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09/672348
09/28/00

ISSUE CLASSIFICATION	
Class	Subclass
424	401

PATENT NUMBER
6423327
6423327

U.S. UTILITY Patent Application

O.I.P.E.	PATENT DATE
SCANNED ____ Q.A. ____	JUL 23 2002

APPLICATION NO.	CONT/PRIOR	CLASS	SUBCLASS	ART UNIT	EXAMINER
09/672348	D	424	401	1615	CHANNAVAJJALA

APPLICANTS: James Dobson
Michael Ethier
09/179,006

TITLE: Treatment of skin with adenosine or adenosine analog

PTO-2040
12/99

ISSUING CLASSIFICATION

ORIGINAL		CROSS REFERENCE(S)						
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					
424	401	424	447	448	449			
INTERNATIONAL CLASSIFICATION		514	46					
A61K 7/00								

☐ Continued on Issue Slip Inside File Jacket

☐ TERMINAL DISCLAIMER	DRAWINGS			CLAIMS ALLOWED	
	Sheets Drwg.	Figs. Drwg.	Print Fig.	Total Claims	Print Claim for O.G.
	2	4	1A+b	10	1

☐ The term of this patent subsequent to _____ (date) has been disclaimed.

☐ The term of this patent shall not extend beyond the expiration date of U.S Patent. No. _____

☐ The terminal ____ months of this patent have been disclaimed.

Lakshmi Channavajjala 3/16/02
(Assistant Examiner) (Date)

THURMAN K PAGE
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(Primary Examiner) (Date)

Harmon 4/5/02
(Legal Instruments Examiner) (Date)

NOTICE OF ALLOWANCE MAILED: 3/21/02

ISSUE FEE

Amount Due	Date Paid
640 00	6/3/02

ISSUE BATCH NUMBER

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L'OREAL USA, INC. EX. 1009

(FACE)

PATENT APPLICATION

09672348

jc836 U.S. PTO
09/672348
09/28/00

INITIALS _____

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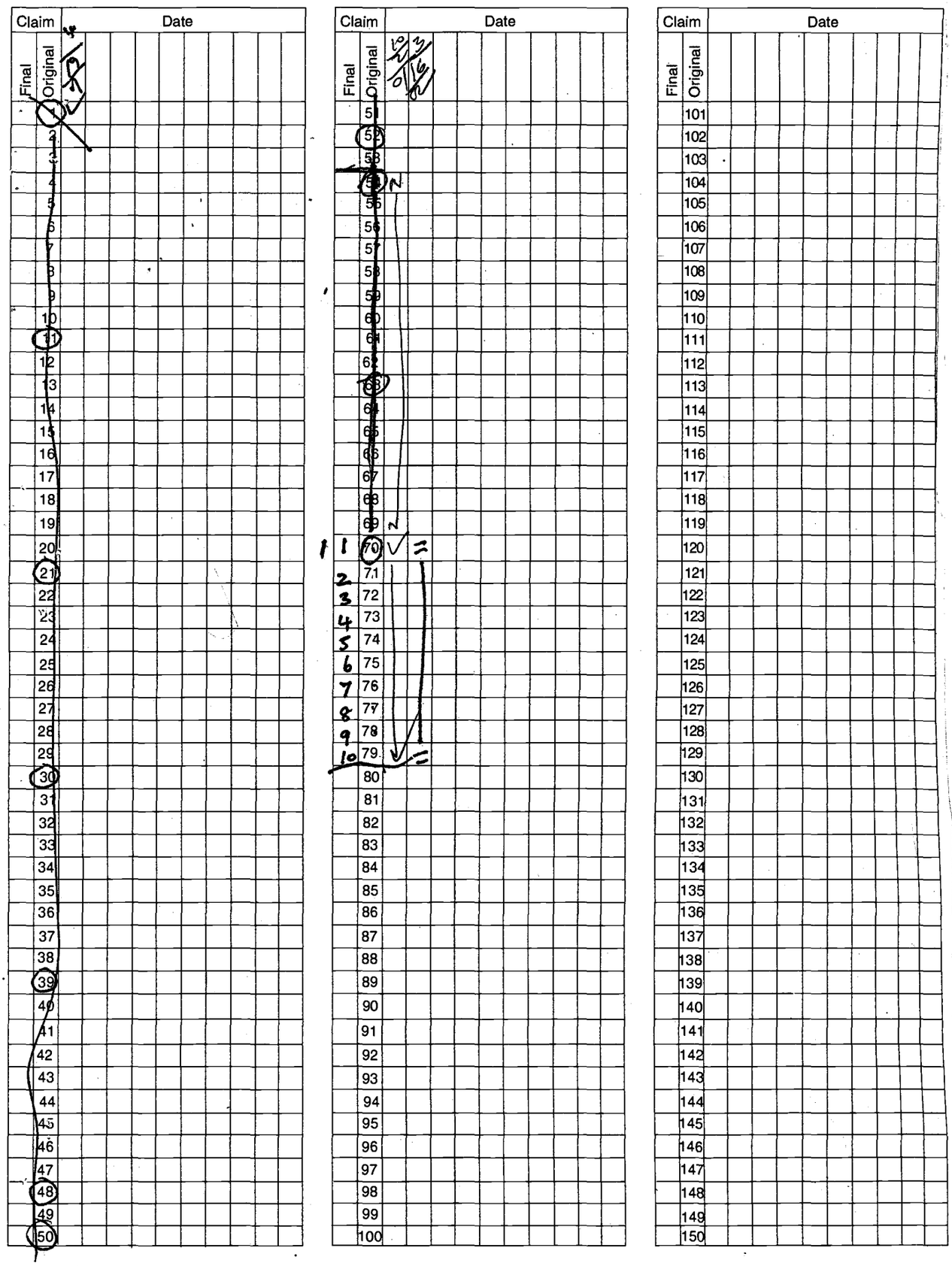
ISSUE SLIP STAPLE AREA (for additional cross references)

POSITION	INITIALS	ID NO.	DATE
			10/12/00
FEE DETERMINATION			
O.I.P.E. CLASSIFIER			5 10-20-00
FORMALITY REVIEW		66959	11/15/00
RESPONSE FORMALITY REVIEW			

INDEX OF CLAIMS

✔	Rejected	N	Non-elected
=	Allowed	I	Interference
—	(Through numeral)... Canceled	A	Appeal
÷	Restricted	O	Objected



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SEARCHED

Class	Sub.	Date	Exmr.
424	407		
514	46		
424	442 443 447	4/19/01	
Updated Search		10/2/01	
Updated		3/16/02	

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
424	401		
514	46		
424	~~442~~ 447		
424	448		
424	449	3/14/02	

SEARCH NOTES
(INCLUDING SEARCH STRATEGY)

	Date	Exmr.
West/CAS from parent Parent Case 09/179,006	4/19/01	
West, STN Guide (CAPlus, Medline, embase, biosis)	10/1/01	
	10/2/01	
Discussed E Gstishvili	3/12/02	

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Bib Data Sheet

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/672,348	09/28/2000 RULE _	424	1615	07917-045002

APPLICANTS

James G. Dobson, Auburn, MA ;
Michael F. Ethier, Grafton, MA ;

** CONTINUING DATA ********** Verified

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

** FOREIGN APPLICATIONS ********** none

IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 11/15/2000

** SMALL ENTITY **

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☒ no	MA	2	1	1
35 USC 119 (a-d) conditions met ☐ yes ☒ no ☐ Met after Allowance				
Verified and Acknowledged Examiner's Signature Initials				

ADDRESS

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Boston ,MA 02110-2804

TITLE

Treatment of skin with adenosine or adenosine analog

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
420	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

09-29-00

A

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September 28, 2000

Attorney Docket No.: 07917-045002

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

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
Drawing(s)	2

In addition to the above-listed pages, the following items are enclosed herewith:

- Copies of Petition for Extension of Time, filed in the parent application (to be entered in this application);
- Preliminary Amendment
- Return postcard

CERTIFICATE OF MAILING BY EXPRESS MAIL

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September 28, 2000
Date of Deposit

Samantha Bell
Signature

Samantha Bell
Typed or Printed Name of Person Signing Certificate

This application is a continuation (and claims the benefit of priority under 35 USC §120) of U.S. application Serial no. 09/179,006, filed October 26, 1998. The disclosure of the prior application is considered part of (and is incorporated by reference in) the disclosure of this application.

The present application is entitled to small entity status. Small entity status from the parent application is still proper. The filing fee has been calculated as follows:

Basic filing fee	$345
Total claims in excess of 20 times $9	$0
Independent claims in excess of 3 times $39	$0
Fee for multiple dependent claims	$0
Total filing fee:	$345

Under 37 CFR §1.53(d), no filing fee is being paid at this time. Please apply any other required fees, **EXCEPT FOR THE FILING FEE**, to Deposit Account 06-1050, referencing the attorney docket number shown above.

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

Please send all correspondence to:

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Fish & Richardson P.C.
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Boston, MA 02110-2804

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.

Respectfully submitted,

Gary L Creason

Gary L. Creason
Reg. No. 34,310

Enclosures

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.

227728.B11

Attorney's Docket 07917-045002 / (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

09/672,348 (vertical stamp in left margin: 09672348 . 092800)

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Samantha Bell

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TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

INS A1

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.

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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

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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

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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

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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 $1x10^4$ 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 $1x10^4$ 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 x 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.

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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^{-4} 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.

PATENT
ATTORNEY DOCKET NO: 07917/045001

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; Gary 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

Residence Address: Auburn, Massachusetts

Citizen of: United States of America

Post Office Address: 41 Potter Farm Road, Auburn, Massachusetts 01501

COMBINE ECLARATION AND POWER OF TORNEY CONTINUED

Full Name of Inventor: Michael F. Ethier

Inventor's Signature: Michael F. Ethier Date: 1-4-99

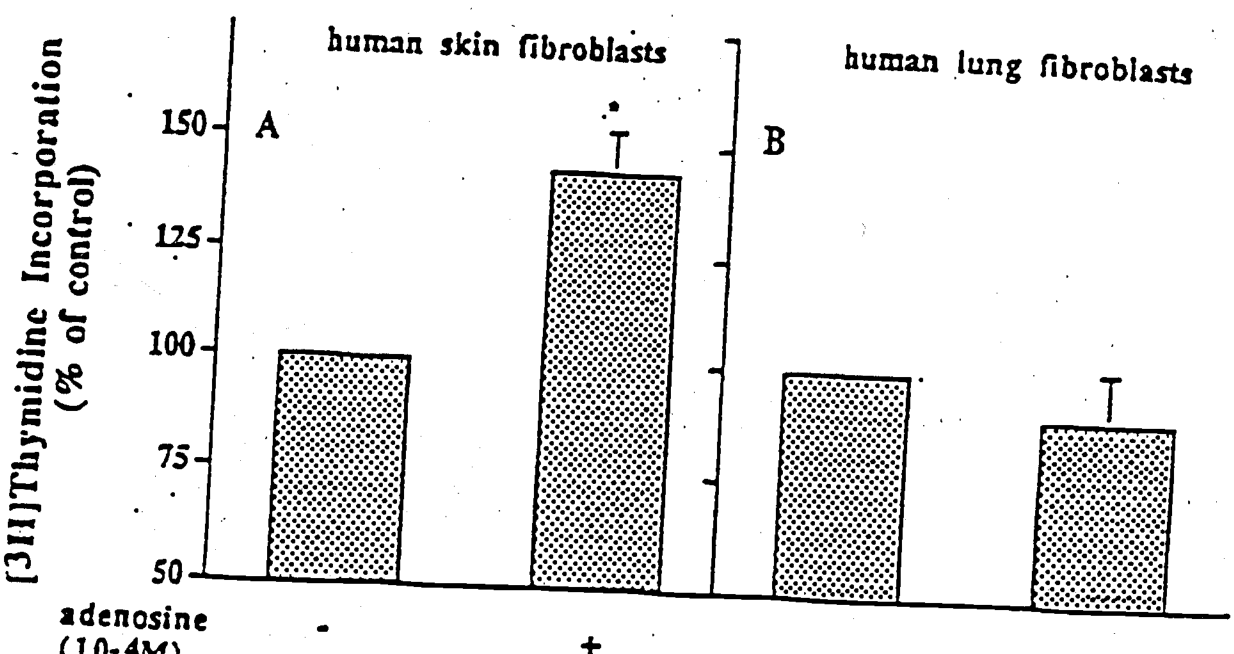
Residence Address: Grafton, Massachusetts

Citizen of: United States of America

Post Office Address: 57 Sunrise Avenue, Grafton, Massachusetts 01519

336875.B11

Revised: August 24, 1994 (391DECL.MRG)



human skin fibroblasts
human lung fibroblasts
A
B
[3H]Thymidine Incorporation
(% of control)
150
125
100
75
50
adenosine
(10-4M)
-
+
-
+

