{2+} or Mg^{2+}.

Incorporation of [^{3}H]Thymidine

As an index of DNA synthesis incorporation of [^{3}H]thymidine was measured as described in Ethier et al., Am. J. Physiol. 272:H1470-79 (1997). Confluent monolayers of human skin fibroblasts in MEM plus 10% FBS were seeded into 16 mm diameter culture wells (24-well plates) at a density of 1 x 10^4 cells/cm^2. Cells were grown at 37°C under standard culture conditions (5% CO_2-95% air) until they were approximately 75% confluent. Medium was then removed and the cells were made "serum-free" by incubation in MEM with no FBS for 24 hours. Adenosine or vehicle (MEM) was added for an additional 18 hours. This medium was then replaced with fresh MEM, and the cells were pulsed with 1mCi/ml [^{3}H] thymidine (6.7 Ci/mmol). After a 2 hour incubation period, the medium was discarded and the cells were rinsed twice with cold (4°C) Hank's balanced salt solution (HBSS) and incubated for 5 minutes with 0.5 ml cold 10% (w/v) trichloroacetic acid (TCA). The wells were then rinsed with 8% TCA and the TCA-insoluble material was solubilized with 0.5 ml of a solution of 0.2M NaOH and 0.2% sodium decyl sulfate (SDS). The radioactivity of this

fraction was determined by standard liquid scintillation spectrometric techniques.

Incorporation of [^{3}H] thymidine was expressed as counts per minute (cpm) of ^{3}H per culture. Data in each experiment was derived from 4 identically treated wells. Since the cpm/well exhibited variation between experiments, data representing combined experiments are expressed herein as a percent of their respective mean control value.

Incorporation of [^{3}H]phenylalanine

Incorporation of [^{3}H]phenylalanine was measured as an index of protein synthesis. Human skin fibroblasts were seeded into 24-well culture plates in MEM containing 10% FBS. When cells had grown to approximately 75% confluence the culture medium was replaced with serum-free MEM with or without adenosine. After 48 hours, 2μCi/ml [^{3}H]phenylalanine was added to the cultures. Unlabeled phenylalanine (0.36 mM) was also added to equalize concentrations of intracellular and extracellular phenylalanine. After 8 hours, medium was removed and the cells were washed twice with cold (4°C) HBSS and incubated for 20 minutes in cold 10% (w/v) TCA. Cells were then incubated 5 minutes in 95% ethanol (4°C) and the TCA-insoluble material was solubilized with a solution of 0.2M NaOH and 0.2% SDS. The radioactivity of this fraction was determined by standard liquid scintillation spectrometric techniques.

Incorporation of [^{3}H] phenylalanine was expressed as cpm of ^{3}H per culture well and data in each experiment were derived from six identically treated wells. Since the cpm/well exhibited variation between experiments, data representing combined experiments are expressed as a percent of their respective mean control value.

Determination of Cell Size

Human fibroblasts in MEM 10% FBS were seeded into 25 cm^2 culture flasks at a density of 1×10^4 cells/cm^2. When the cells had grown to approximately 80% confluence the culture medium was removed and the cells were incubated in serum-free MEM for 24 hours. Adenosine or vehicle (MEM) was added for 18 hours and cells were then washed twice with cold (4°C) HBSS. Cells were removed with 0.25% trypsin in calcium-and magnesium-free MEM and diluted in cold (4°C) HBSS for measurement of relative cell size with a fluorescence-activated cell sorter (FACS; Becton Dickinson Vantage). Cell size was determined by forward light scatter on a minimum of 1×10^4 cells per experiment.

Experimental Materials

MEM, FBS, penicillin, streptomycin, trypsin, and HBSS were obtained from GIBCO (Grand Island, NY), [^{3}H] thymidine (6.7 Ci/mmol) and phenylalanine, L-ring-2,3,4,5,6-^{3}H] (92 Ci/mmol) were obtained from Dupont NEN (Boston, MA). Adenosine was from Boehringer Mannheim, SDS was from National Diagnostics, (Highland Park, NJ) and TCA and ethanol were obtained from Fisher Scientific (Pittsburgh, PA).

Data Analysis

Analysis of variance (ANOVA) was used to determine statistical differences between means. The Dunett's test was applied for multiple comparisons as described in Zar, J.H., Biostatistical Analysis. Englewood Cliffs, N.J., Prentice Hall, Inc. pp. 150-153, 1984. In addition, the Wilcoxon test was employed to verify differences between values expressed as a percentage. Differences were considered statistically different when $P < 0.05$.

DNA Synthesis

Exposure to 10^{-4}M adenosine increased [^{3}H]thymidine incorporation by 43 ±9% in five studies on cultures of human fibroblasts (AG607720B) made quiescent by serum removal. These results are summarized in Fig. 1A. In contrast, adenosine (10^{-4}M) had no effect on [^{3}H]thymidine incorporation in cultures of human lung fibroblasts (IMR-90) (Fig. 1B). Concentrations of adenosine ranging from 10-7 M to 10^{-3}M also failed to stimulate [^{3}H]thymidine incorporation in IMR-90 lung fibroblasts (data not shown).

The effect of adenosine on DNA synthesis was additionally determined on skin fibroblast cultures from six different human donors. Adenosine (10^{-4}M) stimulated DNA synthesis in all three cultures derived from young human donors (Table 1). Values shown are means ±SEM, where *n* is number of experiments. Exposure to adenosine and determination of [^{3}H] thymidine incorporation were as described above. The asterisk denotes a value significantly different from the corresponding control (100%).

Table 1. Effect of adenosine on [^{3}H]thymidine incorporation into cultured human skin fibroblasts derived from young donors

Cell Strain	Adenosine (10^{-4} M)	Donor		[^{3}H]thymidine incorporation (% of control)	*n*
		Age	Sex		
AG07720B	-	24	F	100	24
	+			124±7*	24
AG07306A	-	28	F	100	6
	+			193±20*	6
AG09605	-	30	M	100	12
	+			133±15*	12

Peak stimulation of [^{3}H]thymidine incorporation (93±20%, n=6) was achieved in human skin fibroblast cultures derived from a 28 year old female (AG07306A).

Adenosine (10^{-4}M) stimulated DNA synthesis in 2 of 3 cultures derived from aged human donors (Table 2). As in Table 1, values are means ±SEM, and *n* is the number of experiments performed. The asterisk denotes a measurement significantly different from the corresponding control (100%). Adenosine exposure increased [^{3}H]thymidine incorporation by 53±31% and 54 ±22% in human skin fibroblast cultures derived from a 70 year-old male and a 84 year-old male, respectively. Adenosine had no effect on cultures derived from a 67-year old female.

Table 2. Effect of adenosine on [^{3}H]thymidine incorporation into cultured human skin fibroblasts derived from aged donors

Cell Strain	Adenosine (10^{-4} M)	Donor		[^{3}H]thymidine incorporation (% of control)	*n*
		Age	Sex		
AG11728	-	67	F	100	6
	+			91±6	6
AG12949	-	70	M	100	11
	+			150±31*	11
AG11730	-	84	M	100	10
	+			154±22*	10

Protein Synthesis

The effect of adenosine on protein synthesis was determined by measuring [^{3}H]phenylalanine incorporation into cultures of human fibroblasts from a young and aged donor. Cultures made quiescent by serum removal were exposed to adenosine (10^{-6}M to 10^{-4}M) for 48 hours and then pulsed with phenylalanine. In skin fibroblast cultures derived from a 28-year old female (AG073060A) and an 84-year old male (AG11730), adenosine(10^{-4}M) increased protein synthesis by 13 ± 4% (n=25) and 13 ± 6% (n=17), respectively (Fig. 2).

Cell Size

The effect of adenosine on cell size was determined on human skin fibroblasts from young and aged donors by measuring forward light scatter in a FACS analyzer. Cultures made quiescent by serum removal were exposed to adenosine for 18 hours, removed by trypsinization, and

diluted in 4°C HBSS. A minimum of 1×10^4 cells were measured for each experiment. The results are shown in Table 2. Values are mean ± SEM for relative cell size determined by forward light scatter (FLS) in a fluorescence-activated cell sorter, and *n* = number of cells measured. The asterisk denotes the measurement is significantly different from corresponding control.

In skin fibroblast cultures from a 28 year old female (AG073060A) adenosine (10^{-4}M) significantly increased cell size by 1.8 and 2.2% in two of three experiments (Table 3).

The effect of adenosine on cell size was also measured on skin fibroblasts from an aged donor. The results are shown in Table IV. Values are mean ± SEM for relative cell size determined by forward light scatter (FLS) in a fluorescence-activated cell sorter, where *n* is the number of cells measured. An asterisk indicates a value significantly different from corresponding control.

In cultures derived from an 84-year old male (AG11730), adenosine (10^{-4}M) significantly increased cell size by 2.7-4.9% in 3 of 3 experiments (Table 4).