Fig. 1A

Fig. 1B

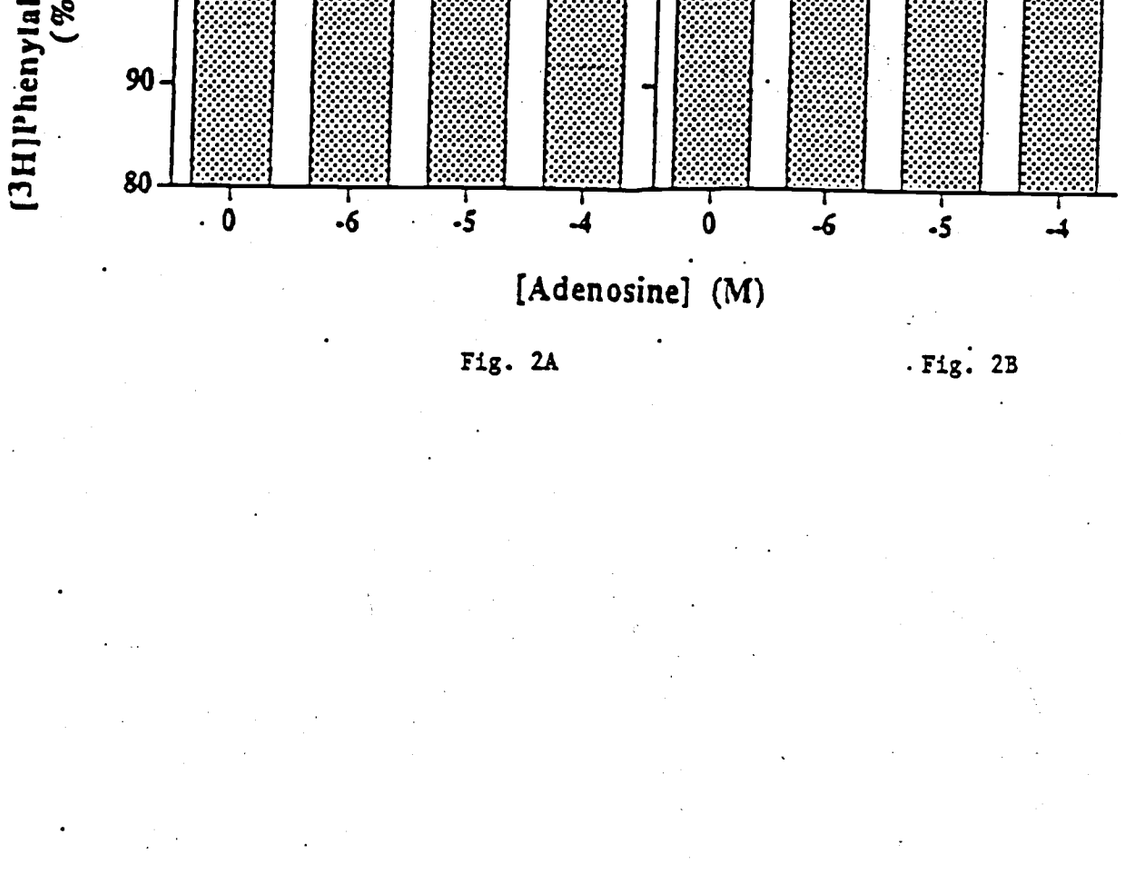


Fig. 2A

Fig. 2B

PRINT OF DRAWINGS
AS ORIGINALLY F[illegible]D

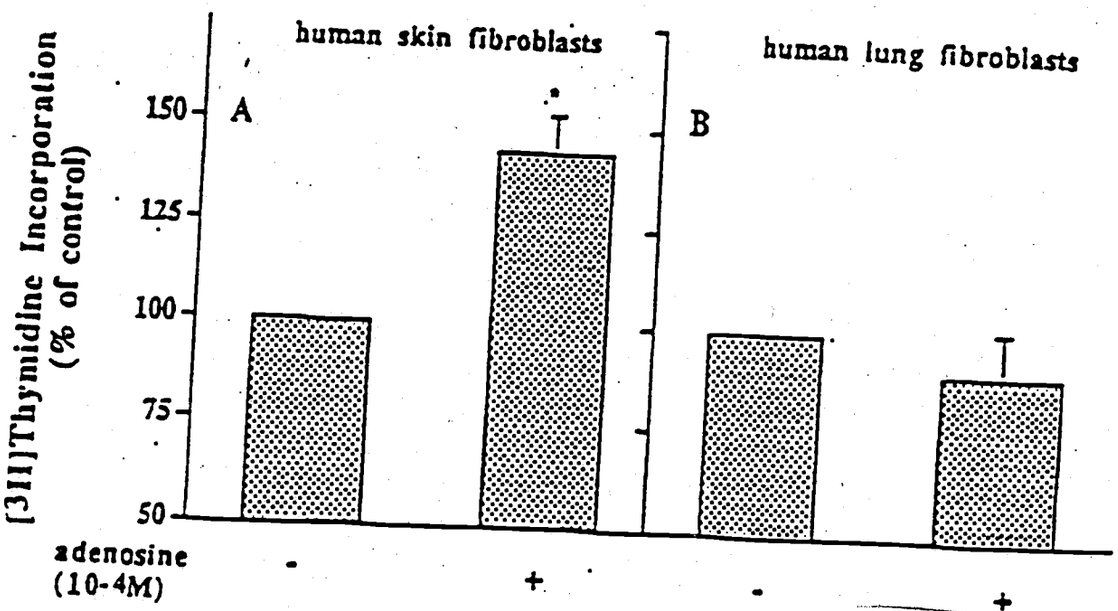


Fig. 1A

Fig. 1B

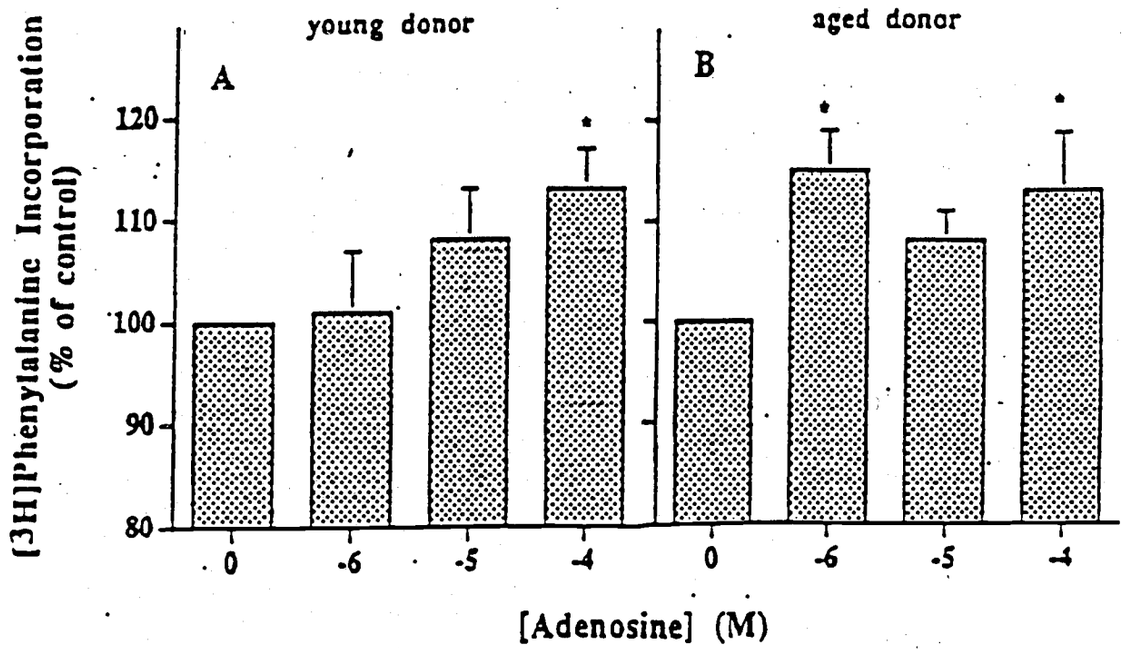


Fig. 2A

Fig. 2B

#2

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
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APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
09/672,348	09/28/2000	James G. Dobson	07917-045002

FORMALITIES LETTER

OC000000005559788

Gary L Creason
Fish & Richardson PC
225 Franklin Street
Boston, MA 02110-2804

Date Mailed: 11/16/2000

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given TWO MONTHS from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit **$ 345** *to complete the basic filing fee and/or file a small entity statement claiming such status (37 CFR 1.27).*
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

- **The balance due by applicant is $ 410.**

A copy of this notice MUST be returned with the reply.

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 3 - OFFICE COPY

Attorney's Docket No.: 07917-045002 / (UMMC 97-32)

#3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Dobson, Jr. et al. Art Unit :
Serial No. : 09/672,348 Examiner : Unknown
Filed : September 28, 2000
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

BOX MISSING PARTS
Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO NOTICE TO FILE MISSING PARTS OF APPLICATION

In response to the Notice to File Missing Parts of Application under 37 CFR §1.53(b) mailed November 16, 2000 (copy enclosed), applicant as a small entity submits herewith the following:

☒ Payment of the basic filing fee of $355;
☒ Payment of $65 surcharge for filing the basic filing fee on a date later than the filing date of the application;

It is understood that this perfects the application and no additional papers or filing fees are required. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 2-16-01

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
20200353.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, Washington, D.C. 20231.

February 16, 2001
Date of Deposit

Lisa G. Gray
Signature

Lisa G. Gray
Typed or Printed Name of Person Signing Certificate

GLC

#3

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
09/672,348	09/28/2000	James G. Dobson	07917-045002

Gary L Creason
Fish & Richardson PC
225 Franklin Street
Boston, MA 02110-2804

FORMALITIES LETTER

OC000000005559788

Date Mailed: 11/16/2000

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given TWO MONTHS from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit **$ 345** *to complete the basic filing fee and/or file a small entity statement claiming such status (37 CFR 1.27).*
- To avoid abandonment, a late filing fee or oath or declaration surcharge as set forth in 37 CFR 1.16(e) of $65 for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this letter.

Docketed By Practice Systems
Action Code: Missing Parts
Base Date: 11-16-00
Due Date: 1-16-01
Deadline: 5-16-01
Initial: JMG

- **The balance due by applicant is $ 410.**

02/27/2001 SDENBOB1 00000066 09672348

01 FC:201 355.00 OP
02 FC:205 65.00 OP

A copy of this notice MUST be returned with the reply.

Customer Service Center
Initial Patent Examination Division (703) 308-1202
PART 2 - COPY TO BE RETURNED WITH RESPONSE

Docketed By Billing Secretary
Due Date:
Deadline:
Initials:

Attorney's Docket 07917-045002 / (UMMC 97-32) #4/A BP 4-4-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James G. Dobson, Jr. and Michael F. Ethier
Art Unit : Unknown
Examiner : Unknown
Serial No. :
Filed :
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Prior to examination, please amend the application as follows:

In the Specification:

On page 1, after title, insert --This application is a continuation of co-pending application Serial No. 09/179,006, filed October 26, 1998.--

In the Claims:

Cancel claims 2 - 53.

CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Label No. EL298431056US

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.

September 28, 2000
Date of Deposit

Samantha Bell
Signature

Samantha Bell
Typed or Printed Name of Person Signing Certificate

23

Remarks

Applicant submits that all of the claims are now in condition for examination, which action is requested. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 28 SEP 2000

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Reg. No. 34,310

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Telephone: (617) 542-5070
Facsimile: (617) 542-8906

A

Attorney's Docket No.: 07917-045002 / (UMMC 97-32)

#5
BP
4-4-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Dobson et al. Art Unit : Unknown
Serial No. : 09/672,348 Examiner : Unknown
Filed : September 28, 2000
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Applicants submit the references listed on the attached form PTO-1449, copies of which are enclosed.

Under 35 USC §120, this application relies on the earlier filing date of 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 of these references are not provided with this statement.

This statement is being filed before the receipt of a first Office action on the merits. Please apply any charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 07917-045002.

Respectfully submitted,

Date: 2-16-01

J. Peter Fasse
Reg. No. 32,983

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February 16, 2001
Date of Deposit

Signature

Lisa B. Gray
Typed or Printed Name of Person Signing Certificate

Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 07917-045002	Application No. 09/672,348
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))		Applicant: James G. Dobson, Jr. and Michael F. Ethier	
		Filing Date: September 28, 2000	Group Art Unit: 1615

U.S. Patent Documents

Examiner Initial	Desig. ID	Patent Number	Issue Date	Patentee	Class	Subclass	Filing Date If Appropriate
	AA	4,088,756	5/78	Voorhees	424	180	
	AB	5,399,349	3/95	Paunescu et al.	424	195.1	
	AC	5,460,959	10/95	Mulligan et al.	435	172.3	
	AD	5,821,237	10/1998	Bissett et al	514	75	
	AE	4,454,122	6/12/84	Stramentionoli et al	424	180	
	AF	5,770,582	6/23/98	Von Borstel et al.	514	45	
	AG	5,932,558	8/3/99	Crostein et al	514	46	
	AH	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
	AI	19,545,107	6/1997	DE				

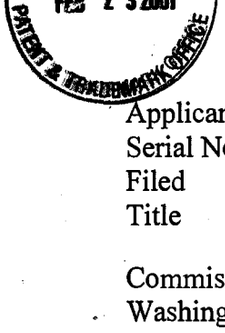
Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig.. ID	Document
	AJ	Adair et al., "Vascular development in chick embryos: a possible role for adenosine" American Physiological Society; 0363-6135/89 1989
	AK	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
	AL	Ethier et al., "Adenosine Stimulation of DNA Synthesis in Human Endothelial Cells," The American Physiological Society, 272:H1470-H1479, 1997
	AM	Grove et al., "Optical profilometry: An objective method for quantification of facial wrinkles," Journal of the American Academy of Dermatology, 21:631-637, 1989.
	AN	Gruber et al., "Increased Adenosine Concentration in Blood From Ischemic Myocardium by AICA Riboside," Circulation, 80:1400-1411, 1989
	AO	Kollias-Baker et al., Journal Pharmacology and Experimental Therapeutics, 281: 761-768, 1997.
	AP	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
	AQ	Olsen et al, "Tretinoin emollient cream: a new therapy for photodamaged skin," Journal of the American Academy of Dermatology, 26:215-224, 1992
	AR	Olsen et al., "Tretinoin emollient cream for photodamaged skin: Results of 48-week, multicenter, double-bir studies," Journal of the American Academy of Dermatology, 37:217-226, 1997

Examiner Signature	Date Considered
L. Chanavajala	4/19/01

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)



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Attorney's Docket No.: 07917-045002 / (UMMC 97-32)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Dobson et al
Serial No. : 09/672,348
Filed : September 28, 2000
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Art Unit : Unknown
Examiner : Unknown

Commissioner for Patents
Washington, D.C. 20231

PETITION FOR ONE-MONTH EXTENSION OF TIME

Pursuant to 37 CFR §1.136, applicant hereby petitions that the period for response to the action dated November 16, 2000, be extended for one month to and including February 16, 2001.

Enclosed is a check for $55 for the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 07917-045002.

Respectfully submitted,

Date: 2-16-01

J. Peter Fasse
Reg. No. 32,983

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

20200378.doc

02/27/2001 SDENBOB1 00000066 09672348
03 FC:215 55.00 OP

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.

February 16, 2001
Date of Deposit

Lisa G. Gray
Signature

Lisa G. Gray
Typed or Printed Name of Person Signing Certificate

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/672,348	09/28/00	DOBSON J	07917-045002

HM12/0420

GARY L CREASON
FISH & RICHARDSON PC
225 FRANKLIN STREET
BOSTON MA 02110-2804

EXAMINER	
CHANNAVAJJALA,L	
ART UNIT	PAPER NUMBER
1615	6

DATE MAILED: 04/20/01

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

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/672,348	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 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 is/are rejected.

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

8)☐ Claims _____ 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 objected to by the Examiner.

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

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

Priority under 35 U.S.C. § 119

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)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Receipt of declaration, fee, dated 2-23-01; preliminary amendment A, dated 9-28-00 and Information disclosure statement, dated 2-23-01 is acknowledged.

Claim Rejections - 35 USC § 112

Claim 1 is 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.

Claim 1 recite "method of enhancing" the skin condition, which is vague because it is not clear as to enhance from what and to achieve what effect. A correction and clarification is requested.

Claim Rejections - 35 U.S.C. § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

2. Claims 1 is rejected under 35 U.S.C. 102(e) as being anticipated by US patent 5,998,423 to Manneth et al (hereafter '423) or US patent 5,932,558 to Cronstein et al ('558).

'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). '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). Enhancing the tanning process on the skin, taught by '423, reads on the enhancing the condition of non-diseased skin.

'558 teaches composition comprising adenosine agonists for the healing wounds, burns (abstract, lines bridging col. 3 and 4) by promoting influx of fibroblasts and epithelial cells (col. 4). '558 further teaches topical application of the composition containing various additives or carriers (col. 8, lines 41 -68). Skin wounds and burns do not read on skin diseases and accordingly, treating wounds and burns only results in enhancing skin condition.

3. Claim 1 is 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 teaches 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), '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). Skin aging does not involve any underlying disease process. Accordingly treating aged skin reads on enhancing non-diseased skin condition.

Claim Rejections - 35 U.S.C. §103

4. 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.

5. Claims 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over 5,998,423 ('423) or 5,932,558 ('558) or 5,770,582 to von Borstel et al (hereafter '582).

'423, '582 and '558 have been discussed in the above sections. The references do not explicitly state enhancing the condition of a non-diseased skin. However, as explained above, none of the utilities taught by '582 (treatment of aged skin), '558 (burns or wounds) or '423 (skin tanning) involves a diseased skin. Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention that adenosine or adenosine agonist could be used to treat skin conditions which does not involve any diseases and instead to enhance the cosmetic effect of the skin (tanning, cuts, abrasions, burns, abrasions etc.).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 7-3-308-2438. 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 703-308-7921 for regular communications and 703-308-7921 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.

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.

5. Claims 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over 5,998,423 ('423) or 5,932,558 ('558) or 5,770,582 to von Borstel et al (hereafter '582).

'423, '582 and '558 have been discussed in the above sections. The references do not explicitly state enhancing the condition of a non-diseased skin. However, as explained above, none of the utilities taught by '582 (treatment of aged skin), '558 (burns or wounds) or '423 (skin tanning) involves a diseased skin. Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention that adenosine or adenosine agonist could be used to treat skin conditions which does not involve any diseases and instead to enhance the cosmetic effect of the skin (tanning, cuts, abrasions, burns, abrasions etc.).

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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 Channavajjala
April 19, 2001

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Form PTO 948 (Rev. 03/01) U.S. DEPARTMENT OF COMMERCE - Patent and Trademark Office Application No. 9/672,348

NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

The drawing(s) filed (insert date) 9-28-00 are:-

A. ☑ approved by the Draftsperson under 37 CFR 1.84 or 1.152.

B. ☑ objected to by the Draftsperson under 37 CFR 1.84 or 1.152 for the reasons indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawing must be sumitted according to the instructions on the back of this notice.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings: Black ink. Color.
   - ____ Color drawings are not acceptable until petiton is granted. Fig(s) _____
   - ____ Pencil and non black ink not permitted. Fig(s) _____
2. PHOTOGRAPHS. 37 CFR 1.84(b)
   - ____ 1 full-tone set is required. Fig(s) _____
   - ____ Photographs may not be mounted. 37 CFR 1.84(e)
   - ____ Poor quality (half-tone). Fig(s) _____
3. TYPE OF PAPER. 37 CFR 1.84(e)
   - ____ Paper not flexible, strong, white, and durable. Fig(s) _____
   - ____ Erasures, alterations, overwritings, interlineations, folds, copy machine marks not accepted. Fig(s) _____
   - ____ Mylar, velum paper is not acceptable (too thin). Fig(s) _____
4. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable sizes:
   - ____ 21.0 cm by 29.7 cm (DIN size A4)
   - ____ 21.6 cm by 27.9 cm (8 1/2 x 11 inches)
   - ____ All drawing sheets not the same size. Sheet(s) _____
   - ____ Drawings sheets not an acceptable size. Fig(s) _____
5. MARGINS. 37 CFR 1.84(g): Acceptable margins:

   Top 2.5 cm Left 2.5cm Right 1.5 cm Bottom 1.0 cm
   SIZE: A4 Size

   Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm
   SIZE: 8 1/2 x 11

   Margins not acceptable. Fig(s) _____
   _____ Top (T) _____ Left (L)
   _____ Right (R) _____ Bottom (B)
6. VIEWS. 37 CFR 1.84(h)
   REMINDER: Specification may require revision to correspond to drawing changes.
   Partial views. 37 CFR 1.84(h)(2)
   - ____ Brackets needed to show figure as one entity. Fig(s) _____
   - ____ Views not labeled separately or properly. Fig(s) _____
   - ____ Enlarged view not labeled separetely or properly. Fig(s) _____
7. SECTIONAL VIEWS. 37 CFR 1.84 (h)(3)
   - ____ Hatching not indicated for sectional portions of an object. Fig(s) _____
   - ____ Sectional designation should be noted with Arabic or Roman numbers. Fig(s) _____
8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)
   - ____ Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s) _____
9. SCALE. 37 CFR 1.84(k)
   - ____ Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s) _____
10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(i)
    - ✓ Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (poor line quality). Fig(s) 1A-2B
11. SHADING. 37 CFR 1.84(m)
    - ____ Solid black areas pale. Fig(s) _____
    - ____ Solid black shading not permitted. Fig(s) _____
    - ____ Shade lines, pale, rough and blurred. Fig(s) _____
12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p)
    - ✓ Numbers and reference characters not plain and legible. Fig(s) 1A-2B
    - ____ Figure legends are poor. Fig(s) _____
    - ____ Numbers and reference characters not oriented in the same direction as the view. 37 CFR 1.84(p)(1) Fig(s) _____
    - ____ English alphabet not used. 37 CFR 1.84(p)(2) Figs _____
    - ____ Numbers, letters and reference characters must be at least .32 cm (1/8 inch) in height. 37 CFR 1.84(p)(3) Fig(s) _____
13. LEAD LINES. 37 CFR 1.84(q)
    - ____ Lead lines cross each other. Fig(s) _____
    - ____ Lead lines missing. Fig(s) _____
14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)
    - ____ Sheets not numbered consecutively, and in Arabic numerals beginning with number 1. Sheet(s) _____
15. NUMBERING OF VIEWS. 37 CFR 1.84(u)
    - ____ Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s) _____
16. CORRECTIONS. 37 CFR 1.84(w)
    - ____ Corrections not made from prior PTO-948 dated _____
17. DESIGN DRAWINGS. 37 CFR 1.152
    - ____ Surface shading shown not appropriate. Fig(s) _____
    - ____ Solid black shading not used for color contrast. Fig(s) _____

COMMENTS

REVIEWER J. CHASE DATE 3-18-02 TELEPHONE NO. 703 305 8430

ATTACHMENT TO PAPER NO. _____

REMINDER

Drawing changes may also require changes in the specification, e.g., if Fig. 1 is changed to Fig 1A, Fig. 1B, Fig.1C, etc., the specification, at the Brief Description of the Drawing, must likewise be changed. Please make such changes by 37 CFR 1.312 Amendment at the time of submitting drawings.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Drawings - 37 CFR 1.85

File new drawings with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. The drawing should be filed as a separate paper with a transmittal letter addressed to the Drawing Reveiw Branch.

2. Timing for Corrections

Applicant is required to submit **acceptable** corrected drawings within the three-month shortened statutory period set in the Notice of Allowability (PTOL-37).

Failure to take corrective action within set period will result in **ABANDONMENT** of the Application.

3. Corrections other than Defects Noted by the Drawing Review Branch on the Form PTO-948

All changes to the drawings, other than defects noted by the Drawing Review Branch, **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted other than correction of defects, unless the examiner has approved the proposed changes.

Attorney's Docket No.: 07917-045002 / (UMMC 97-31)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James G. Dobson et al. Art Unit : 1615
Serial No. : 09/672,348 Examiner : L. Channavajjala
Filed : September 28, 2000
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION DATED APRIL 20, 2001

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

In the Claims:

Please cancel claim 1.

Please add new claims 54 to 79 as follows:

54. A method for increasing DNA synthesis in a dermal cell of a mammal without increasing proliferation of the cell, the method comprising applying to the cell a concentration of about 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to increase DNA synthesis in the cell without increasing proliferation of the cell.

55. The method of claim 54, wherein the cell is a fibroblast cell.

56. The method of claim 54, wherein the cell is a skin cell, and the composition is applied topically to skin of the mammal.

57. The method of claim 54, wherein the cell is a skin cell within a skin graft.

58. The method of claim 54, wherein the adenosine concentration is 10^{-4} M to 10^{-6} 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.

July 20, 2001
Date of Deposit

Joanne D Boyle
Signature

Joanne D. Boyle
Typed or Printed Name of Person Signing Certificate

59. The method of claim 54, wherein the adenosine concentration is about 10^{-4} M.

60. The method of claim 54, wherein the mammal is a human.

61. The method of claim 54, further comprising an angiogenic factor.

62. The method of claim 54, wherein the adenosine analog is selected from the group consisting of 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; 5'-adenosine triphosphate; phenylisopropyl-adenosine ("PIA"); 1-methylisoguanosine; N6-cyclohexyladenosine ("CHA"); N6-cyclopentyladenosine ("CPA"); 2-chloro-N6-cyclopentyladenosine; 2-chloroadenosine; adenosine amine congener (ADAC); 2-p-(2-carboxy-ethyl) phenethyl-amino-5'-N-ethylcarboxamido-adenosine; N-ethylcarboxamido-adenosine ("NECA"); napthyl-substituted aralkoxyadenosine; 5'(N-cyclopropyl)-carboxamidoadenosine; 2-chloroadenosine; N6-phenyladenosine; N6-phenylethyladenosine; and 2-phenylaminoadenosine.

63. A method of increasing protein synthesis in a dermal cell of a mammal without increasing proliferation of the cell, the method comprising applying to the cell a concentration of about 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to increase protein synthesis in the cell without increasing proliferation of the cell.

64. The method of claim 63, wherein the cell is a fibroblast cell.

65. The method of claim 63, wherein the cell is a skin cell, and the composition is applied topically to skin of the mammal.

66. The method of claim 63, wherein the cell is a skin cell within a skin graft.

67. The method of claim 63, wherein the adenosine concentration is 10^{-4} M to 10^{-6} M.

68. The method of claim 63, wherein the adenosine concentration is about 10^{-4} M.

69. The method of claim 63, wherein the mammal is a human.

70. 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.

71. The method of claim 70, wherein the composition further comprises an angiogenic factor.

72. The method of claim 70, wherein the adenosine concentration is 10^{-4} M to 10^{-6} M.

73. The method of claim 70, wherein the adenosine concentration is about 10^{-4} M.

74. The method of claim 70, wherein the composition further comprises a conditioning agent.

75. The method of claim 74, wherein the conditioning agent is a humectant, an emollient, or an occlusive agent.

76. The method of claim 70, wherein the mammal is a human.

77. The method of claim 70, wherein the skin comprises a skin graft.

78. The method of claim 70, wherein the composition further comprises a transdermal delivery agent.

79. The method of claim 70, 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 79 are pending in this application. Applicants have cancelled claim 1 without prejudice and added new claims 54 to 79. These new claims add no new matter. In particular, claims to specific concentrations are supported by the original claims and in the application, e.g., at page 3, lines 15-18. Claims to specific adenosine analogs are supported in the application, e.g., at page 6, line 17, to page 7, line 6. 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.

These and all of the other new claims are supported by the claims filed in the original application. For example, independent claim 54 to a method for increasing DNA synthesis in a dermal cell of a mammal without increasing proliferation of the cell is supported by original claim 21. Independent claim 63 to a method of increasing protein synthesis in a dermal cell of a mammal without increasing proliferation of the cell is supported by original claim 30. Independent claim 70 to 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 is supported by original claims 1 and 8.

The Invention

The invention is based on the discovery that adenosine stimulates DNA synthesis, increases protein synthesis, and increases cell size in cultures of human dermal cells, such as fibroblasts, all without increasing cell proliferation. Based on this discovery, the invention provides various methods for increasing DNA or protein synthesis in dermal cells using specific concentrations of adenosine or adenosine analogs (10^{-3} M to 10^{-7} M)(claims 54 to 69), and for enhancing the condition of the skin using an effective amount of adenosine applied topically (claims 70 to 79). In these methods, the adenosine, or in some methods, adenosine analogs, are applied to the cells or topically to the skin to increase the cell size, and the function and abundance of products produced by the dermal cells, such as fibroblasts, e.g., by increasing DNA synthesis and/or protein synthesis.

However in all of these methods, it is important to avoid increasing proliferation of the dermal cells, which could lead to scarring, keloids, and other effects of excess dermal proliferation that are detrimental to the complexion of the skin. This important aspect of avoiding increased cell proliferation is not considered or described in any of the references cited in the Office Action.

Applicants will now address the Office Action rejections in the order they were presented by the Examiner.

35 U.S.C. § 112, Second Paragraph

Claim 1 has been rejected as being allegedly indefinite for reciting a "method of enhancing" the skin condition, which the Office Action states to be "vague." This rejection is moot in view of the cancellation of claim 1. However, applicants submit that the rejection should not apply to new claim 70, which is based on claim 1, for the following reasons.

Applicants submit that this phrase is not vague, because it is defined in the specification at page 3, lines 3-6. However, in the interests of moving this application towards allowance, and not for any reason related to patentability, applicants have drafted new claim 70 to recite "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." Support for this amendment appears in the specification, for example, at page 4, lines 3-6 and lines 13-15.

In addition, the phrase "unbroken skin" in claim 70 is supported in the application based on the overall intent and general nature of the claimed invention. Specifically, page 2, lines 7-8, describes one general method of the invention as "a method for enhancing the condition of non-diseased skin of a mammal." In the very next paragraph, the specification states, "[t]he invention also provides a method for promoting healing of broken, non-diseased skin in a mammal." Although applicants are not presently pursuing this second method in the present application, its recitation implies to one of skill in this field that the discussion in the previous paragraph in the application must relate to enhancing the condition of unbroken, non-diseased skin, even though the term "unbroken" is not expressly stated. Taken in the context of the application as a whole,

the concepts of enhancing the condition of unbroken skin, as well as treating broken skin, are both supported in the application as originally filed.

Applicants remind the Examiner that the courts have long held that amendments that merely render explicit what is implicitly disclosed in the specification do not to constitute new matter. See, e.g., In re Wright, 343 F.2d 761, 767 (C.C.P.A. 1965). In Wright, the court said:

> We feel that the amendments to the specification merely render explicit what had been implicitly disclosed originally, and, while new *language* has certainly been added, we are not prone to view all new "language" ipso facto as "new matter." (emphasis in original).

Therefore, applicants submit that new claim 70 is fully supported by the originally filed specification, and avoids the indefiniteness rejection of original claim 1.

35 U.S.C. § 102

Claim 1 has been rejected as being allegedly anticipated by Manneth, U.S. Patent No. 5,998,423 (Manneth) or Cronstein, U.S. Patent No. 5,932,558 (Cronstein). This rejection is moot in view of applicants' cancellation of claim 1. Applicants respectfully submit that these rejections do not apply to new claims 54 to 79 for the following reasons.

Applicants have claimed the invention in three independent claims, 54, 63, and 70, to cover variations on the overall method of using adenosine, or in some methods, adenosine or adenosine analogs, to affect dermal cells, e.g., fibroblasts, without increasing proliferation of the dermal cells. Claim 54 covers a method for increasing DNA synthesis in a dermal cell by applying to the cell a concentration of about 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to increase DNA synthesis in the cell without increasing proliferation of the cell. Claim 63 covers a method of increasing protein synthesis in a dermal cell by applying to the cell a concentration of about 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to increase protein synthesis in the cell without increasing proliferation of the cell. Claim 70 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 cell proliferation, by topically applying to the skin a composition comprising a concentration of adenosine, but not adenosine

analogs, in an amount effective to enhance the condition of the skin without increasing cell proliferation.

These claims are distinguished from the cited prior art for the following reasons.

First, 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 2). Manneth also discloses various formulations of the composition including topical formulation containing various thickeners, castor oil and other additives.

However, Manneth fails to describe increasing DNA or protein synthesis by using a specific concentration of 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to achieve increased DNA or protein synthesis while avoiding detrimental dermal cell proliferation. Thus, Manneth does not anticipate independent claims 54 and 63.

Furthermore, Manneth describes the use of specific adenosine-1 and adenosine-2 receptor agonists and antagonists that are required for his invention. 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. Therefore, Manneth does not anticipate applicants' claim 70 to a method of enhancing the condition of skin by topically applying adenosine.

Next, according to the Office Action, Cronstein describes a composition comprising adenosine agonists for the healing wound and burns by promoting influx of fibroblasts and epithelial cells. Cronstein is further said to describe topical application of the composition containing various additives or carriers (Office Action at page 3).

As the Examiner correctly notes, Cronstein limits his application of adenosine receptor agonists to open wounds such as burns. Cronstein also describes that his invention promotes the migration of endothelial cells, fibroblasts, and epithelial cells to the wound site. However, Cronstein fails to describe increasing DNA or protein synthesis by using a specific concentration of 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to achieve increased DNA or protein synthesis while avoiding detrimental dermal cell proliferation. To the contrary, Cronstein would want the dermal cells to proliferate to repair the wound. Thus, independent claims 54 and 63 are not anticipated by Cronstein.

With respect to new claim 70, applicants submit that Cronstein is limited to treating wounds that naturally involve broken skin, whereas claim 70 recites enhancing the condition of unbroken skin. Cronstein simply does not describe or suggest that adenosine should be applied to unbroken skin. Applicants apply adenosine as a cosmetic approach to enhance the condition or complexion of the skin, whereas Cronstein describes a medical therapy for open wounds such as burns. Thus, Cronstein does not anticipate claim 70.

Next, claim 1 has been rejected as allegedly anticipated by von Borstel, U.S. Patent No. 5,770,582 (von Borstel). Applicants traverse this rejection with respect to the new claims.

According to the Office Action, the von Borstel patent describes "deoxyribonuclosides such as 2'-deoxayadenosine for accelerating the healing of wounds, cuts, abrasions and to ameliorate the effects of aging" (at page 3). 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 independent claims all recite the use of "adenosine" or "adenosine or adenosine analogs." As the Examiner correctly points out, Von Borstel describes the use of **deoxy**ribonucleosides, not ribonucleosides. However, adenosine and adenosine analogs are ribonucleosides, **not** deoxyribonucleosides. The two classes of compounds differ structurally and are quite distinct in their chemical and biological properties. The structural difference is well known. Deoxyribonucleosides would not be expected to bind to adenosine receptors to elicit a biological response, and thus, the deoxyriboncleosides described by von Borstel are not

the same as applicants' claimed adenosine and adenosine analogs. For this reason, von Borstel cannot anticipate applicants' pending claims. Therefore, this rejection should be withdrawn.

35 U.S.C. § 103

Claim 1 has been rejected as being allegedly unpatentable over Manneth, Cronstein, or von Borstel. Applicants submit that this rejection is moot in view of the cancellation of claim 1, and that this rejection does not apply to the new claims.

As the Office Action concedes, these patents "do not explicitly state enhancing the condition of a non-diseased skin" (Office Action at page 4). Moreover, these references do not describe or even suggest that one can increase DNA or protein synthesis of dermal cells by using a specific concentration of 10^{-3} M to 10^{-7} M of adenosine or an adenosine analog to achieve beneficial results while avoiding detrimental dermal cell proliferation.

Based on the discussions above, applicants submit that the new claims are not rendered obvious by any of the cited patents, either singly or in combination.

CONCLUSION

Applicants submit that all of the new claims are in condition for allowance. Please apply

charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-045002.

Respectfully submitted,

Date: July 20, 2001

J. Peter Fasse
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20290413.doc

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/672,348	09/28/00	DOBSON J	07917-045002

HM12/1010

GARY L CREASON
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225 FRANKLIN STREET
BOSTON MA 02110-2804

EXAMINER	
CHANNAVAJJALA, L	
ART UNIT	PAPER NUMBER
1615	8

DATE MAILED: 10/10/01

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

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/672,348	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 *30 July 2001* .

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) *54-79* is/are pending in the application.

4a) Of the above claim(s) *54-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-79* 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) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt of amendment B, dated 7-30-01 is acknowledged.

Claim 1 is canceled and new claims 54-79 have been presented.

Response to Arguments

Applicant's arguments with respect to claim 1 have been considered but are moot in view of the new ground(s) of rejection.

Election/Restrictions

Newly submitted claims 54-69 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

The newly presented claims 54-62 are directed to a method of increasing DNA synthesis and new claims 63-69 are directed to a method of protein synthesis, which were not presented in the original claims. The original claims are directed to a method of enhancing the skin condition and is different from claims 54-69.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 54-69 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

However, instant claims 70-79 are considered for examination.