Table 3. Effect of adenosine on cell size in cultured human skin fibroblasts derived from young donors

Experiment Number	Adenosine (10^{-4} M)	Relative Size (FLS)	% increase	*n*
1	-	524±0.55	-	1.5×10^4
	+	526±0.55	0.4	1.5×10^4
2	-	319±1.24	-	1.0×10^4
	+	326±1.16*	2.2*	1.0×10^4
3	-	342±0.94	-	1.0×10^4
	+	348±0.95*	1.8*	1.0×10^4

Table 4. Effect of adenosine on cell size in cultured human skin fibroblasts derived from aged donors

Experiment Number	Adenosine (10^{-4} M)	Relative Size (FLS)	% increase	*n*
1	-	333±0.79	-	1.0×10^4
	+	342±0.75*	2.7*	1.0×10^4
2	-	323±1.01	-	1.0×10^4
	+	337±0.96*	4.3*	1.0×10^4
3	-	306±0.81	-	1.0×10^4
	+	321±0.81*	4.9*	1.0×10^4

Other Embodiments

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention. For example, while the

invention has been described using adenosine and adenosine agonists, other compounds structurally similar to adenosine can also be used, e.g., purine-containing compounds and compounds having a ribosyl moiety. Other aspects, advantages, and modifications of the invention are within the scope of the following claims.

We claim:

Claims

1. A method for enhancing the condition of non-diseased skin of a mammal, comprising topically applying a therapeutically effective amount of a composition comprising adenosine or an adenosine agonist to non-diseased skin of said mammal.

2. The method of claim 1, wherein said composition further comprises an angiogenic factor.

3. The method of claim 1, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

4. The method of claim 3, wherein said adenosine concentration is 10^{-4} M to 10^{-6} M.

5. The method of claim 4, wherein said adenosine concentration is about 10^{-4} M.

6. The method of claim 1, wherein said composition further comprises a conditioning agent.

7. The method of claim 6, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

8. The method of claim 1, wherein addition of adenosine does not affect skin cell proliferation.

9. The method of claim 1, wherein said skin comprises a skin graft.

10. The method of claim 1, wherein said mammal is a human.

11. A method for promoting healing of broken, non-diseased skin in a mammal, comprising topically administering a composition comprising a therapeutically effective amount of adenosine or an adenosine agonist to said mammal.

12. The method of claim 11, wherein said composition further comprises an angiogenic factor.

13. The method of claim 11, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

14. The method of claim 13, wherein said adenosine concentration is 10^{-4} M to 10^{-6} M.

15. The method of claim 14, wherein said adenosine concentration is about 10^{-4} M.

16. The method of claim 11, wherein said composition further comprises a conditioning agent.

17. The method of claim 16, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

18. The method of claim 11, wherein addition of adenosine does not affect skin cell proliferation.

19. The method of claim 11, wherein said region of skin comprises a skin graft.

20. The method of claim 11, wherein said mammal is a human.

21. A method for increasing DNA synthesis in a dermal cell of non-diseased skin of a mammal, comprising topically administering a therapeutically effective amount of adenosine to a region of non-diseased skin of said mammal containing said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell.

22. The method of claim 21, wherein said composition further comprises an angiogenic factor.

23. The method of claim 21, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

24. The method of claim 23, wherein said adenosine concentration is 10^{-4} M to 10^{-6} M.

25. The method of claim 24, wherein said adenosine concentration is about 10^{-4} M.

26. The method of claim 21, wherein said composition further comprises a conditioning agent.

27. The method of claim 26, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

28. The method of claim 21, wherein said region of skin comprises a skin graft.

29. The method of claim 21, wherein said mammal is a human.

30. A method of increasing protein synthesis in a dermal cell of non-diseased skin of a mammal, comprising topically administering a composition comprising a therapeutically effective amount of adenosine to a region of skin of said mammal containing said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell.

31. The method of claim 30, wherein said composition further comprises an angiogenic factor.

32. The method of claim 30, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

33. The method of claim 32, wherein said adenosine concentration is 10^{-5} M to 10^{-6} M.

34. The method of claim 33, wherein said adenosine concentration is about 10^{-4} M.

35. The method of claim 30, wherein said composition further comprises a conditioning agent.

36. The method of claim 35, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

37. The method of claim 30, wherein said region of skin comprises a skin graft.

38. The method of claim 30, wherein said mammal is a human.

39. A method of increasing cell size in a dermal cell in non-diseased skin of a mammal, comprising topically administering a composition comprising a therapeutically effective amount of adenosine to a region of skin of said mammal containing said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell, wherein addition of said adenosine does not cause proliferation of said dermal cell.

40. The method of claim 39, wherein said composition further comprises an angiogenic factor.

41. The method of claim 39, wherein the therapeutically effective amount of adenosine is an adenosine concentration of 10^{-3} M to 10^{-7} M.

42. The method of claim 41, wherein said adenosine concentration is 10^{-4} M to 10^{-6} M.

43. The method of claim 42, wherein said adenosine concentration is about 10^{-4} M.

44. The method of claim 39, wherein said composition further comprises a conditioning agent.

45. The method of claim 44, wherein said conditioning agent is selected from the group consisting of a humectant, an emollient, and occlusive agent.

46. The method of claim 39, wherein said region of skin comprises a skin graft.

47. The method of claim 39, wherein said mammal is a human.

48. A method for enhancing skin condition in a mammal, comprising

providing fibroblasts from said mammal *ex vivo*,

culturing said fibroblasts in the presence of adenosine; and

reintroducing said fibroblasts into said mammal.

49. The method of claim 48, wherein the adenosine concentration in said culturing step is from about 10^{-3} M to about 10^{-7} M.

50. A method for increasing protein synthesis in a cultured skin fibroblast, comprising culturing said fibroblast in a culture medium comprising about 10^{-3} M to about 10^{-7} M adenosine.

51. The method of claim 50, wherein the adenosine concentration is about 10^{-4} M.

52. A composition comprising 10^{-3} M to 10^{-7} M adenosine and an angiogenesis factor.

53. The composition of claim 52, wherein the concentration of said adenosine is about 10^{-4} M.

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG, the specification of which

- ☐ is attached hereto.
- ■ was filed on October 26, 1998 as Application Serial No. 09/179,006 and was amended on _____.
- ☐ was described and claimed in PCT International Application No. _____ filed on _____ and as amended under PCT Article 19 on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: J. Peter Fasse, Reg. No. 32,983; Garv L. Creason, Reg. No. 34,310; David E. Johnson, Reg. No. 41,874; Janis K. Fraser, Reg. No. 34,819; Y. Rocky Tsao, Reg. No. 34,053; John F. Hayden, Reg. No. 37,640; and Eldora L. Ellison, Reg. No. 39,967.

Address all telephone calls to J. Peter Fasse at telephone number 617/542-5070.

Address all correspondence to J. Peter Fasse, Fish & Richardson P.C., 225 Franklin Street, Boston, MA 02110-2804.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

12/26/98

Full Name of Inventor: James G. Dobson, Jr

Inventor's Signature: James G. Dobson, Jr Date: 12/26/98

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COMBINED DECLARATION AND POWER OF ATTORNEY CONTINUED

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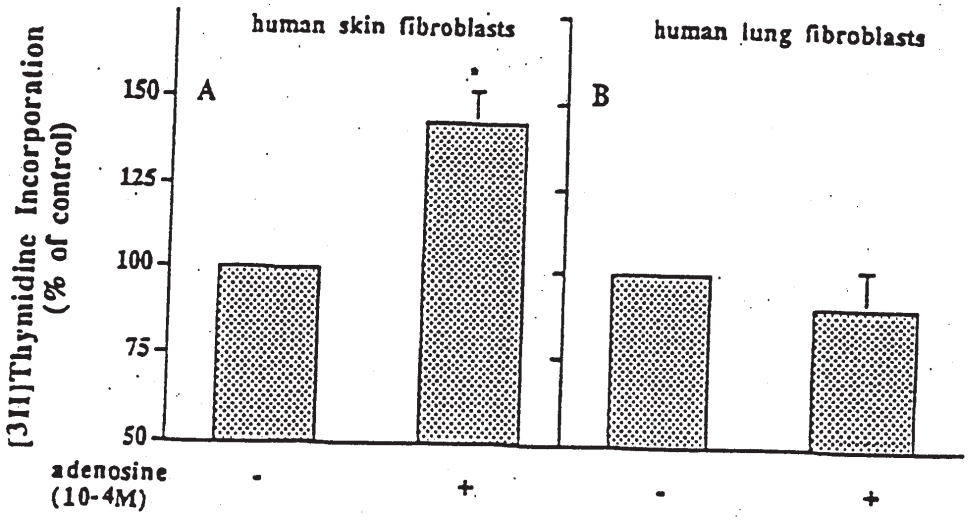

Fig. 1A Fig. 1B

4b-B

Claim / Sub-id
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Mat[illegible].: 07917-045003
App[illegible](s): Dobson et al.
TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