Claim Rejections - 35 USC § 112

Claims 70-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Instant claims recite the limitation " a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation". Applicants state that adenosine does not cause cell proliferation of dermal cells, in the instant specification. However, applicants does not show any experimental evidence if there is any increase or any absence of increase in the cell proliferation. On the other hand, it is well known in the art that adenosine stimulates proliferation of cells, such as endothelial cells or in particular cells in the skin. For instance, German patent, DE 19545107 discloses that adenosine is useful in treating skin aging and its sequelae by stimulating cell proliferation in skin.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 70, 74-76 and 78 are rejected under 35 U.S.C. 102(b) as being anticipated by DE 19545107 (DE).

DE discloses a cosmetic and dermatological preparation containing adenosine for the treatment of natural, chemical induced or UV-induced skin aging and its sequelae. While DE states that adenosine **stimulates** cell proliferation, DE does not state that adenosine **increases** cell proliferation. Also refer to the 35 USC 112, rejection, with respect to the claim limitation "increase cell proliferation". Accordingly, DE anticipates the instant method. At this time a complete document is not available and abstract is therefore relied upon. DE teaches other cosmetic ingredients in the composition such as glycerin, cyclomethicone etc., which read on the "conditioning agent" of the instant claims. Further, instant claim 78 merely states "a transdermal delivery agent", which is broad and can include any topical agent, unless otherwise shown on the contrary. Accordingly, isopropyl palmitate, glycerin or cyclomethicone of DE also meet the requirement of claim 78. It is also well known that aging of skin is associated with skin dryness, wrinkles or loss of elasticity etc. Accordingly, the method of DE, which employs adenosine as claimed, also reduces one or more conditions such as dryness, wrinkles etc.

Claims 70 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Hartzshtark et al (Experentia, 1985).

Hartzshtark et al discloses that application of adenosine along with isoproterenol bitartarate, terbutaline sulfate, papaverine etc., reduced the degree of skin indentation, which is an indication of a firmer and younger skin. Hartzshtark et al does not teach the increase or decrease of cell proliferation or even stimulation of cell proliferation, with adenosine application. Absent showing evidence on the contrary, it is the position of the examiner that adenosine

treatment of Hartzshtark et al, does not increase the stimulation of dermal cell proliferation and therefore, Hartzshtark et al anticipates the instant method.

Claim Rejections - 35 USC § 103

Claims 70 and 72-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of DE 19545107 and Hartzshtark et al or DE in view of Hartzshtark et al.

DE and Hartzshtark et al, discussed above, teach adenosine for the treatment of aging and it sequelae. With respect to the limitation "without increasing the cell proliferation", see the explanation above. Neither reference discloses the exact amounts of adenosine. However, Hartzshtark et al states that the reduced skin indentation, which is an indication of firmer and younger skin, occurs at those concentrations of adenosine, which is known to increase the cAMP concentrations. Therefore it would have been obvious for a skilled artisan at the time of the instant invention to optimize the amounts of adenosine such that the cAMP levels of skin increase and thus contribute for the reduced skin indentation and hence a firmer skin.

Claim 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of DE 19545107 and Hartzshtark et al as applicable to claims 70 and 72-78 above, and further in view of US patent 5,618,544 to Brown.

DE and Hartzshtark et al, discussed above fails to teach angiogenic factors in their composition.

Brown teaches a method of decreasing cutaneous senescence in aging humans, which involves administering a cosmetic composition comprising a mixture of growth factors such epidermal growth factor, fibroblast growth factor (FGF), transforming growth factor etc., in a pharmaceutically acceptable carrier. Brown also teaches that the lifetime damaging effects of include wrinkling and hardening of the skin, with loss of elasticity (col. 1-2 and claims). Instant claim does not specify any angiogenic factor. However, FGF is known angiogenic factors in the art, as also described by applicants in the instant application. Therefore, it would have been obvious for a skilled artisan at the time of the instant invention to add FGF of Brown to the cosmetic composition containing adenosine of DE (or Hartzshtark et al), with an expectation to reduce or delay the cutaneous atrophy because Brown suggests that the reduced senescence in epidermal cells improves the youthful appearance of human skin.

Claims 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of DE 19545107 and Hartzshtark et al as applicable to claims 70 and 72-78 above, and further in view of US patent 5,785,978 to Porter.

DE and Hartzshtark do not specifically teach a transdermal patch or a transdermal delivery agent of the instant claims. However, as explained in the 102 rejection above, DE teaches isopropyl palmitate, glycerin etc., which read on the transdermal agent.

Alternatively, Porter teaches a skin care composition for the improving the appearance of skin affected by aging, comprising antioxidant vitamins and moisturizers. The composition of Porter is applied in the form of a patch (cols.1, 4 & 6). Further, Porter suggests permeability enhancing agents such as isopropyl palmitate (also taught by DE) for the delivery of

antioxidant vitamins from the transdermal patch. Therefore, it would have been obvious for a skilled artisan at the time of the instant invention to administer adenosine containing cosmetic compositions of DE or Hartzshtark et al either as cosmetic cream (DE) or as a transdermal patch (Porter) and still achieve improvement in the appearance of aging skin.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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 703-308-7921 for regular communications and 703-308-7921 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 Channavajjala
October 2, 2001

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice of References Cited	Application/Control No. 09/672,348	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-5,618,544	04-1997	Brown	424	401
	B	US-5,785,978	07-1998	Porter et al.	424	401
	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	DE 19545107	06-1997	Germany	Shoenrock et al.	-	-
	O						
	P						
	Q						
	R						
	S						
	T						

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Hartzshtark et al. The use of indentometry to study the effect of agents known to increase skin cAMP content. Experentia. 41(3), 378-379, 1985.
	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.

Attorney's Docket No.. 07917-045002 / (UMMC 97-32)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Dobson, Jr. et al. Art Unit : 1615
Serial No. : 09/672,348 Examiner : L. Channavajjala
Filed : September 28, 2000
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Commissioner for Patents
Washington, D.C. 20231

PETITION FOR ONE-MONTH EXTENSION OF TIME

Pursuant to 37 CFR §1.136, applicant hereby petitions that the period for response to the action dated October 10, 2001, be extended for one month to and including February 11, 2002 (February 10th being a Sunday).

Enclosed is a check for $55 for the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 02-11-2002

J. Peter Fasse
Reg. No. 32,983

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03/05/2002 TGEDAMU1 00000081 09672348
01 FC:215 55.00 OP

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.

February 11, 2002
Date of Deposit

Signature

Lisa G. Gray
Typed or Printed Name of Person Signing Certificate

Attorney's Docket No. 07917-045002 / (UMMC 97-32)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James G. Dobson, Jr. and Michael F. Ethier
Art Unit : 1615
Examiner : L. Channavajjala
Serial No. : 09/672,348
Filed : September 28, 2000
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

10/C w/att (RE) o/m 2-11-02

BOX AF
Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO FINAL OFFICE ACTION DATED OCTOBER 10, 2001

PURSUANT TO 37 C.F.R. 1.116(A)

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

In the claims

Cancel claims 54 to 69 without prejudice as directed to a non-elected invention.

Amend claim 70 as follows.

Ref 3-8-02

~~70.~~ 1 (Amended) 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^{-4} M to 10^{-7} 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.

February 11, 2002
Date of Deposit

Lisa G. Gray
Signature

Lisa G. Gray
Typed or Printed Name of Person Signing Certificate

25

C

REMARKS

Claims 70 to 79 are pending in this application. Applicants propose canceling claims 54 to 69 as allegedly directed to a non-elected invention. Applicants also propose to amend claim 70. This amendment would add no new matter, as it merely includes a range of concentrations of adenosine recited in dependent claims and in the specification at page 3, lines 15-18.

In addition, the amendment set forth above would raise no new issues that would require further consideration and/or search. Applicants submit that this amendment would place the claims into condition for allowance, or at least present the rejected claims in better form for consideration on appeal, and should therefore be entered after the final rejection under 37 C.F.R. § 1.116 (a).

Restriction

Applicants disagree with the Examiner's conclusion that the present claims 54 to 69 are directed to a separate invention than that claimed in claims 70 to 79, because all are based on the application of certain concentrations of adenosine to the skin to achieve certain results. Nevertheless, applicants propose to cancel these claims as directed to a non-elected invention unless the Examiner reconsiders and withdraws this restriction. Thus, claims 70 to 79 would be pending.

35 U.S.C. § 112, First Paragraph

Claims 70 to 79 have been rejected as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants traverse this rejection in view of experimental test results as described in a declaration (attached hereto) by the two co-inventors of this application, Dr. James G. Dobson, Jr. and Dr. Michael F. Ethier ("the Declaration").

According to the Office Action, applicants state that adenosine does not cause cell proliferation of dermal cells, but the application provides no experimental evidence to show whether there is an increase or decrease in the cell proliferation. Applicants now provide that evidence. As described in the Declaration, applicants conducted tests of skin fibroblast cells,

which make up a significant portion of dermal cells, from two different donors (an 84 year-old man and 30 year-old female), with varying concentrations of adenosine (10^{-4} or 10^{-5} M). The added adenosine had no significant effect on cell proliferation over a 5 day period, i.e., the adenosine did not increase cell proliferation at concentrations of 10^{-4} or 10^{-5} M (see Declaration, paragraph 3).

Although applicants believe that claim 70 as written covers this result by functional language, in the interests of moving this application towards allowance, they have proposed to amend claim 70 to reflect this experimental result. Based on this new information, applicants request the Examiner to reconsider and withdraw this rejection under Section 112, first paragraph.

As for the Office's assertion that "it is well known in the art that adenosine stimulates proliferation of cells, such as endothelial cells or in particular cells in the skin" based on German patent DE 19545107, applicants will discuss this reference in more detail below in relation to the alleged anticipation.

35 U.S.C. § 102

Claims 70, 74 to 76, and 78 have been rejected as allegedly anticipated by DE 19545109 (the German patent application). Applicants traverse this rejection in view of the new data described in the enclosed Declaration.

According to the Office Action, the German patent application "discloses a cosmetic and dermatological preparation containing adenosine for the treatment of natural, chemical induced or UV-induced skin aging and its sequelae. While DE states that adenosine stimulates cell proliferation, DE does not state that adenosine increases cell proliferation. ... Accordingly, DE anticipates the instant method" (Office Action, page 4). Applicants submit that this rejection is based on information in the German patent application that contradicts applicants' test results, and request the Examiner to reconsider this rejection in view of applicants testing, the Declaration, and the following comments.

Applicants have obtained a translation of the German patent application, which is attached to the Declaration as Exhibit B. Applicants' comments in their Declaration and here are

based on this translation. As the Examiner has noted, the German patent application describes the use of adenosine for increasing cell proliferation in human skin (see, e.g., the title and claim 1). However, applicants' claims require no increase in dermal cell proliferation, because such excess cell proliferation can cause scarring, discoloration, and a variety of other skin anomalies associated with hyperplasia. See, Declaration at paragraph 2.

Furthermore, applicants' testing, as described above, has shown that low concentrations of adenosine do not increase dermal cell proliferation. Thus, when the German patent application states that concentrations of adenosine as low as 0.001% can be used for increasing cell proliferation, the German patent application must be mistaken in that adenosine was not likely actually administered at this low concentration. There is one paragraph in the German patent application that recites the 0.001% number, and this is in an extremely broad range from 0.001 to 10% by weight of a cosmetic composition (at page 9, 4th full paragraph). Other sections of the German patent application recite higher concentrations for a lower limit of adenosine. For example, the claims, recite 0.01 to 10%, with a preferred concentration of 0.1 to 6%. More importantly, each of the six Examples at pages 9 to 12 in the translation lists a relatively high concentration of 0.1% adenosine. See also the Declaration at paragraph 5.

Thus, based on applicants' test results, applicants submit that the extremely broad range of adenosine concentrations listed in the German patent application is not supported by reality. The low end of this unsupported range is 0.001%, which corresponds to 3.8×10^{-5} M adenosine. This is between the 10^{-4} M and 10^{-5} M concentrations recited in the claims of the present application. However, the presently claimed invention is based on the demonstration that the recited concentrations of adenosine do not increase cell proliferation. This is the exact opposite of the assertions in the German patent application. It is for these reasons that the German patent application recitation of adenosine concentrations less than 10^{-4} M (0.00265%) cannot be valid, and thus the German patent application does not disclose the same invention as the proposed claims in the present application. See Declaration, paragraph 5.

In addition, applicants submit that the dependent claims 74 to 76, and 78 are also not anticipated for the same reasons discussed above for independent claim 70. Thus, applicants

respectfully request that the Examiner reconsider and withdraw the rejection of the claims in view of the German patent application.

Next, claims 70 and 76 have been rejected as being allegedly anticipated by Hartzshtark et al. (Experentia, 1985). Applicants disagree for the following reasons.

According to the Office Action, Hartzshtark discloses that the application of adenosine along with isoproterenol bitartarate, terbutaline sulfate, papavarine etc., reduced the degree of skin indentation, which is an indication of a firmer and younger skin (Office Action, page 4). The Examiner concedes that Hartzshtark does not discuss whether the addition of adenosine increases or decreases cell proliferation, but states, "[a]bsent showing evidence on the contrary, it is the position of the examiner that adenosine treatment of Hartzshtark et al, does not increase the stimulation of dermal cell proliferation and therefore, Hartzshtark et al. anticipates the instant method" (Office Action, pages 4-5).

As discussed above, applicants have demonstrated that certain low concentrations of adenosine do not increase cell proliferation. In the enclosed Declaration, applicants describe their review of the two main prior art references, and the testing they have done that supports the present claims.

Hartzshtark states that certain concentrations of various agents, including adenosine, increase skin cyclic-AMP content and thus cause a decrease in skin indentation. Specifically, Hartzshtark indicates in the Table on page 379 that the adenosine concentration effective to reduce indentation was 0.1% (3.8×10^{-3} M), but also notes that they tested adenosine "at one-third of the concentrations shown in the table [e.g., about 1.27×10^{-3} M], and at this level [adenosine was] ineffective" (bottom of page 378 to top of page 379). Applicants discuss these results of Hartzshtark in their Declaration, at paragraph 4.

The proposed amended claims would recite a maximum concentration of adenosine of 10^{-4} M. The results in Hartzshtark indicate that a concentration of adenosine of 10^{-4} M or lower would be even less effective than one-third of 0.1% (1.27×10^{-3} M), which was ineffective in their testing. See Declaration, paragraph 4. Thus, Hartzshtark does not anticipate claim 70 as amended, and does not anticipate dependent claim 76, which depends from claim 70.

35 U.S.C § 103

Claims 70 and 72 to 78 have been rejected as allegedly obvious over the combination of the German patent application and Hartzshtark. Applicants traverse this rejection for the reasons stated above and as follows.

The Office Action states that "[n]either reference discloses the exact amounts of adenosine," but concludes that "it would have been obvious for a skilled artisan at the time of the instant invention to optimize the amounts of adenosine such that the cAMP levels of skin increase and thus contribute for the reduced skin indentation and hence a firmer skin" (Office Action, page 5).

As discussed above, Hartzshtark indicates that adenosine was effective at a concentration of 0.1%, which is 3.8×10^{-3} M. However, when they tested adenosine at a lower concentration, at one-third of 0.1%, there was no effect. Thus, applicants submit that one skilled in this field would not have "optimized" the concentrations described in Hartzshtark to lower them even further. Thus, there would have been no suggestion or motivation in any of the cited references for one of skill in this field to use **a maximum** concentration of 10^{-4} M adenosine as recited in applicants' claim 70. Thus, claim 70, and dependent claims 72 to 78, are not obvious in view of the cited prior art.

Claim 71 has been rejected as being allegedly unpatentable over a combination of the German patent application of DE 1955107 and Hartzshtark in view of Brown, U.S. Patent No. 5,618,544 ("Brown"). Similarly, claims 78 and 79 have been rejected as obvious over the combination of the German patent application and Hartzshtark in view of Porter, U.S. Patent No. 5,785,978 ("Porter").

Claims 71, 78, and 79 depend from claim 70, which is patentable for all the reasons discussed above. Thus, these dependent claims are also patentable. However, applicants note further that Brown's suggestion to apply epidermal and fibroblast growth factors to the skin would not lead one of skill in the art to avoid an increase in cell proliferation, as recited in applicants' claims, because these growth factors are known to increase cell proliferation (Brown notes that these factors increase "the rate of cellular replication," at column 3, lines 25-26). Thus, applicants see no suggestion or motivation to combine Brown with any of the other cited

references, and even if such a combination were made, one would not have achieved the claimed invention.

As for Porter, if one of skill in the art were to use the transdermal patch that this patent describes, the dosage of adenosine would, according to the cited prior art, cause an increase in skin cell proliferation and/or provide a higher concentration of adenosine than recited in applicants' claims. Thus, applicants submit that even if Porter were combined with the German patent application or Hartzshtark, the result would not be the presently claimed invention.

CONCLUSION

Attached is a marked-up version of the changes being made by the current amendment.

Applicants request that the proposed claim amendment be entered and that all pending claims then be allowed. No excess claims fee is required. Applicants enclose a $55.00 check and a Petition for Extension of Time. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-045002.

Respectfully submitted,

Date: 02-11-02

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Version with Markings to Show Changes Made

In the claims:

Claims 54 to 69 have been cancelled as directed to a non-elected invention.

Claim 70 has been amended as follows.

70. (Amended) 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^{-4} M to 10^{-7} M.

Attorney's Docket No.. 07917-045002 / (UMMC 97-32)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James G. Dobson, Jr. and Michael F. Ethier
Art Unit : 16415
Examiner : L. Channavajjala
Serial No. : 09/672,348
Filed : September 28, 2000
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132

We, James G. Dobson, Jr., Ph.D. and Michael F. Ethier, declare that:

1. We are the co-inventors of the subject matter claimed in the patent application captioned above ("the present application").

2. The present application claims methods of enhancing the condition of unbroken skin of a mammal, but without increasing dermal cell proliferation. Excess skin cell proliferation can cause scarring, discoloration, and a variety of other skin anomalies associated with hyperplasia. The method claims recite applying to the skin a composition including a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation. These claims have been rejected by the U.S. Patent & Trademark Office Examiner in a Final Office Action dated October 10, 2001, as allegedly anticipated by German Patent No. DE 195 45 107 A1 ("the German patent application) and by Hartzshtark et al., Experentia, 41:378-379 (1985) ("Hartzshtark et al.). We have reviewed these two references, and based on a careful review of the references and our experimental test results, we believe that they do not disclose the methods claimed in our present application.

3. We have conducted testing to show that an important feature of our claimed methods is correct, i.e., that concentrations of adenosine recited in the pending claims do not increase

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.

February 11, 2002
Date of Deposit

Lisa A Gray
Signature

Lisa A. Gray
Typed or Printed Name of Person Signing Certificate

proliferation of a major type of dermal cells, i.e., skin fibroblasts. In this testing, we cultured skin fibroblasts from two subjects, a 30 year-old female and an 84 year-old male. For each experiment, we used 35 mm culture dishes plated with fibroblasts at a density of 1×10^4 cells/cm^2. Adenosine was added to dishes the following day. For each adenosine-treated dish, a matching control dish was treated with vehicle. After 5 days in culture, we counted the total number of cells in the control dish, and then in the test dish. For each pair of culture dishes, the number of cells in the control dish was designated as 100% and the number of cells in the adenosine-treated dish was expressed as a percentage of the control dish. In each experiment, the mean and standard error for adenosine-treated dishes was generated from the total number of samples (n = 6 or 7) for each test and expressed as a percent of the control. The adenosine concentrations and results are listed in Table 1 attached to this declaration as Exhibit A. As shown, adenosine concentrations of both 10 μM (10^{-5} M) and 100 μM (10^{-4} M) caused no significant change in cell proliferation, i.e., the number of cells did not change. Based on these results, we believe that lower adenosine concentrations, e.g., 10^{-6} M and 10^{-7} M, would also not increase cell proliferation.

4. Hartzshtark et al. states that certain concentrations of various agents, including adenosine, increase skin cyclic-AMP content and thus cause a decrease in skin indentation. More specifically, Hartzshtark et al. indicates in a Table on page 379 that the adenosine concentration effective to reduce indentation was 0.1% (3.8×10^{-3} M). In addition, they note that they also tested adenosine "at one-third of the concentrations shown in the table [e.g., about 1.27×10^{-3} M], and at this level [adenosine was] ineffective" (bottom of page 378 to top of page 379). The presently pending claims recite a maximum concentration of adenosine of 10^{-4} M, and require that there is no increase in dermal cell proliferation. The results in Hartzshtark indicate that a concentration of adenosine of 10^{-4} M or lower would be even less effective than one-third of 0.1% (1.27×10^{-3} M), which was ineffective in their testing.

5. We have obtained a translation of the German patent application, which is attached to this declaration as Exhibit B. Our comments are based on this translation. The German patent application describes the use of adenosine for increasing cell proliferation in human skin (see, e.g., the title and claim 1). However, our testing, as described above, has shown that low

concentrations of adenosine do not increase dermal cell proliferation. Thus, when the German patent application states that concentrations of adenosine as low as 0.001% are useful for increasing cell proliferation, we believe that the German patent application must be mistaken. There is one paragraph in the German patent application that states the 0.001% number, and this is in a very broad range from 0.001 to 10% by weight of a cosmetic composition (at page 9, 4th full paragraph). Other sections of the German patent application recite higher concentrations. For example, the claims, recite 0.01 to 10%, with a preferred concentration of 0.1 to 6%. More importantly, each of the six Examples lists a relatively high concentration of 0.1% adenosine. Thus, based on our own testing of skin fibroblasts, which make up a large part of the dermis, we believe that the extremely broad range of adenosine concentrations listed in the German patent application is not supported by reality. The low end of this unsupported range is 0.001%, which corresponds to 3.8×10^{-5} M adenosine. This is between the 10^{-4} M and 10^{-5} M concentrations recited in the claims of the present application. However, our claimed invention is based on the demonstration that the recited concentrations of adenosine do not increase cell proliferation. This is the exact opposite of the assertions in the German patent application. It is for these reasons that we believe the German patent application recitation of adenosine concentrations less than 10^{-4} M (0.00265%) cannot be valid, and thus the German patent application does not disclose the same invention as the claims in the present application.

We further declare that all statements made herein of our 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 issuing thereon.

Date:_____

_____
James G. Dobson, Jr., Ph.D

Date:_____

_____
Michael F. Ethier, Ph.D

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B

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The following documents are to be considered in the determination of patentability:

(56)

DE	34 47 618 C2
DE	43 23 615 A1
DE	33 19 282 A1
DE	26 17 919 A1
DE-OS	24 01 450
US	40 88 756
FR	26 51 434 A1
FR	26 49 610 A1
FR	26 47 342 A1
FR	26 34 374 A1
US	39 37 809
EP	04 84 199 B1
EP	02 56 472 A3
EP	02 56 472 A2

Derwent abstract, 84-227814/37 relating to J5 9134-707-A; JP Patents Abstracts of Japan: 63-152309 A., C-541, Nov. 8, 1988, Vol. 12, N° 421; 6-80564 A., C-1217, June 27, 1994, Vol. 18, N° 337;

(54) Use of an Effective Adenosine Concentration in Cosmetic or Dermatological Preparations.

(57) Use of Adenosine for Increasing Cell Proliferation in Human Skin.

DE 195 45 1 107 A1

The following information has been taken from the documents submitted by the applicant.

National Printing Office 04.97 702 023/445 9/24

DESCRIPTION

The present invention relates to the use of adenosine in cosmetic and dermatological preparations.

In a separate embodiment, the present invention relates to cosmetic and dermatological preparations for the prevention and therapy of cosmetic or dermatological skin changes such as, for example, skin aging.

The skin ages because of endogenous, genetically determined influences. Exogenous factors, such as UV-light and chemical irritants, can have cumulative effects and accelerate the natural aging processes. This produces a number of degenerative processes whose results include the following structural changes and insult in the dermis and epidermis (dermatoheliosis), depending on the magnitude of the factors:

a) Involution of the microvascular system.

b) Loosening and formation of wrinkles in part due to the reduction and cross-linking of collagen and accumulation of glucosaminoglycans (basic substance).

c) Flattening of the reticular plugs. In conjunction with this is the surface reduction between dermis and epidermis, through which substances for the nourishment and cleansing of the skin are exchanged.

d) Limited regenerative turnover in the epidermis in conjunction with abnormal formation of the horny layer (hornification) that leads to drying out of the skin.

e) Abnormal regulation of cell division (proliferation) and cell maturation (differentiation) in the epidermis resulting in atypical cells and polarity loss.

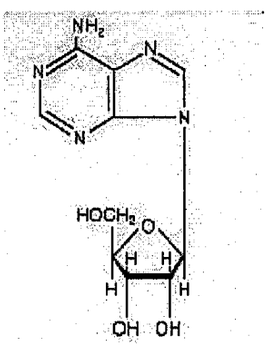
f) Local hyper-, hypo-, and abnormal pigmentations (age spots).

Accordingly, the present invention relates to products for the care and prevention of aged skin and for the therapy of the damage resulting from skin aging, in particular those phenomena listed in a) to f).

It was surprising and unforeseeable by the specialist that for enhancement of cell proliferation in human skin, preferably in cosmetics or dermatological preparations, remedies the drawbacks of the prior art [sic].

In one particular embodiment, the present invention accordingly relates to the use of adenosine for the care and prevention of aged skin and for the therapy of the damage resulting from skin aging, in particular those phenomena listed in a) to f).

Adenosine is characterized by the structural formula:



DE-OS 24 01 450 discloses pharmaceutical preparations for the relief of proliferative skin diseases containing of an active adenosine component. Furthermore, several prior art documents are known that deal with the cosmetic or dermatological use of adenosine phosphates (cyclic adenosine-3'5'-monophosphate = cAMP, adenosine monophosphate = AMP, adenosine diphosphate = ADP, adenosine triphosphate = ATP), for example US patent 4,702,913, in which the use of ATP and cAMP as substances enhancing skin moisture is discussed. The prior art does not, however, provide an indication of the use according to this invention.

According to the use as described in the invention, cosmetic or dermatological formulations can be composed as usual and used for the treatment, care and cleansing of the skin and/or hair, and as a make-up product in decorative cosmetics. They contain preferably 0.001 percent by weight to 10 percent by weight, in particular 0.01 percent by weight to 6 percent by weight, of the active substance combinations relative to the total weight of the product.

For use according to the invention, the cosmetic and dermatological preparations are applied in sufficient quantity to the skin and/or hair in the manner conventional for cosmetics.

The cosmetic and dermatological preparations can be in various forms for use according to the invention. For example, they can be a solution, a non-aqueous preparation, a water-in-oil (W/O) or oil-in-water (O/W) emulsion or microemulsion, a multiple emulsion such as a water-in-oil-in-water (W/O/W) emulsion, a gel, a solid stick, a salve or even an aerosol. Adenosine can also be advantageously administered in an encapsulated form according to the invention, for example in collagen matrices and other conventional encapsulation materials, for example as cellulose encapsulations, in gelatins, wax matrices or encapsulated in liposomes. In particular, wax matrices as disclosed in DE-OS 43 08 282 have been shown to be advantageous.

The addition of adenosine to aqueous systems or tenside preparations for cleansing the skin and the hair is also possible and advantageous according to the present invention.

In keeping with the use according to the invention, cosmetic and dermatological preparations can contain cosmetic adjuvants as conventionally used in such preparations, for example preservatives, bactericides, fragrances, anti-foaming agents, dyes, pigments having a coloring effect, thickeners, surfactants, emulsifiers, softening , wetting , and/or moisture-retaining substances, fats, oils, waxes or other conventional components of cosmetic or dermatological formulations like alcohols, polyols, polymers, foam stabilizers, electrolytes, organic solvents or silicone derivates.

In particular, adenosine can also be combined with antioxidants.

According to the invention, all antioxidants suitable or usable in cosmetic and/or dermatological applications can be used advantageously as antioxidants.

It is advantageous to select the antioxidants from the group comprised of the amino acids (for example, glycine, histidine, tyrosine, tryptophan) and their derivatives, imidazole (for example, urocanic acid) and their derivatives, peptides like D,L-carnosine, D-carnosine, L-carnosine and their derivatives (for example, anserine); carotenoids, carotene (for example, α-carotene, β-carotene, lycopine) and their derivatives; chlorogenic acid and its derivatives, liponic acid and its derivatives (for example, dihydroliponic acid), aurothioglucose, propylthiouracil and other thiols (for example, thioredoxin, glutathion, cysteine, cystine, cystamine, and their glycosyl-, N-acetyl-, methyl-, ethyl-, propyl-, amyl-, butyl-, and lauryl-, palmitoyl-, oleyl-, γ-linoleyl-, cholesteryl-, and glyceryl esters) and their salts, dilaurylthiodipropionate, distearylthiodipropionate, thiodipropionic acid and their derivatives (esters, ethers, peptides, lipids, nucleotides, nucleosides, and salts) and sulfoximine compounds (for example, buthionine sulfoximine, homocysteine sulfoximine, buthionine sulfone, penta-, hexa-, heptathionine sulfoximine) in very low, tolerable doses (for example, pmol to μmol/kg); in addition, (metal) chelators (for example, α-hydroxy fatty acids, palmitic acid, phytinic acid, lactoferrin), α-hydroxy acids (for example, citric acid, lactic acid, malic acid), humic acid, bile acid, bile extracts, bilirubin, biliverdin, EDTA, EGTA and their derivatives; unsaturated fatty acids and their derivatives (such as γ-linoleic acid, linolic acid, oleic acid), folic acid and its derivatives, ubiquinone and ubiquinol and their derivatives; vitamin C and its derivatives (for example, ascorbyl palmitate, Mg-ascorbyl phosphate, ascorbyl acetate), tocopherols and derivatives (for example, vitamin E acetate), vitamin A and derivatives (for example, vitamin A palmitate) and coniferyl benzoate of benzoic resin, rutic acid and its derivatives; butylhydroxytoluene, butylhydroxyanisol, nor-dihydroguaiac resin acid, nordihydroguaiaretic acid, trihydroxybutyrophenone, uric acid and its derivates, mannose and its derivatives, sesamol, sesamolin, zinc and its derivatives (for example, ZnO, $ZnSO_4$), selenium and its derivatives (for example, selenium methionine), stilbene and its derivatives (for example, stilbene oxide, trans-stilbene oxide) and the suitable derivatives according to the inventions (salts, esters, ethers, sugars, nucleotides, nucleosides, peptides, and lipids) of said active substances.

The quantity of the above antioxidants (one or a plurality of compounds) in the preparations is advantageously preferably 0.001 to 30 percent by weight, particularly preferred 0.05 – 20 percent by weight relative to the total weight of the formulation.

In so far as vitamin E and/or its derivatives represent the antioxidant or antioxidants, it is advantageous if their respective concentrations are chosen from the range of 0.001 – 10 percent by weight relative to the total weight of the formulation.

Insofar as vitamin A or vitamin A derivatives, or carotene or its derivatives are the antioxidant(s), it is advantageous if their respective concentrations are chosen from the range of 0.001 – 10 percent by weight relative to the total weight of the formulation.

Emulsions according to the invention are advantageous and contain, for example, the said fats, oils, waxes and other aliphatics, water and an emulsifier as it is conventionally used for such a formulation.

The lipid phase can thus be advantageously selected from the following group of substances:

- natural, synthetic and/or semi-synthetic oils like triglycerides of capric or caprylic acid, preferably castor oil;
- fats, waxes and other natural, synthetic and/or semi-synthetic aliphatics, preferably esters of fatty acids with low-carbon alcohols, for example with isopropanol, propylene glycol or glycerin, or esters of fatty alcohols with low-carbon alkanoic acids or with fatty acids;
- silicone oils like dimethylpolysiloxane, diethylpolysiloxane, diphenylpolysiloxane, and mixed forms of same;
- saturated compounds like hydrocarbons of natural or synthetic origin (vaseline, squalane).

The aqueous phase of the preparations according to the invention may advantageously contain low-carbon alcohols, diols or polyols and their ethers, preferably ethanol, isopropanol, propylene glycol, glycerin, ethylene glycol, ethylene glycol monoethyl or monobutyl ether, propylene glycol monomethyl, monoethyl or monobutyl ether, diethylene glycol monomethyl or monoethyl ether and analog products, further low-carbon alcohols such as ethanol, isopropanol, 1,2-propane diol, glycerin and particularly one or a plurality of thickeners which can be advantageously selected from the group of silicon dioxide, aluminum silicates, polysaccharides or their derivatives such as hyaluronic acid, xanthan gums, hydroxypropylmethyl cellulose, particularly advantageously from the polyacrylate group, preferably a polyacrylate from the group of so-called carbopols, for example type 980, 981, 1382, 2984, 5984 carbopols, or even the ETD (easy-to-disperse) 2001, 2020, 2050 types, either singly or in any combinations.

In particular, mixtures of the solvents mentioned above are used. When alcoholic solvents are used, water can be a further component.

According to the invention, emulsions are advantageous and contain, for example, the mentioned fats, oils, waxes and other aliphatics, and water and an emulsifier as are conventionally used for such formulations.

Gels according to the invention conventionally contain low-carbon alcohols, for example ethanol, isopropanol, 1,2-propane diol, glycerin and water or one of the above-named oils in the presence of a thickening agent, which in the case of oil-alcohol gels is preferably silicon dioxide or an aluminum silicate, or in the case of aqueous-alcoholic or alcoholic gels is preferably a polyacrylate.