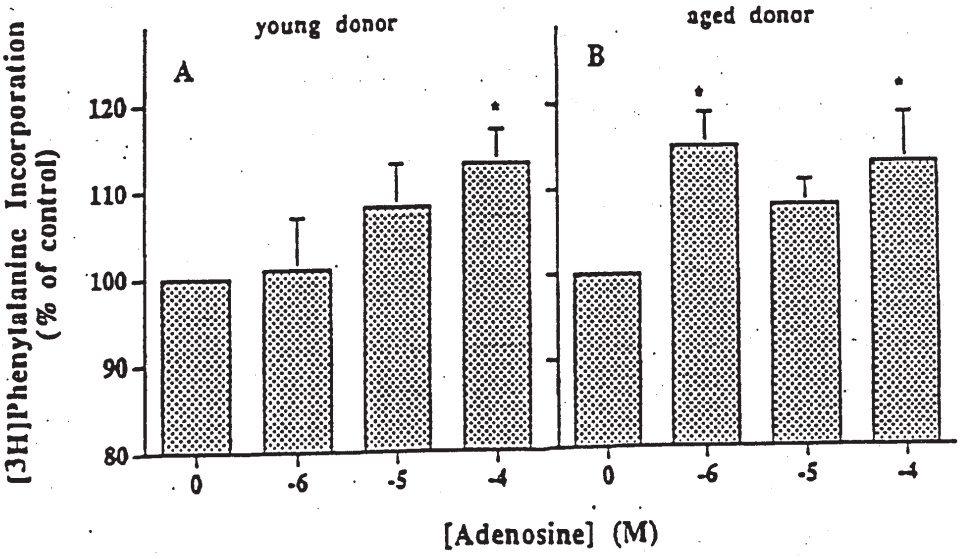

Fig. 2A

Fig. 2B

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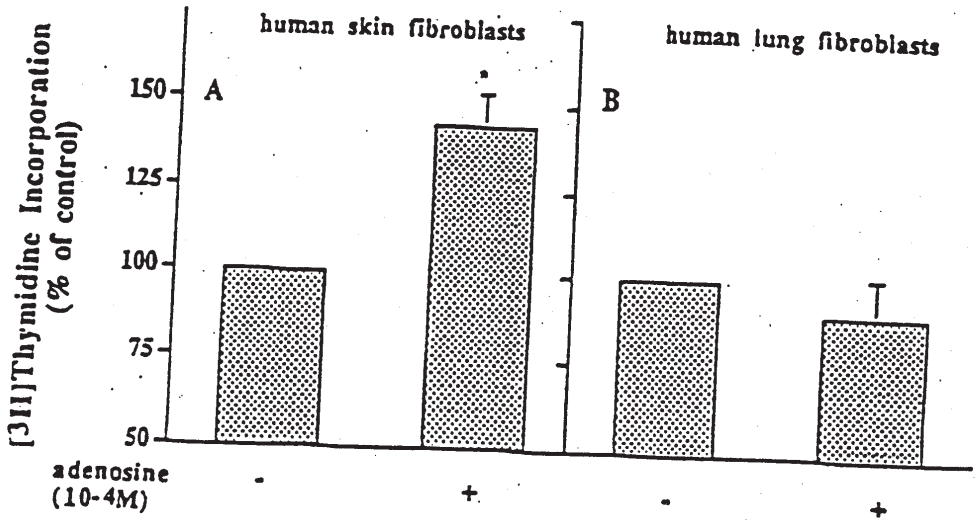

Fig. 1A

Fig. 1B

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Ma No.: 07917-045003
Ap nt(s): Dobson et al.
TRE TMENT OF SKIN WITH ADENOSINE OR ADE INE
ANALOG

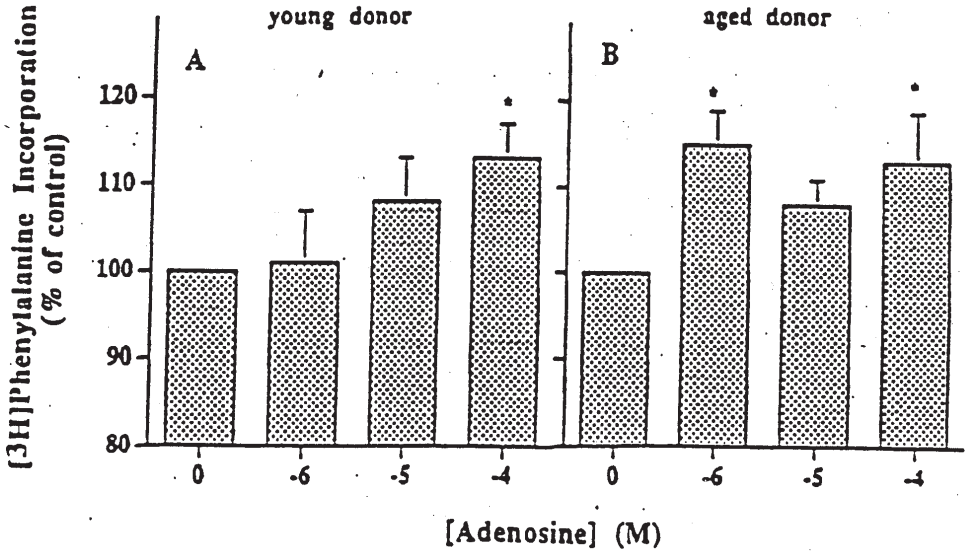

Fig. 2A

Fig. 2B

10184810.062802

Attorney's Docket No 917-045003 / UMMC 97-32

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Dobson et al. Art Unit : Unknown
Serial No. : Unknown Examiner : Unknown
Filed : Herewith
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

BOX PATENT APPLICATION
Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Prior to examination, please amend the application as follows:

In the specification:

Under the title line at page 1, line 5, add the following paragraph:

-- Cross-Reference to Related Applications

This application ~~claims priority from~~ is a continuation of U.S. Patent Application No. 09/672,348, filed on September 28, 2000, now U.S. Patent No. 6,423,327, which is a continuation of U.S. Patent Application No. 09/179,006, filed on October 26, 1998, now abandoned, which are incorporated herein by reference in their entirety.--

In the claims

Cancel claims 11 to 51 without prejudice.

CERTIFICATE OF MAILING BY EXPRESS MAIL

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I hereby certify under 37 CFR §1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office to Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

6/28/02
Date of Deposit

Signature

Leroy Jenkins
Typed or Printed Name of Person Signing Certificate

Applicant : Dobson et al.
Serial No. : Unknown
Filed : Herewith
Page : 2

Attorney's Docket N. 7917-045003 / UMMC 97-32

REMARKS

Applicants have canceled claims 11 to 51 without prejudice, and intend to submit new claims in a supplemental preliminary amendment. Attached is a marked-up version of the changes being made by the current amendment.

Applicants ask that the Examiner contact the undersigned if a supplemental preliminary amendment has not been entered by the time the Examiner is set to examine this application. Please apply any charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 07917-045003.

Respectfully submitted,

Date: June 28, 2002

J. Peter Fasse

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A

Version with markings to show changes made

In the specification:

The following paragraph has been added under the title line at page 1, line 5:

-- Cross-Reference to Related Applications

This application claims priority from U.S. Patent Application No. 09/672,348, filed on September 28, 2000, which is a continuation of U.S. Patent Application No. 09/179,006, filed on October 26, 1998, now abandoned, which are incorporated herein by reference in their entirety.--

In the claims:

Claims 11 to 51 have been canceled.

A

Attorney's Docket No.: 07917-045003 / UMMC 97-32

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Dobson et al. Art Unit : Unknown
Serial No. : Unknown Examiner : Unknown
Filed : Herewith
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Box Patent Application
Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Applicants submit the references listed on the attached form PTO-1449.

Under 35 USC §120, this application relies on the earlier filing date of application serial number 09/672,348, filed on September 28, 2000, and application serial number 09/179,006, filed on October 26, 1998. The references listed on form PTO-1449 were submitted to and/or cited by the Office in the prior application and, therefore, copies are not provided in this application.

This statement is being filed with the application. Please apply any charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 07917-045003.