As a propellant for sprayable preparations in aerosol containers according to the invention, the conventionally known highly-volatile, liquidized propellants, for example hydrocarbons (propane, butane, isobutane) are suitable and can be used alone or in mixtures with each other. Compressed air can also be used advantageously.

Preparations according to the invention can furthermore advantageously contain substances that absorb UV-rays in the UVB range, whereby the total quantity of filter substance, for example 0.1 percent by weight to 30 percent by weight, preferably 0.5 to 10 percent by weight, in particular 1.0 to 6.0 percent by weight relative to the total weight of the preparations, in order to provide cosmetic preparations that protect the hair or the skin against the entire range of ultraviolet radiation. They can also be used as sun screens for the hair or the skin.

If the emulsions according to the invention contain UVB filtering agents, they can be oil-soluble or water-soluble. Advantageous oil-soluble UVB filters according to the invention include, for example:

- 3-benzylidene camphor derivatives, preferably 3-(4-methylbenzylidene) camphor, 3-benzylidene camphor;
- 4-amino benzoic acid derivatives, preferably 4-(dimethylamino)- benzoic acid (2-ethylhexyl) ester, 4-(dimethylamino) benzoic acid amyl ester;
- Esters of cinnamic acid, preferably 4-methoxycinnamic acid (2-ethylhexyl) ester, 4-methoxycinnamic acid isopentyl ester
- Esters of salicylic acid, preferably salicylic acid (2-ethylhexyl) ester, salicylic acid (4-isopropylbenzyl) ester, salicylic acid homomenthyl ester;
- Derivatives of benzophenone, preferably 2-hydroxy-4-methoxybenzophenone, 2-hydroxy-4-methoxy-4'-methlylbenzophenone, 2,2'-dihydroxy-4-methoxybenzophenone;
- Esters of benzalmalonic acid, preferably 4-methoxybenzalmalonic acid di(2-ethylhexyl)ester, -2,4,6-trianilinio-(p-carbo-2'-ethyl-1'-hexyloxy)-1,3,5 triazine.

Advantageous water-soluble UVB filters are, for example:

- Salts of 2-phenylbenzimidazol-5-sulfonic acid like its sodium, potassium, or its triethanol ammonium salt, and sulfonic acid itself;
- Sulfonic acid derivates of benzophenones, preferably 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid and its salts;
- Sulfonic acid derivatives of 3-benzylidene camphor such as 4-(2-oxo-3-bornylidene methyl) benzene sulfonic acid, 2-methyl-5-(2-oxo-3-bornylidene methyl) sulfonic acid and its salts.

The list of cited UVB filters that can be used together with the active substance combinations according to the invention is, of course, not restricted.

The subject of the invention is also the use of a combination of adenosine with at least one UVB filter as an antioxidant, or the use of adenosine with at least one UVB filter as an antioxidant in a cosmetic or dermatological preparation.

It can also be advantageous if adenosine is combined with UVA filters that are conventionally contained in cosmetic preparations. These substances are preferably derivatives of dibenzoyl methane, in particular 1-(4'-tert.-butylphenyl)-3-(4'-methoxyphenyl) propane-1,3-dione and 1-phenyl-3-(4'-isopropylphenyl) propane-1,3-dione. The combinations or preparations that contain these combinations, are also the object of the invention. Those quantities used for the UVB combination can be used.

A subject of the invention is also the use of combinations of adenosine with at least one UVA filter as an antioxidant, or the use of a combination of adenosine with at least one UVA filter as an antioxidant in a cosmetic or dermatological preparation.

A subject of the invention is also the use of a combination of adenosine with at least one UVA filter and at least one UVB filter as an antioxidant, or the use of a combination of adenosine with at least one UVA filter and at least one UVB filter as an antioxidant in a cosmetic or dermatological preparation.

Cosmetic and dermatological preparations having an active adenosine content can also contain inorganic pigments that are conventionally used in cosmetics for the purpose of protecting the skin against UV rays. These are oxides of titanium, zinc, iron, zirconium, silicon, manganese, aluminum, cerium and mixtures thereof as well as alterations in which the oxides are the active substances.

Titanium-dioxide-based pigments are particularly preferred.

The cosmetic and dermatological preparations for the protection of hair against UV rays pursuant to the invention, are for example, shampoos, preparations applied when rinsing the hair before or after shampooing, before or after permanent waving, before or after dying or bleaching the hair, preparations for blow drying or setting the hair, preparations for dying or bleaching, hairdressing and treatment lotion, hair lacquer, or permanent waving agents.

The cosmetic and dermatological [preparations] contain active ingredients and adjuvants as in conventional preparations of this type for hair care and hair treatment. The adjuvants that are used are preservatives, surfactants, foam inhibiting substances, thickeners, emulsifiers, fats, oils, waxes, organic solvents, bactericides, perfumes, dyes or pigments whose purpose is to color the hair or the cosmetic or dermatological preparation itself, electrolytes, and substances against oily hair.

According to the present invention, electrolytes are understood to be water-soluble alkali, ammonia, alkaline earth (including magnesium) and zinc salts of inorganic anions and a variety of mixtures of said salts, whereby it must be assured that said salts are pharmaceutically and cosmetically safe.

The anions according to the invention are preferably chosen from the group of chlorides, sulfates and hydrogen sulfates, phosphates, hydrogen phosphates and linear and cyclic oligophosphates as well as carbonates and hydrogen carbonates.

Cosmetic preparations as represented by skin cleansing agents or shampoos preferably contain at least one anionic, non-ionic or amphoteric surface-active substance or also a mixture of said substances, adenosine in aqueous medium and an adjuvant as are conventionally used. The surface-active substances or the mixtures of said substances can be used at a concentration between 1 percent by weight and 60 percent by weight in the shampoo.

If the cosmetic and dermatological preparations are in the form of a lotion that is rinsed out, for example before or after bleaching, before or after shampooing, between two shampoo applications, before or after permanent wave treatment, then aqueous or water-alcohol solutions are used that may contain surface-active substances whose concentration can be between 0.1 and 10 percent by weight, preferably between 0.2 and 5 percent by weight

Said cosmetic or dermatological preparations can also be aerosols having the conventional adjuvants.

A cosmetic preparation in the form of a lotion that is not rinsed out, in particular a hair setting lotion, a lotion that is used when blow-drying hair, a hairdressing and treatment lotion

generally is an aqueous, alcoholic or water-alcohol solution and contains at least one cationic, anionic, non-ionic, or amphoteric polymer, or their mixture as well as adenosine in an effective concentration. The quantity of the polymers used is, for example, between 0.1 and 10 percent by weight, preferably between 01. and 3 percent by weight

Cosmetic preparations for the treatment and care of hair that contain adenosine can be non-ionic or anionic type emulsions. Along with water, non-ionic emulsions contain oils or fatty alcohols that can be also polyethoxylated or polypropoxylated, for example, or mixtures comprised of both organic components. Said emulsions may contain cationic surface-active substances.

According to the invention, cosmetic preparations for the treatment and care of the hair can be gels that, along with an effective concentration of adenosine and conventional solvents, preferably contain water, organic thickening agents such as gum arabic, xanthan gum, sodium alginate; derivatives of cellulose, preferably methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose or inorganic thickening agents like aluminum silicates such as bentonite, or a mixture of polyethylene glycol and polyethylene glycol stearate or distearate. The gel contains the thickening agent in a quantity e.g. between 0.1 and 30 percent by weight, and preferably between 0.5 and 15 percent by weight.

Preferably, the quantity of adenosine in a particular product for the hair is 0.05 percent by weight to 10 percent by weight, in particular 0.5 percent by weight to 5 percent by weight, relative to the total weight of the product.

According to the invention, aqueous cosmetic cleansing agents or low-water or anhydrous cleansing concentrates used for aqueous cleansing can contain anionic, non-ionic and/or amphoteric tensides, such as:

- conventional soaps, for example sodium salts of fatty acids
- alkyl sulfates, alkyl ether sulfates, alkane and alkylbenzene sulfonates
- sulfoacetate
- sulfobetaine
- sarcosinate
- amidosulfobetaine
- sulfosuccinate
- butanedioic acid half-ester
- alkylether carboxylate
- protein-fatty acid condensates
- alkyl betaine and amidobetaine
- fatty acid alkanolamide
- polyglycol ether derivatives

Cosmetic preparations that are cosmetic cleansing preparations for the skin can be in liquid or solid form. Along with adenosine, they preferably contain at least one anionic, non-

ionic or amphoteric surface-active substance or mixtures thereof, and one or a plurality of conventional electrolytes as desired. The surfactants can be present in the cleansing preparation at a concentration between 1 and 94% by weight relative to the total weight of the preparation.

Along with an effective concentration of adenosine, cosmetic preparations that are shampoos contain preferably at least one anionic, non-ionic or amphoteric surface-active substance or a mixture thereof, or possibly a conventional electrolyte and adjuvant according to the invention. The surface-active substance can be in a concentration between 1% by weight and 94% by weight in the shampoo.

In addition to the above-cited tensides, the preparations according to the invention contain water and possibly the conventional cosmetic additives such as fragrance, thickeners, dyes, deodorants, antimicrobial substances, moisturizing agents, complexing and sequestration agents, pearl luster agents, plant extracts, vitamins, active substances, and the like.

The present invention also includes a cosmetic process for protection of the skin and hair against oxidative or photoxidative processes which is characterized in that a cosmetic agent containing an effective adenosine concentration is applied in sufficient quantity to the skin or hair.

The adenosine content in said preparations is preferably 0.001% to 10 % by weight, and especially 0.01 to 6 percent by weight relative to the total weight of the preparations.

The subject of the invention is also the method for manufacturing the cosmetic products according to the invention and is characterized in that adenosine is incorporated into cosmetic and dermatological formulations in a manner known per se.

The following examples are intended to clarify the invention but not restrict it. All indications of quantities, portions and percentages, unless otherwise indicated, refer to the weight and the total quantity or to the total weight of the preparation.

Example 1

O/W Sunscreen Lotion

	Wt. %
Cetearyl alcohol	2.50
PEG-40 castor oil / sodium cetearyl sulfate	
Caprylic / capric triglyceride	4.00
Octyl stearate	4.00
Octyl methoxycinnamate	5.50
Butyl methoxydibenzolyl methyl	0.70
Cyclodimethicone	1.00
Carbomer	0.27
NaOH (45%)	0.22
Na_3 HEDTA	1.00

Butylene glycol	5.00
Adenosine	0.10
Preservative / fragrance	q.s.
Water, add until	100.00

Example 2

O/W After-Sun Lotion

	Wt.-%
Stearic acid	2.00
Glyceryl stearate	1.00
Isopropyl palmitate	6.00
Caprylic / capric triglyceride	5.00
Buxus chinensis	2.00
Carbomer	0.20
NaOH (45%)	0.20
Glycerin	5.00
Ethanol	5.00
Adenosine	0.10
Preservative / fragrance	q.s.
Water, add until	100.00

Example 3

O/W Sun Cream

	Wt.-%
Stearic acid	3.50
Octyl dodecanol	1.00
Isopropyl palmitate	5.00
Cyclomethicone	4.00
Methylbenzylidene camphor	1.00
Butyl methoxy dibenzoyl methane	3.00
Cetyl alcohol	1.00
Na_3 HEDTA	5.00
NaOH (45%)	1.00

Glycerin	0.40
Adenosine	0.10
Preservative / fragrance	q.s.
Water, add until	100.00

Example 4

O/W Cream

	Wt.-%
Trilaureth-4-phosphate	2.00
Cera microcristallina, paraffinum liquidum	5.00
Isopropyl palmitate	5.00
Cetyl alcohol	5.00
Adenosine	0.10
Glycerin	5.00
Preservative / fragrance	q.s.
Water, add until	100.00

Example 5

O/W Cream

	Wt.-%
Glyceryl stearate	3.00
Behenyl alcohol	5.00
Isopropylene palmitate	3.00
Octyl dodecanol	3.00
Glycerin	5.00
Adenosine	0.10
Preservative / fragrance	q.s.
Water, add until	100.00

Example 6

O/W Cream

	Wt.-%
Polyglyceryl-3-diisostearate	2.50

Paraffin oil	15.00
Ceresin	3.00
Magnesium stearate	3.00
Magnesium sulfate	0.70
Adenosine	0.10
Glycerin	3.00
Preservative / fragrance	q.s.
Water, add until	100.00

PATENT CLAIMS

1. The use of adenosine for enhancing cell proliferation in human skin.
2. The use of adenosine for combating and relief of the symptoms of exogenous aging of the skin, preferably in cosmetic or dermatological preparations.
3. The use of adenosine according to Claim 1 or 2, characterized in that the adenosine in cosmetic or dermatological preparations is present in concentrations of 0.01% by weight to 10% by weight but particularly 0.1% by weight to 6% by weight relative to the total weight of the preparations.

Table 1. Adenosine Does Not Stimulate Human Skin Fibroblast Proliferation

Skin Fibroblast Cell Strain	Age	Sex	Adenosine	Cell Number (% of control)	
AG09605	30	F	control	100	7
AG09605	30	F	10μM	104±14	7
AG11730	84	M	control	100	7
AG11730	84	M	10μM	102±9	7
AG09605	30	F	control	100	6
AG09605	30	F	100μM	102±7	6
AG11730	84	M	control	100	7
AG11730	84	M	100μM	93±13	7

Values are mean ± SEM. n=number of experiments. There was no significant difference in adenosine-treated cells compared to controls.

Attorney's Docket No. 7917-045002 / (UMMC 97-32)

11/Declaration 1.132

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James G. Dobson, Jr. and Michael F. Ethier
Art Unit : 16415
Examiner : L. Channavajjala
Serial No. : 09/672,348
Filed : September 28, 2000
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Bet 3-15-02

Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132

We, James G. Dobson, Jr., Ph.D. and Michael F. Ethier, declare that:

1. We are the co-inventors of the subject matter claimed in the patent application captioned above ("the present application").

2. The present application claims methods of enhancing the condition of unbroken skin of a mammal, but without increasing dermal cell proliferation. Excess skin cell proliferation can cause scarring, discoloration, and a variety of other skin anomalies associated with hyperplasia. The method claims recite applying to the skin a composition including a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation. These claims have been rejected by the U.S. Patent & Trademark Office Examiner in a Final Office Action dated October 10, 2001, as allegedly anticipated by German Patent No. DE 195 45 107 A1 ("the German patent application) and by Hartzshtark et al., Experentia, 41:378-379 (1985) ("Hartzshtark et al.). We have reviewed these two references, and based on a careful review of the references and our experimental test results, we believe that they do not disclose the methods claimed in our present application.

3. We have conducted testing to show that an important feature of our claimed methods is correct, i.e., that concentrations of adenosine recited in the pending claims do not increase

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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.

February 13, 2002
Date of Deposit

Signature

Jeanine Mecherkany
Typed or Printed Name of Person Signing Certificate

proliferation of a major type of dermal cells, i.e., skin fibroblasts. In this testing, we cultured skin fibroblasts from two subjects, a 30 year-old female and an 84 year-old male. For each experiment, we used 35 mm culture dishes plated with fibroblasts at a density of 1×10^4 cells/cm^2. Adenosine was added to dishes the following day. For each adenosine-treated dish, a matching control dish was treated with vehicle. After 5 days in culture, we counted the total number of cells in the control dish, and then in the test dish. For each pair of culture dishes, the number of cells in the control dish was designated as 100% and the number of cells in the adenosine-treated dish was expressed as a percentage of the control dish. In each experiment, the mean and standard error for adenosine-treated dishes was generated from the total number of samples (n = 6 or 7) for each test and expressed as a percent of the control. The adenosine concentrations and results are listed in Table 1 attached to this declaration as Exhibit A. As shown, adenosine concentrations of both 10 ☒M (10^{-5} M) and 100 ☒M (10^{-4} M) caused no significant change in cell proliferation, i.e., the number of cells did not change. Based on these results, we believe that lower adenosine concentrations, e.g., 10^{-6} M and 10^{-7} M, would also not increase cell proliferation.

4. Hartzshtark et al. states that certain concentrations of various agents, including adenosine, increase skin cyclic-AMP content and thus cause a decrease in skin indentation. More specifically, Hartzshtark et al. indicates in a Table on page 379 that the adenosine concentration effective to reduce indentation was 0.1% (3.8×10^{-3} M). In addition, they note that they also tested adenosine "at one-third of the concentrations shown in the table [e.g., about 1.27×10^{-3} M], and at this level [adenosine was] ineffective" (bottom of page 378 to top of page 379). The presently pending claims recite a maximum concentration of adenosine of 10^{-4} M, and require that there is no increase in dermal cell proliferation. The results in Hartzshtark indicate that a concentration of adenosine of 10^{-4} M or lower would be even less effective than one-third of 0.1% (1.27×10^{-3} M), which was ineffective in their testing.