CERTIFICATE OF MAILING BY EXPRESS MAIL

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6/28/02
Date of Deposit

Signature

Leroy Jenkins
Typed or Printed Name of Person Signing Certificate

Respectfully submitted,

Date: June 28, 2002

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Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 07917-045003	Application No.
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))		Applicant Dobson et al.	
		Filing Date	Group Art Unit

U.S. Patent Documents

Examiner Initial	Desig. ID	Patent Number	Issue Date	Patentee	Class	Subclass	Filing Date If Appropriate
	AA	4,088,756	5/9/78	Voorhees	424	180	
	AB	4,454,122	6/12/84	Stramentionoli et al.	424	180	
	AC	5,399,349	3/21/95	Paunescu et al.	424	195.1	
	AD	5,460,959	10/24/95	Mulligan et al.	435	172.3	
	AE	5,618,544	04/97	Brown	424	401	
	AF	5,770,582	6/23/98	Von Borstel et al.	514	45	
	AG	5,785,978	07/98	Porter et al.	424	401	
	AH	5,821,237	10/1998	Bissett et al.	514	75	
	AI	5,932,558	8/3/99	Crostein et al.	514	46	
	AJ	5,998,423	12/7/99	Manneth et al.	514	260	

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
	AK	19,545,107	6/1997	DE				

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	AL	Adair et al., "Vascular development in chick embryos: a possible role for adenosine" American Physiological Society; 0363-6135/89 1989
	AM	Ahmed et al., "Presence of Both A_1 and A_2 Adenosine Receptors in Human Cells and Their Interaction," Biochemical and Biophysical Research Communications, 208:871-878, 1995
	AN	Ethier et al., "Adenosine Stimulation of DNA Synthesis in Human Endothelial Cells," The American Physiological Society, 272:H1470-H1479, 1997
	AO	Grove et al., "Optical profilometry: An objective method for quantification of facial wrinkles," Journal of the American Academy of Dermatology, 21:631-637, 1989
	AP	Gruber et al., "Increased Adenosine Concentration in Blood From Ischemic Myocardium by AICA Riboside," Circulation, 80:1400-1411, 1989
	AQ	Hartzshtark et al. "The use of indentometry to study the effect of agents known to increase skin cams content" *Experentia* 41:378-379 (1985)
	AR	Kollias-Baker et al., "Agonist-independent effect of an ellosteric enhancer of the A1 adenosine receptor in CHO cells stably expressing the recombinant human A1 receptor" *Journal Pharmacology and Experimental Therapeutics* 281: 761-768, 1997
	AS	Newby et al., "Critical Evaluation of the Role of Ecto – and Cytosolic 5' Nucleotidase in Adenosine Formation Topics and Perspectives in Adenosine Research, 155-168, 1987

Examiner Signature	Date Considered
L. Chamavajjala	10-23-02

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Disclosure Form (PTO-1449)

Substitute Form PTO-1449 (Modified) U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 07917-045003	Application No. 10/134,516
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))	Applicant Dobson et al.	
	Filing Date	Group Art Unit

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	AT	Olsen et al, "Tretinoin emollient cream: a new therapy for photodamaged skin," Journal of the American Academy of Dermatology, 26:215-224, 1992
	AU	Olsen et al., "Tretinoin emollient cream for photodamaged skin: Results of 48-week, multicenter, double-blind studies," Journal of the American Academy of Dermatology, 37:217-226, 1997

Examiner Signature L. Chanavajala	Date Considered 6/23/04

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Disclosure Form (PTO-1449)

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/03824

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4):C07H 19/073,19/173; A61K 31/70,7/40,7/42,7/48, A61K 7/26
U.S. CL.: 536/23,24,26; 514/45,46,49,50,846,847; 424/59

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	536/23, 24, 26; 514/45,46,49,50,846,847; 424/59

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

Computer Search:The generic compounds of claims 1,3,5,7,9,11 and 13 and skin lotion, treating sun-light,radiation,wounds, tissue,burns,heart and liver using the said compounds.

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	US, A, 3,975,367 (GISH ET AL), 17 August 1976, See column 1, formula 1 and lines 42-43 and 46-47	5-6,15-25 30-31
X Y	EP, A, 0,056,265 (THILO & CO GMBH), Published 21 July 1982, see the English abstract, formula (I)	7-8,32-33, 37,45-46 5-6,15-25
Y	DE, A, 2,147,094 (ROBUGEN GMBH) 05 April 1973, see the acylation products in the English abstract.	7-12,15-25
Y	DE , A, 1,941,942 (SYLVEN B.), 18 August 1969, see the English abstract.	15-27,30-31 33-34,36-38
Y	JP, A, 60-28929 (HOKURIKV PHARM KK), Published 28 July 1983, see the English abstract.	3-4,15-25
Y,P	US, A, 4,757,139 (KAWAGUCHI ET AL.) 12 July 1988, see column 2, lines 39-48.	32,45-46

* Special categories of cited documents: [10]

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
29 December 1988	07 MAR 1989
International Searching Authority	**Signature of Authorized Officer**
ISA/US	JENNY TOU

Form PCT/ISA/210 (second sheet) (Rev.11-87)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	JP, A, 58-49315 (MITSUI PHARM INC), Published 23 March 1983, See the English abstract.	32,45-46
Y	US, A, 3,991,045 (ISHIDA ET AL), 09 November 1976, See column 1, lines 61-62, column 2 lines 1-15.	32 and 45-46
X	JP, A 60-174797 (FUNAI PHARM IND KK), Published 09 September 1985, See the English abstract, formula (I)	13-14, 15-25, 33-34, 36-38
Y	FR, Al 2,096,712 (GIRAUX GL), Published 25 February 1972, See the English abstract.	21 and 24
Y	JP, A, 57-91995 (FUJI CHEIMCAL IND KK) Published 08 June 1982, See the English abstract. formula (1)	1-2,4-5, 15-25
Y	JP, A, 58-167598 (TANABE SEIYAKU KK), Published 03 October 1983, see the English abstract, formula (I)	1-2,15-25
Y	US, A, 4,675,189 (KENT ET AL), 23 June 1987 see column 1, lines 34-35.	30-31
A	JP, A, 60-64907 (RISUBURAN PRODUCTS) Published 13 April 1985, see the English abstract.	34-37
A P	US, A, 4,758,533 (OGOSHI), 19 July 1988 see column 2, lines 51 and 66-68.	33

Form PCT/ISA/210 (extra sheet) (Rev.11-87)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/184,810	06/28/2002	James G. Dobson JR.	07917-045003	5640

7590 10/28/2002

J. PETER FASSE
Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804

EXAMINER
CHANNAVAJJALA, LAKSHMI SARADA

ART UNIT	PAPER NUMBER
1615	4

DATE MAILED: 10/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No.	Applicant(s)	
	10/184,810	DOBSON ET AL.	
	Examiner	Art Unit	
	Lakshmi S Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-10,52 and 53 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-10,52 and 53 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of preliminary amendment A and Information Disclosure Statement, both dated 6-28-02 is acknowledged.

Status of claims

Claims 11-51 have been canceled. Claims 1-10, 52 and 53 are pending.

Claim 1 recites a method for enhancing the condition of non-diseased skin comprising topically applying a therapeutically effective amount of a composition comprising adenosine agonist to non-diseased skin of a mammal.

Dependent claims 2-7 include an angiogenic factor in addition to the agonist, specific amounts of adenosine agonist and a conditioning agent.

Claim 8 recites that adenosine does not affect skin cell proliferation.

Claim 9 recites that skin is a skin graft.

Claim 10 recites mammal is a human.

Claim 52 is directed to a composition comprising 10-3 to 10-7 M adenosine and an angiogenic factor. Claim 53, dependent on 52, recites 10-4 M adenosine.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claim 1 states a method of enhancing the condition of a non-diseased skin. However, claim 1 recites, "applying a therapeutically effective amount". It is unclear to the examiner as what therapeutic effect is intended or is being achieved when the composition is being applying for a non-diseased skin. Instant specification recites "enhancement of skin conditions" means a noticeable decrease in the amount of wrinkling, roughness, dryness etc., of skin and none of them include any diseased conditions in order to provide any therapeutic effect. Accordingly, the claim is indefinite. Claims 2-10 are being rejected for their being dependent upon claim 1. It is suggested that the above limitation be changed to "applying an effective amount to enhance the skin condition".

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 52 and 53 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,423,327. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claimed non-diseased skin conditions are defined as wrinkling, roughness, dryness etc., which are also the skin conditions being treated by the patented method. Besides,

both the instant method and the patented claims utilize the adenosine (in the same amount as claimed), angiogenic factor and conditioning agent. Furthermore, the composition of the patented claims read on the instant composition claims. Accordingly, it would have been obvious for one of an ordinary skill in the art to use the patented method to enhance the condition of a non-diseased skin with an expectation to reduce the dryness, wrinkles, roughness and other non-diseased conditions of the skin.

Claim Rejections - 35 USC § 102

Claims 1 and 3-10 are rejected under 35 U.S.C. 102(e) as being anticipated by US 5,998,423 to Manneth et al (hereafter '423).

'423 teaches compositions comprising adenosine, cyclohexyladenosine or cyclopentyladenosine and their use for the modulation of melanin production in the skin and hair and in enhancing the tanning process and providing protection for the skin against UV radiation (see col. 1, lines 7-13; col. 2, lines 44-63; col. 5, lines 10-18). Enhancing the tanning process on the skin, taught by '423, reads on the enhancing the condition of non-diseased skin. With respect to claimed amounts of adenosine agonists, '423 discloses preferred amounts of adenosine receptor antagonists (which is same as adenosine agonists), in the range of 100nM or 10nM, which is within the claimed range (10-4 M= 10nM) (col. 3, lies 8-12 and col. 4, lines 7-17).

For claims 6 and 7, '423 discloses various formulations of the composition including topical formulation containing various thickeners, castor oil and other additives (Cols. 5 and 6 and examples 2 and 3). With respect to the skin graft claimed (claim 9), '423 tested the adenosine agonists in neonatal foreskins (col. 7, example1, lines 5-37), which are nothing but skin grafts. With respect to claim 8, '423 disclose that increased camp causes increase in

tyrosinase activity, which in turn increases melanogenesis. However, '423 do not show that their adenosine agonists show any increase in cell proliferation.

Thus, the instant claims are anticipated by '423.

Claims 1, 6, 7 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by US patent 5,770,582 to von Borstel et al (hereafter '582).

'582 discloses deoxyribonuclosides such as 2'-deoxyadenosine for accelerating the healing of wounds, cuts & abrasions and to ameliorate the effects of aging (see abstract, col. 1, field of the invention, col. 5, 6). Skin aging does not involve any underlying disease process. Accordingly treating aged skin reads on enhancing non-diseased skin condition. 582 discloses several materials such as mineral oils, collagen, polyethylene glycol that read on the instant conditioning agents. Accordingly, '582 anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-5, 9, 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,770,582 to von Borstel et al (hereafter '582).

'582 teaches deoxyribonuclosides such as 2'-deoxyadenosine for accelerating the healing of wounds, cuts, and abrasions and to ameliorate the effects of aging (see abstract, col. 1, field of

the invention, col. 5, 6). As explained in the above section, skin aging does not involve any underlying disease process. Accordingly treating aged skin reads on enhancing non-diseased skin condition. '582 teaches angiogenic factors (col. 8, lines 24), growth factors such as fibroblast growth factor (col.7 and 8) and other additives for topical application (col. 7, lines 19-65 and col. 8). '582 do not teach the exact claimed amounts of adenosine or its analogs. However, optimizing the amount of adenosine in the composition of '582, with an expectation to achieve enhanced and quick wound healing effect would have been obvious for one of an ordinary skill in the art at the time of the instant invention. '582 fail to exemplify a combination of angiogenic factor and 2'-deoxyadenosine. However, '582 teaches that glycosaminoglycans, angiogenic factors, peptide growth factors such as, bFGF, PDGF etc., may be added to the compositions containing 2-deoxyribonucleosides (col. 8, lines 24-31). Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to incorporate peptide growth factors or glycosaminoglycans, all of which read on angiogenic factors of the instant claims, in the wound healing composition of '582 with an expectation to enhance and hasten the wound healing effect.

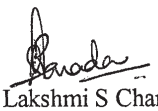
No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S Channavajjala whose telephone number is 703-308-2438. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-308-7924 for regular communications and 703-308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.



Lakshmi S Channavajjala
Examiner
Art Unit 1615
October 23, 2002

Notice of References Cited	Application/Control No. 10/184,810	Applicant(s)/Patent Under Reexamination DOBSON ET AL.	
	Examiner Lakshmi S Channavajjala	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-6,423,327-B1	07-2002	Dobson Jr. et al.	424/401
*	B	US-5,770,582	06-1998	von Borstel et al.	514/45
*	C	US-5,998,423	12-1999	Manneth et al.	514/260
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

#5 B.H. 1-3-03

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THIS FILE IS ASSIGNED TO GAU 1615.

PTO-FMD
TALBOT-1/97

Attorney's Docket No.: 07917-045003 / (UMMC 97-

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James G. Dobson et al. Art Unit : 1615
Serial No. : 10/184,810 Examiner : L. Channavajjala
Filed : June 28, 2002
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION DATED OCTOBER 28, 2002

Please amend the application as indicated below and consider the following remarks.

In the Claims:

Please cancel claims 1 to 10, 52 and 53 without prejudice.

Please add new claims 54 to 63 as follows:

54. A method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, the method comprising topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M.

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55. The method of claim 54, wherein the composition further comprises an angiogenic factor.

56. The method of claim 54, wherein the adenosine concentration is 10^{-3} M to 10^{-6} M.

57. The method of claim 54, wherein the adenosine concentration is about 10^{-3} M.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

1/9/03
Date of Deposit

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Signature

Dawn Marie Class
Typed or Printed Name of Person Signing Certificate

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58. The method of claim 54, wherein the composition further comprises a conditioning agent.

59. The method of claim 58, wherein the conditioning agent is a humectant, an emollient, or an occlusive agent.

60. The method of claim 59, wherein the mammal is a human.

61. The method of claim 54, wherein the skin comprises a skin graft.

62. The method of claim 54, wherein the composition further comprises a transdermal delivery agent.

63. The method of claim 54, wherein the composition is in a transdermal patch and the composition is topically applied by contacting the patch to the skin.

REMARKS

Claims 54 to 63 are pending in this application. Applicants have cancelled claims 1 to 10, 52, and 53 without prejudice and have added new claims 54 to 63. All of these new claims are supported by the claims filed in the original application. For example, new independent claim 54 is supported by original claims 1 and 8. The recitation of specific concentrations of adenosine in claims 54, 56, and 57 are supported by the original claims and in the application, e.g., at page 3, lines 15-18. Claims to the use of transdermal patches and delivery agents are also described in the application, e.g., at page 9, line 30, to page 10, line 2. Thus, the new claims add no new matter.

35 U.S.C. § 112, Second Paragraph

Claims 1 to 10 have been rejected as allegedly indefinite for reciting, "applying a therapeutically effective amount." Applicants have cancelled claim 1, and the phrase has not been repeated in the new claims. Thus, this rejection is moot.

Double Patenting

Claims 1 to 10, 52, and 53 have been rejected as unpatentable over claims 1 to 10 of U.S. Patent No. 6,423,327, which is the patent that issued in the "parent" of the present application. Without admitting the correctness of the double-patenting rejection, applicants will submit a terminal disclaimer in the present application upon notification of allowable subject matter.

35 U.S.C. § 102

Claims 1 and 3 to 10 have been rejected as allegedly anticipated by Manneth, U.S. Patent No. 5,998,423 (Manneth). This rejection is moot in view of applicants' cancellation of claims 1 to 10, and applicants respectfully submit that this rejection does not apply to new claims 54 to 63 for the following reasons.

Claim 54 covers a method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, by topically applying to the skin a composition including a concentration of adenosine in an amount effective to enhance the condition of the skin without

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increasing dermal cell proliferation, where the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M. This claim is distinguished from the cited prior art for the following reasons.

According to the Office Action, Manneth describes "compositions comprising adenosine, cyclohexyladenosine or cyclopentyladenosine and their use for the modulation of melanin production in the skin and hair and in enhancing the tanning process and providing protection for the skin against UV radiation" (Office Action at page 4). Manneth also discloses various formulations of the composition including topical formulations containing various thickeners, castor oil, and other additives.

Applicants respectfully disagree with this characterization of Manneth, because this patent does not describe the use of "adenosine" in any of the described methods, but instead describes only the use of adenosine analogs or derivatives. In particular, Manneth requires compounds that will selectively activate the adenosine-2 (A2) receptor or inactivate the adenosine-1 (A1) receptor to increase melanin production (see column 4, lines 29-41), or selectively inactivate the A2 receptor and activate the A1 receptor to decrease melanin production. That is why Manneth describes useful compounds for his methods as "analogs or derivatives of adenosine" (at column 3, lines 11-12), but not adenosine.

Manneth does not describe the use of adenosine itself for a simple reason - adenosine activates both the A2 and A1 receptors, and would thus negate the selective effect required to modulate melanin production. Compounds such as adenosine that activate both A1 and A2 receptors will not work in Manneth's method of modulating melanin production. Thus, Manneth fails to anticipate the method of claim 54, which recites applying adenosine to the skin.

Furthermore, the Office Action states that Manneth describes "preferred amounts of adenosine receptor antagonists ...., in the range of 100nM or 10nM, which is within the claimed range (10-4 M = 10nM)" (Office Action at page 4). Applicants respectfully submit that these statements are in error. First, what Manneth describes at column 4, lines 7-17, are the K_i values of adenosine receptor A1 antagonists and A2 agonists. These values of K*i* are inhibition constants for these compounds, not concentrations to be administered. The K*i* is the concentration at which the antagonist will inhibit 50% of the maximum response at a given receptor (technically, when Manneth refers to the A2 receptor agonists he should use K*a*, the

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concentration at which the agonist will activate 50% of the maximum response). The K*i* and K*a* values are used to express the potency of compounds. The more potent the antagonist or agonist is at a given receptor, the lower the K*i* or K*a* will be. This is useful to Manneth in comparing the relative potency of a group of agonists or antagonists, but is certainly not the same as stating a concentration to be administered. Thus, the K*i* values are not relevant to the claimed invention.

Second, the Office Action statement that 10^{-4} M is = 10 nM is simply wrong. Applicants respectfully submit that 10^{-4} M is 0.1 mM (or 100 μM, which is 100,000 nM). Thus, the numbers that Manneth recites for K*i* values are far removed from applicants' claimed concentrations.

Claims 1, 6, 7, and 10 have been rejected as allegedly anticipated by von Borstel et al., U.S. Patent No. 5,770,582 (von Borstel). This rejection is moot in view of applicants' cancellation of claims 1 to 10, and applicants respectfully submit that this rejection does not apply to new claims 54 to 63 for the following reasons.

According to the Office Action, von Borstel describes, "deoxyribonuclosides [sic] such as 2'-deoxayadenosine for accelerating the healing of wounds, cuts & abrasions and to ameliorate the effects of aging" (at page 5). The Office Action also states, "[s]kin aging does not involve any underlying disease process. Accordingly treating aged skin reads on enhancing non-diseased skin condition" (id.).