5. We have obtained a translation of the German patent application, which is attached to this declaration as Exhibit B. Our comments are based on this translation. The German patent application describes the use of adenosine for increasing cell proliferation in human skin (see, e.g., the title and claim 1). However, our testing, as described above, has shown that low

concentrations of adenosine do not increase dermal cell proliferation. Thus, when the German patent application states that concentrations of adenosine as low as 0.001% are useful for increasing cell proliferation, we believe that the German patent application must be mistaken. There is one paragraph in the German patent application that states the 0.001% number, and this is in a very broad range from 0.001 to 10% by weight of a cosmetic composition (at page 9, 4th full paragraph). Other sections of the German patent application recite higher concentrations. For example, the claims, recite 0.01 to 10%, with a preferred concentration of 0.1 to 6%. More importantly, each of the six Examples lists a relatively high concentration of 0.1% adenosine. Thus, based on our own testing of skin fibroblasts, which make up a large part of the dermis, we believe that the extremely broad range of adenosine concentrations listed in the German patent application is not supported by reality. The low end of this unsupported range is 0.001%, which corresponds to 3.8×10^{-5} M adenosine. This is between the 10^{-4} M and 10^{-5} M concentrations recited in the claims of the present application. However, our claimed invention is based on the demonstration that the recited concentrations of adenosine do not increase cell proliferation. This is the exact opposite of the assertions in the German patent application. It is for these reasons that we believe the German patent application recitation of adenosine concentrations less than 10^{-4} M (0.00265%) cannot be valid, and thus the German patent application does not disclose the same invention as the claims in the present application.

We further declare that all statements made herein of our 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 issuing thereon.

Applicant : James G. Dobson, and Michael F. Ethier
Serial No. : 09/672,348
Filed : September 28, 2000
Page : 4

Attorney's Docket 07917-045002 / (UMMC 97-32)

Date: 02/11/02

James G. Dobson, Jr., Ph.D

Date: 2/11/02

Michael F. Ethier

Michael F. Ethier, Ph.D

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Attorney's Docket N 07917-045002 / (UMMC 97-32)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James G. Dobson, Jr. and Michael F. Ethier
Art Unit : 1615
Examiner : L. Channavajjala
Serial No. : 09/672,348
Filed : September 28, 2000
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Commissioner for Patents
Washington, D.C. 20231

SUBMISSION OF SIGNED DELCARATION

Applicants filed a Response on February 11, 2002 that included an unsigned declaration. Applicants submit herewith the signed declaration for entry into the file along with the response.

No fees are believed due. However, please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-045002.

Respectfully submitted,

Date: 02-13-02

J. Peter Fasse
Reg. No. 32,983

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

20390012.doc

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February 13, 2002
Date of Deposit

Signature

Jeanine Mecharicasy
Typed or Printed Name of Person Signing Certificate

Attorney's Docket No.: 07917-045002
Client's Ref. No.: (UMMC 97-32)

OFFICIAL COMMUNICATION

FACSIMILE

FOR THE PERSONAL ATTENTION OF:

EXAMINER L. CHANNAVAJJALA

GROUP 1615 FAX NO: (703) [redacted] ~~7546-5215~~ 308-7924

Number of pages including this page 6

Applicant : James G. Dobson, Jr. and Michael F. Ethier
Serial No. : 09/672,348
Filed : September 28, 2000
Title : Treatment of Skin with Adenosine or Adenosine Analog

Art Unit : 1615
Examiner : L. Channavajjala

FACSIMILE COMMUNICATION

BOX AF
Commissioner for Patents
Washington, D.C. 20231

Examiner Channavajjala:

Attached to this facsimile communication cover sheet is the Submission of Signed Declaration Under 37 C.F.R. § 1.132, originally filed via first class mail on February 13, 2002, faxed this day of March 12, 2002, to Group 1615, the United States Patent and Trademark Office.

Respectfully submitted,

J. Peter Fasse

Date: March 12, 2002

J. Peter Fasse
Reg. No. 32,983

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Attorney's Docket No.: 07917-045002 / (UMMC 97-32)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James G. Dobson, Jr. and Michael F. Ethier	Art Unit	: 1615
		Examiner	: L. Channavajjala
Serial No.	: 09/672,348		
Filed	: September 28, 2000		
Title	: TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG		

BOX AF
Commissioner for Patents
Washington, D.C. 20231

NOTICE OF APPEAL

Applicants hereby appeal to the Board of Patent Appeals and Interferences from the action dated October 10, 2001, finally rejecting claims 70-79.

Applicants enclose herewith a petition for an extension of time under 37 CFR §1.136 to extend the time to respond to the final rejection, previously extended one month to February 10, 2002, for an additional one month to March 11, 2002, March 10, 2002 being a Sunday.

A check in the amount of $160 for the appeal fee is enclosed. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-045002.

Respectfully submitted,

Date: March 11, 2002

J. Peter Fasse
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3/22/2002 AWONDAF1 00000050 09672348
1 FC:219 160.00 OP

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March 11, 2002
Date of Deposit

Signature

Jeanine Mecherkany
Typed or Printed Name of Person Signing Certificate

Attorney's Docket No.: 07917-045002 / (UMMC 97-32)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : James G. Dobson, Jr. and Michael F. Ethier
Art Unit : 1615
Examiner : L. Channavajjala
Serial No. : 09/672,348
Filed : September 28, 2000
Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

Commissioner for Patents
Washington, D.C. 20231

PETITION FOR TWO-MONTH EXTENSION OF TIME

Pursuant to 37 CFR §1.136, applicants petition that the period to respond to the examiner's action mailed October 10, 2001, previously extended one month to February 10, 2002, be extended for an additional one month to March 11, 2002, March 10, 2002 being a Sunday.

A check for $145 (the two months extension fee less the $55 already paid) is enclosed.

Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-045002.

Respectfully submitted,

Date: March 11, 2002

J. Peter Fasse
Reg. No. 32,983

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225 Franklin Street
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3/22/2002 AWONDAF1 00000050 09672348
2 FC:216 145.00 OP

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March 11, 2002
Date of Deposit

Signature

Jeanine Mecherkany
Typed or Printed Name of Person Signing Certificate

Notice of Allowability	Application No.	Applicant(s)	
	09/672,348	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 *2-27-02 and 3-12-02*.
2. ☒ The allowed claim(s) is/are *70-79*.
3. ☐ The drawings filed on _____ 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

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

DETAILED ACTION

Receipt of request for extension of time & amendment, dated 2-27-02 and declaration dated 3-12-02 is acknowledged.

Allowable Subject Matter

Claims 70-79 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^{-4} M to 10^{-7} M, to the skin. The prior art of record teaches administering adenosine to skin for treating aging. However, the art of record utilizes concentrations much higher than claimed and also require that the amounts of adenosine used stimulate cell proliferation for the treatment. Whereas, instant claims are directed to treating skin without increasing the dermal cell proliferation. While the prior art does not recognize that increased cell proliferation result in adverse effects on skin such as discoloration, scarring etc., applicants have shown that using adenosine at the claimed concentrations do not result in adverse affects but still provide skin conditioning effects.

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

March 18, 2002

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

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

7590 03/21/2002

Gary L Creason
Fish & Richardson PC
225 Franklin Street
Boston, MA 02110-2804

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

DATE MAILED: 03/21/2002

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/672,348	09/28/2000	James G. Dobson	07917-045002	7733

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

TOTAL CLAIMS	APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
10	nonprovisional	YES	$640	$0	$640	06/21/2002

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 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

B. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

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. 07-01) Approved for use through 01/31/2004.

PART B - FEE(S) TRANSMITTAL

Complete and mail this form, together with applicable fee(s), to:

Box ISSUE FEE
Assistant Commissioner for Patents
Washington, D.C. 20231

MAILING 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)

7590 03/21/2002

Gary L Creason
Fish & Richardson PC
225 Franklin Street
Boston, MA 02110-2804

Note: The certificate of mailing below 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.

Certificate of Mailing

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(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/672,348	09/28/2000	James G. Dobson	07917-045002	7733

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

TOTAL CLAIMS	APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
10	nonprovisional	YES	$640	$0	$640	06/21/2002

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). Use of PTO form(s) and Customer Number are recommended, but not required.

❑ 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) attached.

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).

The COMMISSIONER OF PATENTS AND TRADEMARKS 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.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending on the needs of the individual case. Any comments on the amount of time required to complete this form should be sent to the Chief Information Officer, United States Patent and Trademark Office, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND FEES AND THIS FORM TO: Box Issue Fee, Assistant Commissioner for Patents, Washington, D.C. 20231

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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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/672,348	09/28/2000	James G. Dobson	07917-045002	7733

EXAMINER
CHANNAVAJJALA, LAKSHMI SARADA

ART UNIT	PAPER NUMBER
1615	

7590 03/21/2002

Gary L Creason
Fish & Richardson PC
225 Franklin Street
Boston, MA 02110-2804

DATE MAILED: 03/21/2002

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)

PTOL-85 (REV. 07-01) Approved for use through 01/31/2004.

PART B - FEE(S) TRANSMITTAL

Complete and mail this form, together with applicable fee(s), to: **Box ISSUE FEE**
Assistant Commissioner for Patents
Washington, D.C. 20231

MAILING 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)

7590 03/21/2002

Gary L Creason
Fish & Richardson PC
225 Franklin Street
Boston, MA 02110-2804

Note: The certificate of mailing below 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.

Certificate of Mailing

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 on the date indicated below.

Janet S. O'Connor	(Depositor's name)
Janet S. O'Conn	(Signature)
5/17/02	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/672,348	09/28/2000	James G. Dobson	07917-045002	7733

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

TOTAL CLAIMS	APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
10	nonprovisional	YES	$640	$0	$640	06/21/2002

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). Use of PTO form(s) and Customer Number are recommended, but not required.

- ☐ 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) attached.

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 (B) RESIDENCE: (CITY and STATE OR COUNTRY)

University of Massachusetts 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.
- ☐ 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).

The COMMISSIONER OF PATENTS AND TRADEMARKS 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) J. Peter Fasse (Date) 5/17/02

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.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending on the needs of the individual case. Any comments on the amount of time required to complete this form should be sent to the Chief Information Officer, United States Patent and Trademark Office, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND FEES AND THIS FORM TO: Box Issue Fee, Assistant Commissioner for Patents, Washington, D.C. 20231

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06/05/2002 CCHAU2 00000095 09672348
01 FC:242 640.00 OP
02 FC:561 30.00 OP

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#13
CK
6-17-02

Attorney's Docket No.: 07917-045002 / (UMMC 97-32)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James G. Dobson, Jr. and Michael F. Ethier	Art Unit	: 1615
		Examiner	: L. Channavajjala
Serial No.	: 09/672,348	Confirmation No.:	7733
Filed	: September 28, 2000	Notice of Allowance Date:	March 21, 2002
Title	: TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG		

BOX ISSUE FEE
Commissioner for Patents
Washington, D.C. 20231

COMMENTS ON STATEMENT OF REASONS FOR ALLOWANCE

These comments are submitted with applicants' Response to Notice of Allowance and payment of the issue fee in this application.

Applicants submit that the claims are allowable for at least all of the reasons of record in applicants' responses, and applicants do not concede that the Examiner's Statement of Reasons for Allowance is the only reason for which claims 70 to 79 are allowable. Futhermore, applicants note that the claimed concentration of adenosine is applied to the dermal cells.

No fees are believed due, however, please apply any charges or credits to our Deposit Account No. 06-1050, referencing Attorney Docket Number 07917-045002.

Respectfully submitted,

Date: May 17, 2002

J. Peter Fasse
Reg. No. 32,983

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

20438396.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, Washington, D.C. 20231.

5/17/02
Date of Deposit

Janet S. O'Connor
Signature

Janet S. O'Connor
Typed or Printed Name of Person Signing Certificate

(2) 09/672,348

Attorney's Docket No.: 07917-045002 / (UMMC 97-32)

#13 $

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Dobson et al.	Art Unit	: 1615
Serial No.	: 09/672,348	Examiner	: L. Channavajjala
Filed	: September 28, 2000	Confirmation No.:	7733
		Notice of Allowance Date: March 21, 2002	

Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

BOX ISSUE FEE
Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO NOTICE OF ALLOWANCE

In response to the Notice of Allowance mailed March 21, 2002, enclosed are a completed issue fee transmittal form PTOL-85b, transmittal of 2 sheets of formal drawings, Applicants' Comments on Statement of Reasons for Allowance, and a check for $670 for the required fee, including patent copies.

Please apply any additional charges or credits to our Deposit Account No. 06-1050, referencing attorney docket number 07917-045002.

Respectfully submitted,

Date: May 17, 2002

J. Peter Fasse
Reg. No. 32,983

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

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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.

5/17/02
Date of Deposit

Janet S. O'Connor
Signature

Janet S. O'Connor
Typed or Printed Name of Person Signing Certificate

OK to Enter

K.A

#14

Attorney's Docket No.: 07917-045002 / (UMMC 97-32)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Dobson et al.	Art Unit	: 1615
Serial No.	: 09/672,348	Examiner	: L. Channavajjala
Filed	: September 28, 2000	Notice of Allowance Date: March 21, 2002	
Title	: TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG		

Attention: Official Draftsman
Commissioner for Patents
Washington, D.C. 20231

TRANSMITTAL OF FORMAL DRAWINGS

In response to the Notice of Allowability mailed March 21, 2002, please substitute the enclosed two (2) sheets of formal drawings for the corresponding drawings presently in the application.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 07917-045002.

Respectfully submitted,

Date: May 17, 2002

J. Peter Fasse
Reg. No. 32,983

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

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CERTIFICATE OF MAILING BY FIRST CLASS MAIL

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5/17/02
Date of Deposit

Janet S. O'Connor
Signature

Janet S. O'Connor
Typed or Printed Name of Person Signing Certificate

03-02

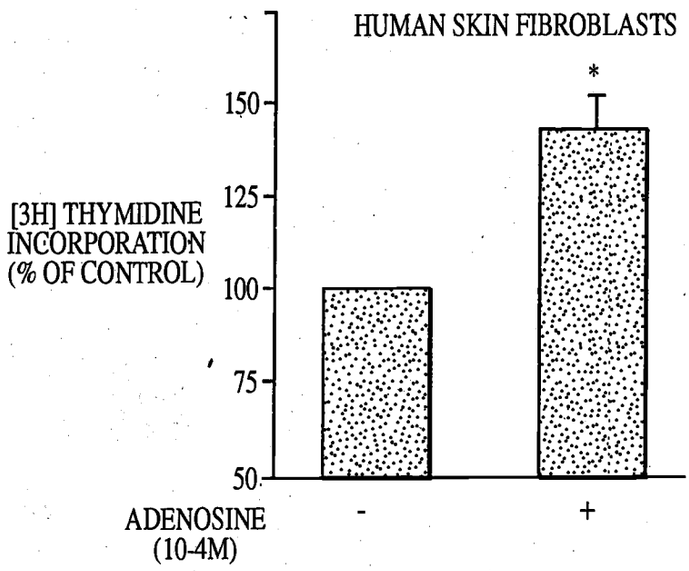

FIG. 1A

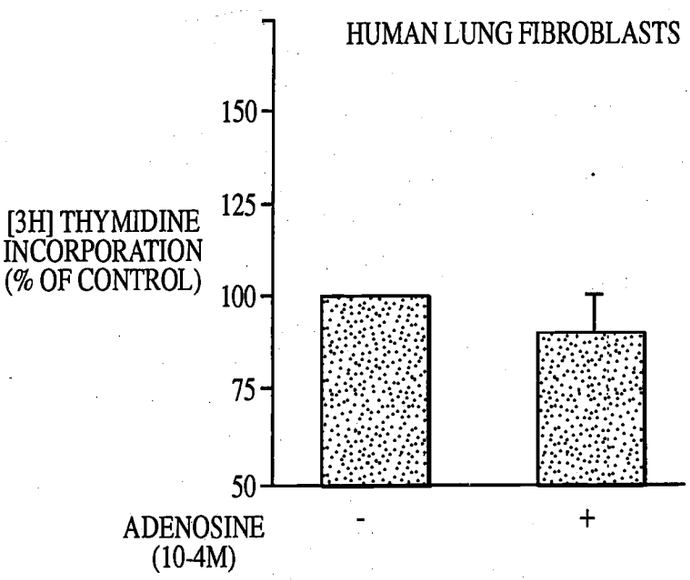

FIG. 1B

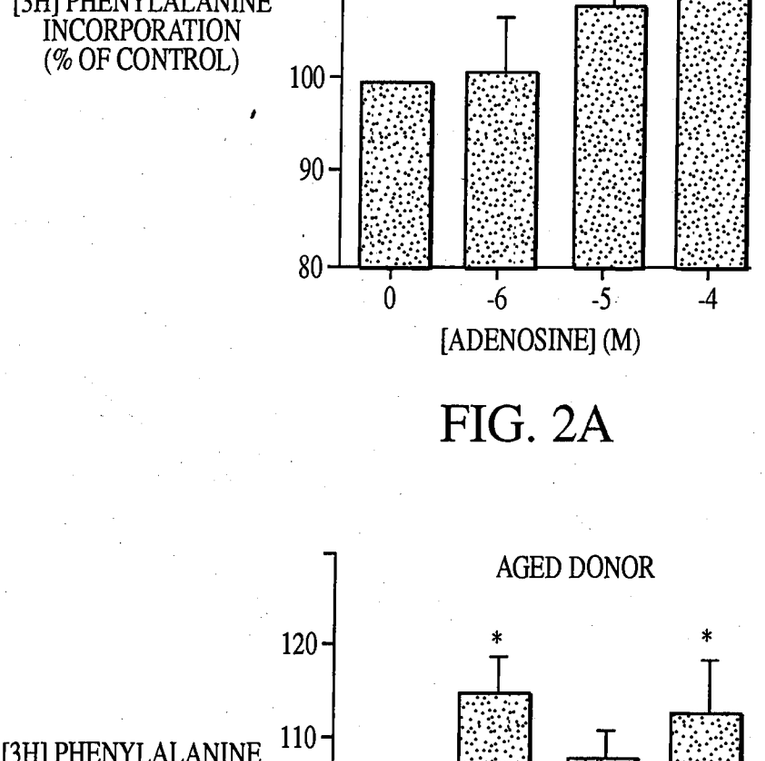
YOUNG DONOR
[3H] PHENYLALANINE INCORPORATION (% OF CONTROL)
120
110
100
90
80
*
0
-6
-5
-4
[ADENOSINE] (M)

FIG. 2A

AGED DONOR
[3H] PHENYLALANINE INCORPORATION (% OF CONTROL)
120
110
100
90
80
*
*
0
-6
-5
-4
[ADENOSINE] (M)

FIG. 2B

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SEP 28 2006

Please type a plus sign (+) inside this box → +

PTO/SB/121 (10-00)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Assistant Commissioner for Patents
Box CN
Washington, DC 20231

Please recognize the following address as the correspondence address:

☑ Customer Number 31127 → *Place Customer Number Bar Code Label here*

OR *Type Customer Number here*

☐ Request for Customer Number (PTO/SB/125) submitted herewith.