The present claims all recite the use of "adenosine." As the Examiner correctly points out, von Borstel describes the use of **deoxy**ribonucleosides, not ribonucleosides. However, adenosine is a ribonucleoside, **not** a deoxyribonucleosides. The two classes of compounds differ structurally and are quite distinct in their chemical and biological properties. The structural differences are well known. Deoxyribonucleosides would not be expected to bind to adenosine receptors to elicit a biological response, and thus, the deoxyribonucleosides described by von Borstel are not the same as applicants' claimed adenosine. For this reason, von Borstel cannot anticipate applicants' pending claims. Therefore, this rejection should be withdrawn.

B

35 U.S.C. § 103

Claims 2 to 5, 9, 52, and 53 have been rejected as being allegedly unpatentable over von Borstel. Applicants submit that this rejection is moot in view of the cancellation of claims 1 to 10, 52, and 53, and that this rejection does not apply to the new claims.

As the Office Action concedes, von Borstel "do not teach the exact claimed amounts of adenosine or its analogs. However, optimizing the amount of adenosine in the composition of '582 [von Borstel], with an expectation to achieve [an] enhanced and quick wound healing effect would have been obvious for one of an ordinary skill in the art at the time of the instant invention" (id. at page 6). Applicants respectfully disagree for the following reasons.

Von Borstel does not describe the use of adenosine at all, and thus it cannot have been obvious to "optimize" the amount of adenosine for use in von Borstel's methods. One of skill in the art would not have thought to use adenosine based on the von Borstel patent, much less known what amount to apply to skin. Moreover, von Borstel fails to describe or even suggest that one can enhance the condition of unbroken skin of a mammal without increasing dermal cell proliferation. This is an unexpected result of the presently claimed methods, and rebuts any alleged *prima facie* case of obviousness.

Based on these discussions, applicants submit that the new claims are not rendered obvious by von Borstel.

CONCLUSION

The claim amendments are recited in the attached Version with Markings to Show Changes Made. Applicants submit that all of the new claims are in condition for allowance, and

request such action. No fees are believed due. However, please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-045003.

Respectfully submitted,

Date: January 9, 2003

J. Peter Fasse
Reg. No. 32,983

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

20564577.doc

B

Version with Markings to Show Changes Made

In the claims:

Claims 1 to 10, 52, and 53 have been cancelled.

Claims 54 to 63 have been newly added.

B

Attorney's Docket No.: 07917-045003 / UMMC 97-32

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Dobson et al.
Serial No. : 10/184,810
Filed : June 28, 2002
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Art Unit : 1615
Examiner : L. Channavajjala

Commissioner for Patents
Washington, D.C. 20231

#7

TERMINAL DISCLAIMER UNDER 37 CFR §§3.73(b) AND 1.321(b)

Pursuant to 37 CFR §3.73(b), UNIVERSITY OF MASSACHUSETTS, certifies that it is the assignee of the entire right, title, and interest in the above application by virtue of an assignment from the inventors of U.S. Patent Application Serial No. 09/179,006, which is the grandparent of the application identified above. The assignment was recorded in the Patent and Trademark Office at Reel 9690, Frame 0305, on January 7, 1999.

The undersigned has reviewed all the documents in the chain of title of the above-identified application and to the best of undersigned's knowledge and belief, title is in University of Massachusetts.

The undersigned is empowered to act on behalf of the assignee.

Pursuant to 37 CFR §1.321(b), and to obviate a double patenting rejection, the assignee identified above hereby waives and disclaims the terminal portion of the term of the entire patent to be granted upon the above identified application subsequent to the expiration date of U.S. Patent No. 6,423,327, whereby the patent granted on this application and U.S. Patent No. 6,423,327, will expire on the same day, provided that any patent granted on the above identified application shall be enforceable only for and during such period that it is commonly owned with U.S. Patent No. 6,423,327.

The assignee identified above does not disclaim any terminal part of any patent granted on the above identified application prior to the expiration date of the full statutory term of U.S. Patent No. 6,423,327 in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR §1.321(a), has all claims cancelled by a reexamination certificate, or is otherwise terminated prior to expiration of its statutory term, except for the separation of legal title as stated above. Assignee herein does not disclaim or otherwise affect any part of U.S. Patent No.

Attorney's Docket No.: 07917-045003 / UMMC 97-32

Applicant : Dobson et al.
Serial No. : 10/184,810
Filed : June 28, 2002
Page : 2 of 2

6,423,327. This disclaimer runs with any patent granted on the above application and is binding upon the grantee, its successors or assigns.

Please charge any fees, or make any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-045003.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

UNIVERSITY OF MASSACHUSETTS

Date: 4/16/03

Title: Executive Director, OTM

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

20403153.doc

Attorney's Docket No.: 07917-045003
Client's Ref. No.: UMMC 97-32

OFFICIAL COMMUNICATION

FACSIMILE

FOR THE PERSONAL ATTENTION OF:

EXAMINER L. CHANNAVAJJALA

GROUP 1615 FAX NO: 703-746-5215

Number of pages including this page 3

Applicant : Dobson et al.
Serial No. : 10/184,810
Filed : June 28, 2002

Art Unit : 1615
Examiner : L. Channaavajjala

FACSIMILE COMMUNICATION

Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Commissioner for Patents
Washington, D.C. 20231

Sir:

Attached to this facsimile communication cover sheet is a Terminal Disclaimer Under 37 CFR §3.73(b) and 1.321(b), faxed this 16th day of April, 2003, to Group 1615, the United States Patent and Trademark Office.

Respectfully submitted,

Date: April 16, 2003

J. Peter Fasse
Reg. No. 32,983

Fish & Richardson P.C.
225 Franklin Street
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Telephone: (617) 542-5070
Fax: (617) 542-8906

20629453.doc

Notice of Allowability	Application No.	Applicant(s)	
	10/184,810	DOBSON ET AL.	
	Examiner	Art Unit	
	Lakshmi S Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *1-14-03 & 4-16-03*.
2. ☒ The allowed claim(s) is/are *54-63*.
3. ☒ The drawings filed on *28 June 2002* are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.
5. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
   (a) ☐ The translation of the foreign language provisional application has been received.
6. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE**

7. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

8. ☐ CORRECTED DRAWINGS must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. ____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the top margin (not the back) of each sheet. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1☒ Notice of References Cited (PTO-892)
2☐ Notice of Informal Patent Application (PTO-152)
3☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
4☐ Interview Summary (PTO-413), Paper No.____ .
5☐ Information Disclosure Statements (PTO-1449), Paper No. ____.
6☐ Examiner's Amendment/Comment
7☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8☒ Examiner's Statement of Reasons for Allowance
9☐ Other

Allowable Subject Matter

Claims 54-63 are allowed.

The following is an examiner's statement of reasons for allowance:

Instant claims are directed to a method of enhancing the condition of unbroken skin by reducing wrinkling or dryness or laxity of skin, without increasing dermal cell proliferation, where the method comprises administering adenosine at a concentration of 10^{-3} M to 10^{-7} M, to the skin. The closest prior art of record teaches administering adenosine in skin care compositions. However, the art of record utilizes concentrations much higher than claimed and also require the presence of epidermal growth factor to stimulate cell proliferation. Whereas, instant claims are directed to treating skin without increasing the dermal cell proliferation. Further, prior art of record does not teach or suggest any reason for the addition of adenosine in skin care compositions, in particular, in amounts as low as those claimed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S Channavajjala whose telephone number is 703-308-2438. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-7924 for regular communications and 703-308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Lakshmi S Channavajjala
Examiner
Art Unit 1615
April 19, 2003

Notice of References Cited	Application/Control No. 10/184,810	Applicant(s)/Patent Under Reexamination DOBSON ET AL.	
	Examiner Lakshmi S Channavajjala	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-4,839,164	06-1989	Smith	424/64
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

26161 7590 04/22/2003

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	CLASS-SUBCLASS
1615	424-401000

DATE MAILED: 04/22/2003

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/184,810	06/28/2002	James G. Dobson JR.	07917-045003	5640

TITLE OF INVENTION: TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$650	$300	$950	07/22/2003

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (REV. 04-02) Approved for use through 01/31/2004.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Box ISSUE FEE
Commissioner for Patents
Washington, D.C. 20231
Fax (703)746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

26161 7590 04/22/2003

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Box Issue Fee address above, or being facsimile transmitted to the USPTO, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/184,810	06/28/2002	James G. Dobson JR.	07917-045003	5640

TITLE OF INVENTION: TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$650	$300	$950	07/22/2003

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHANNAVAJJALA, LAKSHMI SARADA	1615	424-401000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) ❑ individual ❑ corporation or other private group entity ❑ government

4a. The following fee(s) are enclosed:

❑ Issue Fee

❑ Publication Fee

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s):

❑ A check in the amount of the fee(s) is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Commissioner is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____(enclose an extra copy of this form).

Commissioner for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date)

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Washington, DC 20231.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMIT THIS FORM WITH FEE(S)

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/184,810	06/28/2002	James G. Dobson JR.	07917-045003	5640

26161 7590 04/22/2003

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 04/22/2003

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The patent term adjustment to date is 0 days. If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the term adjustment will be 0 days.

If a continued prosecution application (CPA) was filed in the above-identified application, the filing date that determines patent term adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) system. (http://pair.uspto.gov)

Any questions regarding the patent term extension or adjustment determination should be directed to the Office of Patent Legal Administration at (703)305-1383.

PTOL-85 (REV. 04-02) Approved for use through 01/31/2004.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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26161 7590 04/22/2003

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110
UNITED STATES

EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 04/22/2003

Notice of Fee Increase on January 1, 2003

If a reply to a "Notice of Allowance and Fee(s) Due" is filed in the Office on or after January 1, 2003, then the amount due will be higher than that set forth in the "Notice of Allowance and Fee(s) Due" since there will be an increase in fees effective on January 1, 2003. See Revision of Patent and Trademark Fees for Fiscal Year 2003; Final Rule, 67 Fed. Reg. 70847, 70849 (November 27, 2002).

The current fee schedule is accessible from: http://www.uspto.gov/main/howtofees.htm.

If the issue fee paid is the amount shown on the "Notice of Allowance and Fee(s) Due," but not the correct amount in view of the fee increase, a "Notice to Pay Balance of Issue Fee" will be mailed to applicant. In order to avoid processing delays associated with mailing of a "Notice to Pay Balance of Issue Fee," if the response to the Notice of Allowance and Fee(s) due form is to be filed on or after January 1, 2003 (or mailed with a certificate of mailing on or after January 1, 2003), the issue fee paid should be the fee that is required at the time the fee is paid. If the issue fee was previously paid, and the response to the "Notice of Allowance and Fee(s) Due" includes a request to apply a previously-paid issue fee to the issue fee now due, then the difference between the issue fee amount at the time the response is filed and the previously paid issue fee should be paid. See Manual of Patent Examining Procedure, Section 1308.01 (Eighth Edition, August 2001).

Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (REV. 04-02) Approved for use through 01/31/2004.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Box ISSUE FEE
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CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

26161 7590 04/22/2003

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BOSTON, MA 02110

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Box Issue Fee address above, or being facsimile transmitted to the USPTO, on the date indicated below.

Mary Elizabeth Jacoby	(Depositor's name)
	(Signature)
July 7, 2003	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/184,810	06/28/2002	James G. Dobson JR.	07917-045003	5640

TITLE OF INVENTION: TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$650	$300	$950	07/22/2003

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHANNAVAJJALA, LAKSHMI SARADA	1615	424-401000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Fish & Richardson P.C.
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: University of Massachusetts

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Boston, MA

Please check the appropriate assignee category or categories (will not be printed on the patent) ☐ individual ☒ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:

☒ Issue Fee
☒ Publication Fee
☒ Advance Order - # of Copies 10

4b. Payment of Fee(s):

☒ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
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(Authorized Signature) (Date)

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07/11/2003 MBELETE2 00000078 10184810

01 FC:2501 650.00 OP
02 FC:1504 300.00 OP
03 FC:8001 30.00 OP

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Washington, DC 20231.

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TRANSMIT THIS FORM WITH FEE(S)

Attorney's Docket No. 07917-045003 / UMMC 97-32

B 47

#9

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant :	Dobson et al.	Art Unit :	1615
Serial No. :	10/184,810	Examiner :	L. Channavajjala
Filed :	June 28, 2002	Confirmation No.:	5640
		Notice of Allowance Date:	April 22, 2003

Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

MAIL STOP ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE OF ALLOWANCE

In response to the Notice of Allowance mailed April 22, 2003, enclosed are a completed issue fee transmittal form PTOL-85b, Comments on Statement of Reasons for Allowance, and a check for $980 for the required issue fee and publication fee, including patent copies.

Please apply any additional charges or credits to our Deposit Account No. 06-1050, referencing attorney docket number 07917-045003.

Respectfully submitted,

Date: July 7, 2003

J. Peter Fasse
Reg. No. 32,983

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

20677119.doc

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

July 7, 2003
Date of Deposit

Signature

Mary Elizabeth Jacoby
Typed or Printed Name of Person Signing Certificate

#9
10/2/03
SP

Attorney's Docket No.: 07917-045003 / UMMC 97-32

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Dobson et al.	Art Unit :	1615
Serial No.	: 10/184,810	Examiner :	L. Channavajjala
Filed	: June 28, 2002	Confirmation No.:	5640
		Notice of Allowance Date: April 22, 2003	

Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

MAIL STOP ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

COMMENTS ON STATEMENT OF REASONS FOR ALLOWANCE

Applicants submit that in addition to the reasons stated by the Examiner in the Notice of Allowability mailed April 22, 2003, claims 54 to 63 are allowable for the reasons of record in this application.

Respectfully submitted,

Date: July 7, 2003

J. Peter Fasse
Reg. No. 32,983

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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July 7, 2003
Date of Deposit

Signature

Mary Elizabeth Jacoby
Typed or Printed Name of Person Signing Certificate

Attorney Docket No.: 07917-0045003 / UMMS 97-32

#10
EF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Dobson et al.	Art Unit	: 1615
Patent No.	: 6,645,513	Examiner	: L. Channavajjala
Issue Date	: November 11, 2003	Conf. No.	: 5640
Serial No.	: 10/184,810		
Filed	: June 28, 2002		

Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Attn.: Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF REQUEST FOR CERTIFICATE OF CORRECTION

Applicant hereby requests that a certificate of correction be issued for the above patent in accordance with the attached request.

All errors sought to be corrected were made in printing by the Patent and Trademark Office, and no fee is believed to be due. However, please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-0045003.

Respectfully submitted,

Date: May 19, 2010

J. Peter Fasse
Reg. No. 32,983

Customer Number 26161
Fish & Richardson P.C.
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

22417610.doc

EJ

Patent Number Information

Application Number: **10/184810** **Order This File** **Assignments**
Examiner Number: **74459 / CHANNAVAJJALA, LAKSHMI**
Filing or 371(c) Date: **06/28/2002** eDan
Group Art Unit: **1615**
Effective Date: **06/28/2002**
Class/Subclass: **424/401.000**
Application Received: **07/01/2002**
Lost Case: **NO**
Pat. Num./Pub. Num: **6645513/20030044439**
Interference Number:
Issue Date: **11/11/2003**
Unmatched Petition: **NO**
Date of Abandonment: **00/00/0000**
L&R Code: Secrecy Code:**1**
Attorney Docket Number: **07917-045003**
Third Level Review: **NO**
Secrecy Order: **NO**
Status: **150 / PATENTED CASE**
Status Date: **10/23/2003**
Confirmation Number: **5640**
Oral Hearing: **NO**
Title of Invention: **TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG**

Bar Code	PALM Location	Location Date	Charge to Loc	Charge to Name	Employee Name	Location
10184810	9200	05/12/2009	**No Charge to Location**	**No Charge to Name**	**BAIG,ABDUL**	

Appln Info Contents | Petition Info | Atty/Agent Info | Continuity/Reexam | Foreign Data

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file ASSIGNED TO EJ

FORWARD file to EJ

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,645,513 B2
APPLICATION NO. : 10/184810
DATED : November 11, 2003
INVENTOR(S) : James G. Dobson, Jr.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 10, claim 3, line 2:

Delete "10^{-1}" and insert --10^{-3}-- .

Signed and Sealed this

Twenty-second Day of June, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

FISH & RICHARDSON P.C.

SUBSTITUTE FORM PTO/SB/44 (5-03)

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. .: 6,645,513 B2

APPLICATION NO .: 10/184,810

DATED .: NOVEMBER 11, 2003

INVENTOR(S) .: JAMES G. DOBSON, JR., PH.D.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 10, claim 3, line 2:

Delete "10^{-1}" and insert --10^{-3} --

MAILING ADDRESS OF SENDER:

J. Peter Fasse
Fish & Richardson P.C.
P.O. Box 1022
Minneapolis, Minnesota 55440-1022

```
=> d his full

     (FILE 'HOME' ENTERED AT 15:52:13 ON 08 APR 2003)

     FILE 'CAPLUS, MEDLINE, EMBASE' ENTERED AT 15:52:41 ON 08 APR 2003
L1           92 SEA ABB=ON  PLU=ON  ADENOSINE (P) (COMPOSITION OR FORMULATION)
                (P) (SKIN OR TOPICAL OR COSMETIC)
L2           82 DUP REM L1 (10 DUPLICATES REMOVED)

     FILE 'CAPLUS, MEDLINE, EMBASE' ENTERED AT 16:23:47 ON 08 APR 2003
L3            1 SEA ABB=ON  PLU=ON  L2 AND SKIN (P) (DRY OR ROUGHNESS OR
                LAXITY OR WRINKLES OR WRINKLING OR ELASTICITY OR MOISTURE OR
                MOISTURIZATION)
                D L3 IBIB KWIC
L4            2 SEA ABB=ON  PLU=ON  L2 AND SKIN (P) (SMOOTH OR SMOOTHNESS OR
                COLLAGEN OR DRY OR ROUGHNESS OR LAXITY OR WRINKLES OR WRINKLING
                 OR ELASTICITY OR MOISTURE OR MOISTURIZATION)
                D L4 IBIB KWIC 1-
                D HSI FULL
L5            6 SEA ABB=ON  PLU=ON  L2 AND (TOPICAL APPLICATION)
L6            6 DUP REM L5 (0 DUPLICATES REMOVED)
                D L6 IBIB KWIC 1-

     FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE' ENTERED AT 16:48:06 ON 08 APR 2003
L7       418723 SEA ABB=ON  PLU=ON  ADENOSINE NOT (AMP OT CYCLIC-AMP OR
                ADENOSINE ANALOG OR ADENOSINE AGONIST)
L8       347833 SEA ABB=ON  PLU=ON  ADENOSINE NOT (AMP OR CYCLIC-AMP OR
                ADENOSINE ANALOG OR ADENOSINE AGONIST)
L9          668 SEA ABB=ON  PLU=ON  ADENOSINE (P) (TOPICAL OR COSMETIC OR SKIN
                CARE) NOT (AMP OR CYCLIC-AMP OR ADENOSINE ANALOG OR ADENOSINE
                AGONIST)
L10          72 SEA ABB=ON  PLU=ON  L2 NOT (ADENSOINE ANALOG OR ADENOSINE
                AGONIST OR CYCLIC (3A) AMP)
L11           2 SEA ABB=ON  PLU=ON  L10 AND SKIN (P) (WRINKLE OR MOISTURE OR
                SMOOTHNESS OR LAXITY OR ELASTCITY OR DRYNESS)
                D L11 IBIB KWIC 1-
L12          56 SEA ABB=ON  PLU=ON  L2 NOT (ADENSOINE ANALOG OR ADENOSINE
                AGONIST OR CYCLIC (3A) AMP OR ATP OR ADENOSINE (3A) PHOSPHATE)

L13           3 SEA ABB=ON  PLU=ON  L12 AND TOPICAL APPLICATION
                D L13 IBIB KWIC 1-
L14          48 SEA ABB=ON  PLU=ON  L2 NOT (ADENSOINE ANALOG OR ADENOSINE
                AGONIST OR CYCLIC (3A) AMP OR ATP OR ADENOSINE (3A) PHOSPHATE
                OR ADENOSINE (3A) MONOPHOSPHATE OR ADENOSINE (3A) DIPHOSPHATE)

L15          48 DUP REM L14 (0 DUPLICATES REMOVED)
                D L15 IBIB KWIC 1-
```

L15 ANSWER 44 OF 48 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1975:64487 CAPLUS
DOCUMENT NUMBER: 82:64487
TITLE: Pharmaceuticals containing adenosine against psoriasis
INVENTOR(S): Voorhees, John J.
SOURCE: Ger. Offen., 27 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2401450	A1	19740718	DE 1974-2401450	19740112
FR 2213778	B1	19780106	FR 1974-1338	19740115
US 4107306	A	19780815	US 1977-808447	19770621
US 4161525	A	19790717	US 1978-897063	19780417

PRIORITY APPLN. INFO.: US 1973-324012 19730116
US 1973-425338 19731217
US 1973-425065 19731217
US 1976-643633 19760105
US 1977-808447 19770621

AB **Formulations** for capsules, tablets, ointments, creams, and injection solns. useful for the treatment of psoriasis and other **skin** proliferation diseases (no data) contained **adenosine** or according to claims I, e.g. I where R = R1 = H; R2 = CHMeCH2C6H4OMe-4. Thus, capsules contained **adenosine** 200, corn starch 150, talc 75, and Mg stearate 2.5 mg.

WEST Search History

DATE: Tuesday, October 22, 2002

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR		
L6	composition same adenosine same (angiogenic or fibroblast adj growth adj factor or vegf or fgf)	13	L6
L5	L3 and (wrinkles or dryness or moisturizing or smoothness or moisturizer or dry adj skin or roughness)	22	L5
L4	L3 and (wrinkles or dryness or moisturizing or smoothness or moisturizer or dry adj skin orroughness)	22	L4
L3	(topical or cosmetic or skin) and adenosine same (angiogenic or fibroblast adj growth adj factor or vegf or fgf)	104	L3
L2	(composition or formulation or cream or lotion or gel) same (topical or cosmetic or skin) same adenosine same (fibroblast adj growth adj factor or vegf or fgf)	2	L2
L1	adenosine same (angiogenic or fibroblast adj growth adj factor or vegf or fgf)	168	L1

END OF SEARCH HISTORY

WEST Search History

DATE: Tuesday, October 22, 2002

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR		
L8	L7 and (angiogenic or fibroblast adj growth adj factor or vegf or fgf)	10	L8
L7	composition same (adenosine or adenosine adj agonist) same (topical or skin or cosmetic or moisturizing)	145	L7
L6	composition same adenosine same (angiogenic or fibroblast adj growth adj factor or vegf or fgf)	13	L6
L5	L3 and (wrinkles or dryness or moisturizing or smoothness or moisturizer or dry adj skin or roughness)	22	L5
L4	L3 and (wrinkles or dryness or moisturizing or smoothness or moisturizer or dry adj skin orroughness)	22	L4
L3	(topical or cosmetic or skin) and adenosine same (angiogenic or fibroblast adj growth adj factor or vegf or fgf)	104	L3
L2	(composition or formulation or cream or lotion or gel) same (topical or cosmetic or skin) same adenosine same (fibroblast adj growth adj factor or vegf or fgf)	2	L2
L1	adenosine same (angiogenic or fibroblast adj growth adj factor or vegf or fgf)	168	L1

END OF SEARCH HISTORY

17. A method for the treatment of obesity in man, which comprises the steps of giving the overweight patient a daily diet consisting essentially of skimmed milk and a supplement according to claim 1 in an amount equivalent to 18 mg .+-.9 mg of iron, said skimmed milk being given in an amount equivalent to from 61.3 to 123 grams of dried skimmed milk, and in which said diet includes sufficient additional fat, oil or other source of essential fatty acids to supply the patient with his minimum fatty acid requirements.

18. A method for treating obesity in which an individual ingests a daily diet having a total calorie content of not greater than 600 Kcals and consisting essentially of skimmed milk and a supplement according to claim 1 in an amount equivalent to 18 mg .+-.9 mg of iron, said skimmed milk being given in an amount equivalent to from 61.3 to 123 grams of dried skimmed milk, and wherein said individual ingests sufficient additional fat, oil or other source of essential fatty acids to supply the individual with his minimum fatty acid requirements.

19. A method for treating obesity in which an individual ingests a daily diet having a total calorie content of not greater than 600 Kcals and consisting essentially of skimmed milk and a supplement according to claim 9 in an amount equivalent to about 18 mg of iron, said skimmed milk being given in an amount equivalent to from 61.3 to 123 grams of dried skimmed milk, and wherein said individual ingests sufficient additional fat, oil or other source of essential fatty acids to supply the individual with his minimum fatty acid requirements.

2 month old New Case!

PALM INTRANET Day : Tuesday Date: 10/26/2004 Time: 17:59:44

Application Number Information

Application Number: **10/680370**
Assignments
Examiner Number: **78211 / JIANG, SHAOJIA**
Filing Date: **10/07/2003**
Group Art Unit: **1617** **IFW IMAGE**
Effective Date: **10/07/2003**
Class/Subclass: **424/401.000**
Application Received: **10/08/2003**
Lost Case: **NO**
Pat. Num./Pub. Num: **/20040071749**
Interference Number:
Issue Date: **00/00/0000**
Unmatched Petition: **NO**
Date of Abandonment: **00/00/0000**
L&R Code: Secrecy Code:**1**
Attorney Docket Number: **07917-045004**
Third Level Review: **NO**
Secrecy Order: **NO**
Status: **30 /DOCKETED NEW CASE - READY FOR EXAMINATION**
Status Date: **03/11/2004**
Confirmation Number: **4664**
Oral Hearing: **NO**
Title of Invention: **TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG**

Bar Code	PALM Location	Location Date	Charge to Loc	Charge to Name	Employee Name	Location

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | Invi

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PCT / [ ] / [ ] Search **or PG PUBS #** [ ] Search
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PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number: 09917-045003

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS	12	
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	12 minus 20=	* —
INDEPENDENT CLAIMS	2 minus 3 =	* —
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	370.00	OR	BASIC FEE	740.00
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL	370	OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

FORM PTO-875 (Rev. 8/01) *U.S. Government Printing Office: 2001 — 484-484/59268 Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

CLAIMS ONLY

SERIAL NO.	FILING DATE
10184810	06-28-02

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1					
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TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

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	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
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99						
100						
TOTAL IND.	2					
TOTAL DEP.	1	2				
TOTAL CLAIMS	12					

* MAY BE USED FOR ADDITIONAL CLAIMS OR AMENDMENTS

FORM PTO-2022 (1-96)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

95/95

*U.S. Government Printing Office: 1998 - 433-214/70303