In the following listed application(s) or patent(s) :

Patent Number (if appropriate)	Application Number	Patent Date (if appropriate)	U.S. Filing Date
6,424,327	09/373,437	7/23/02	8/11/99

Typed or Printed Name	James J. Murphy	*(check one)* ☐ Applicant or Patentee
Signature		☐ Assignee of record of the entire interest. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
Date	September 28, 2006	☑ Attorney or Agent of record 34,503 (Reg. No.)
Address of signer:	Thompson and Knight LLP 1700 Pacific, Floor 31, Dallas, TX 75201	

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more that one signature is required, see below *.

☑ *Total of 1 forms are submitted.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Box CN, Washington, DC 20231.

FOR: VERIFICATION

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

PAYOR NUMBER
26161

P75M

FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS MN 55440-1022

DATE PRINTED
03/01/10

MAINTENANCE FEE REMINDER

According to the records of the U.S. Patent and Trademark Office (USPTO) the maintenance fee for the patent(s) listed below (for which the above address is on record as the fee address under 37 CFR 1.363) has not been paid within the six-month period set forth in 37 CFR 1.362(d). THE MAINTENANCE FEE MAY STILL BE PAID WITH THE APPLICABLE SURCHARGE SET FORTH IN 37 CFR 1.20(h), WITHIN THE SIX-MONTH GRACE PERIOD SET FORTH IN 37 CFR 1.362(e).

Unless payment of the maintenance fee and the applicable surcharge is received in the USPTO within the six-month grace period, THE PATENT WILL EXPIRE AS OF THE END OF THE GRACE PERIOD. 35 U.S.C. 41(b).

The total payment due is the amount required on the date the fee is paid (and not necessarily the amount indicated below). All USPTO fees (including maintenance fees) are subject to change. Customers should refer to the USPTO Web site (www.uspto.gov) or call the Maintenance Fee Branch at 571-272-6500 for the most current fee amounts for the correct entity status before submitting payment. The total payment due indicated below is based on the entity status according to current Office records (shown below).

Timely payment of the total payment due is required in order to avoid expiration of the patent. A maintenance fee payment can be timely made using the certificate of mailing or transmission procedure set forth in 37 CFR 1.8.

PATENT NUMBER	FEE AMT	MAINT. SURCHG	U.S. APPL NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAY-MENT YEAR	SMALL ENTITY?	TOTAL PYMT DUE	ATTORNEY DOCKET NUMBER
6423327	1240	65	09672348	07/23/02	09/28/00	8	YES	1305	07917-045002
6424982	1240	65	09288994	07/23/02	04/09/99	8	YES	1305	080759-0015

The maintenance fee and the applicable surcharge can be paid quickly and easily over the Internet at www.uspto.gov by electronic funds transfer (EFT), credit card, or USPTO deposit account payment methods. The mailing address for all maintenance fee payments not electronically submitted over the Internet is: U.S. Patent and Trademark Office, P.O. Box 979070, St. Louis, MO 63197-9000.

Direct any questions about this notice to: Mail Stop M Correspondence, Director of the United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.

NOTE: This notice was automatically generated based on the amount of time that elapsed since the date a patent was granted. It is possible that the patent term may have ended or been shortened due to a terminal disclaimer that was filed in the application. Also, for any patent that issued from an application filed on or after June 8, 1995 containing a specific reference to an earlier filed application or applications under 35 U.S.C. 120, 121, or 365(c), the patent term ends 20 years from the date on which the earliest such application was filed, unless the term was adjusted or extended under 35 U.S.C. 154 or 156. Patentee should determine the relevant patent term for a patent before paying the maintenance fee.

MF4401 (7/2007)

L8 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1989:121100 CAPLUS
DOCUMENT NUMBER: 110:121100
TITLE: Skin cosmetics containing evening primrose oil and radical scavengers and spleen extracts
INVENTOR(S): Marty, Jean Pierre
PATENT ASSIGNEE(S): Roussel-UCLAF, Fr.
SOURCE: Fr. Demande, 8 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2606279	A1	19880513	FR 1986-16154	19861120
FR 2606279	B1	19940218		

AB **Cosmetic** and dermatol. compns. contain evening primrose oil, spleen tissue exts., and .gtoreq.1 radical scavengers and singlet O inhibitors. Radical scavengers are e.g. terpenes, lipid-sol. carrot exts., and .alpha.-tocopherol. These **cosmetics** retard the signs of **aging** of the skin. Evening primrose oil contains essential fatty acids that inhibit dryness of the skin, loss of elasticity, and transdermal loss of water. The formulations may optionally contain **adenosine** phosphate, e.g. ATP, and addnl. caffeine or theophylline that inhibits phosphodiesterase and cAMP degrdn. A **cosmetic** cream contained glucate SS 3, glucamate SSE-20 2, evening primrose oil 10, fatty acid esters 7, plant sterols 5, lipid-sol. carrot ext. 0.2, .alpha.-tocopherol 0.05, UV absorbers 3, Mg Al silicate 1.2, spleen ext. 5, preservatives q.s., Na pyrrolidonecarboxylate 2, hyaluronic acid 0.03, phosphorylated ATP riboside 0.025, cAMP 0.02, perfume 0.3, and H2O to 100% by wt.

L8 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:400614 CAPLUS
DOCUMENT NUMBER: 103:614
TITLE: The use of indentometry to study the effect of agents known to increase skin cAMP content
AUTHOR(S): Hartzshtark, A.; Dikstein, S.
CORPORATE SOURCE: Sch. Pharm., Hebrew Univ., Jerusalem, Israel
SOURCE: Experientia (1985), 41(3), 378-9
CODEN: EXPEAM; ISSN: 0014-4754
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Applied to the skin of human forehead, **adenosine** [58-61-7], isoproterenol bitartarte [59-60-9], terbutaline sulfate [23031-32-5], papaverine [58-74-2], and N6-O2-dibutyryl cAMP [362-74-3] reduced the degree of skin indentation resulting from application of standardized wt. It seems that this change (indicative of a firmer, younger skin) involves cAMP [60-92-4], since the decrease in identability occurs at those drug concns. known to increase cAMP concns. in skin. These findings may contribute to the development of **cosmetic** and pharmaceutical prepns. for counteracting the **aging** of human skin.

Cosmetics
Skin aging
Sunscreens
Topical drug delivery systems
(use of **adenosine** against skin **aging**)

L8 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:517347 CAPLUS
DOCUMENT NUMBER: 121:117347
TITLE: Anti-aging cosmetics containing plant extracts and skin-whitening agents
INVENTOR(S): Iwanaga, Atsufumi
PATENT ASSIGNEE(S): Sansei Seiyaku Kk, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 27 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 06048934	A2	19940222	JP 1993-78368	19930405

PRIORITY APPLN. INFO.: JP 1992-141571 19920602
IT 50-81-7, Ascorbic acid, biological studies 56-12-2, .gamma.-Aminobutyric acid, biological studies 60-92-4, **Adenosine**
-3',5'-cyclicmonophosphate 123-31-9, Hydroquinone, biological studies 302-79-4, Retinoic acid 501-30-4, Kojic acid 551-15-5, Liquiritin 7665-99-8, Guanosine-3',5'-cyclic monophosphate 119588-63-5
RL: BIOL (Biological study)
(anti-**aging cosmetics** contg. plant ext. and)

L8 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:405929 CAPLUS
DOCUMENT NUMBER: 127:39497
TITLE: Use of adenosine against skin aging
INVENTOR(S): Schoenrock, Uwe; Pollet, Dieter; Schreiner, Volker; Maerker, Uwe; Kruse, Inge
PATENT ASSIGNEE(S): Beiersdorf A.-G., Germany
SOURCE: Ger. Offen., 8 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19545107	A1	19970605	DE 1995-19545107	19951204

AB **Adenosine** is useful in **cosmetic** and dermatol. prepns. for treatment of natural, chem. induced, or UV-induced skin **aging** and its sequelae by stimulation of cell proliferation in the skin. Thus, an oil-in-water sunscreen cream contained stearic acid 3.50, octyldodecanol 1.00, iso-Pr palmitate 5.00, cyclomethicone 4.00, methylbenzylidenecamphor 1.00, butylmethoxydibenzoylmethane 3.00, cetyl alc. 1.00, tri-Na HEDTA 5.00, 45% NaOH 1.00, glycerin 0.40, **adenosine** 0.10, preservative, perfume, and water to 100.00 wt.%.

IT Cell proliferation

WEST

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Main Menu | Search Form | Posting Counts | Show S Numbers | Edit S Numbers | Preferences

Search Results -

Term	Documents
ADENOSINE.DWPI,EPAB,JPAB,USPT.	15936
ADENOSINES.DWPI,EPAB,JPAB,USPT.	322
(2 AND ADENOSINE).USPT,JPAB,EPAB,DWPI.	4

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Refine Search: `l2 and adenosine` Clear

Search History

Today's Date: 10/1/2001

DB Name	Query	Hit Count	Set Name
USPT,JPAB,EPAB,DWPI	l2 and adenosine	4	L4
USPT,JPAB,EPAB,DWPI	l2 same adenosine	1	L3
USPT,JPAB,EPAB,DWPI	(topical or skin or cosmetic) same (aging or wrinkles or elasticity or moisturiz$ or elasticity) same (angiogenic or pdgf or vegf or fgf or fibroblast adj growth adj factor)	45	L2
USPT,JPAB,EPAB,DWPI	(topical or skin or cosmetic) same (aging or wrinkles or elasticity or moisturiz$ or elasticity) same (angigenic or pdgf or vegf or fgf or fibroblast adj growth adj factor)	38	L1

L8 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:405929 CAPLUS
DOCUMENT NUMBER: 127:39497
TITLE: Use of adenosine against skin aging
INVENTOR(S): Schoenrock, Uwe; Pollet, Dieter; Schreiner, Volker; Maerker, Uwe; Kruse, Inge
PATENT ASSIGNEE(S): Beiersdorf A.-G., Germany
SOURCE: Ger. Offen., 8 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19545107	A1	19970605	DE 1995-19545107	19951204

AB **Adenosine** is useful in **cosmetic** and dermatol. prepns. for treatment of natural, chem. induced, or UV-induced skin **aging** and its sequelae by stimulation of cell proliferation in the skin. Thus, an oil-in-water sunscreen cream contained stearic acid 3.50, octyldodecanol 1.00, iso-Pr palmitate 5.00, cyclomethicone 4.00, methylbenzylidenecamphor 1.00, butylmethoxydibenzoylmethane 3.00, cetyl alc. 1.00, tri-Na HEDTA 5.00, 45% NaOH 1.00, glycerin 0.40, **adenosine** 0.10, preservative, perfume, and water to 100.00 wt.%.

IT Cell proliferation

Office Copy 09/672349

Office Copy 09/672,348

By WL:

L8 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER:	1985:400614 CAPLUS
DOCUMENT NUMBER:	103:614
TITLE:	The use of indentometry to study the effect of agents known to increase skin cAMP content
AUTHOR(S):	Hartzshtark, A.; Dikstein, S.
CORPORATE SOURCE:	Sch. Pharm., Hebrew Univ., Jerusalem, Israel
SOURCE:	Experientia (1985), 41(3), 378-9
	CODEN: EXPEAM; ISSN: 0014-4754
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Applied to the skin of human forehead, **adenosine** [58-61-7], isoproterenol bitartarte [59-60-9], terbutaline sulfate [23031-32-5], papaverine [58-74-2], and N6-O2-dibutyryl cAMP [362-74-3] reduced the degree of skin indentation resulting from application of standardized wt. It seems that this change (indicative of a firmer, younger skin) involves cAMP [60-92-4], since the decrease in identability occurs at those drug concns. known to increase cAMP concns. in skin. These findings may contribute to the development of **cosmetic** and pharmaceutical prepns. for counteracting the **aging** of human skin.

WEST

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Search Results -

Term	Documents
SKIN.DWPI,EPAB,JPAB,USPT.	274095
SKINS.DWPI,EPAB,JPAB,USPT.	18508
GRAFT.DWPI,EPAB,JPAB,USPT.	78226
GRAFTS.DWPI,EPAB,JPAB,USPT.	10959
WRINKLE.DWPI,EPAB,JPAB,USPT.	15312
WRINKLES.DWPI,EPAB,JPAB,USPT.	23264
DRYNESS.DWPI,EPAB,JPAB,USPT.	59566
DRYNESSES.DWPI,EPAB,JPAB,USPT.	7
LAXITY.DWPI,EPAB,JPAB,USPT.	383
LAXITIES.DWPI,EPAB,JPAB,USPT.	10
(SKIN ADJ GRAFT SAME (WRINKLE OR DRYNESS OR LAXITY OR ELASTICITY OR MOISTURIZ$)).USPT,JPAB,EPAB,DWPI.	22

There are more results than shown above. Click here to view the entire set.

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Refine Search: `skin adj graft same (wrinkle or dryness or laxity or elasticity or moisturiz$)` Clear

Search History

Today's Date: 10/2/2001

DB Name	Query	Hit Count	Set Name
USPT,JPAB,EPAB,DWPI	skin adj graft same (wrinkle or dryness or laxity or elasticity or moisturiz$)	22	L5
USPT,JPAB,EPAB,DWPI	skin adj graft same (adenosine or aging)	16	L4
USPT,JPAB,EPAB,DWPI	skin adj5 graft adj10 (adenosine or aging)	0	L3
USPT,JPAB,EPAB,DWPI	transdermal same patch same (aging or adenosine)	13	L2
USPT,JPAB,EPAB,DWPI	transdermal adj patch adj10 (aging or adenosine)	0	L1

```
> d his full

     (FILE 'HOME' ENTERED AT 12:58:54 ON 01 OCT 2001)

     FILE 'CAPLUS, EMBASE, MEDLINE, BIOSIS' ENTERED AT 12:59:05 ON 01 OCT 2001
L1        967228 SEA ABB=ON  PLU=ON  (ADENOSINE OR TOYOCAMYCIN OR METHYLADENOSIN
                 E OR AMP OR ADP OR ATP OR PHENYLISOPROPYL ADENOSINE OR
                 METHYLISOGUANOSINE OR CYCLOPENTYLADENOSINE)
L2         18899 SEA ABB=ON  PLU=ON  L1 (P) (DNA SYNTHESIS OR MITOSIS OR
                 MITOGENESIS OR THYMIDINE (5A) UPTAKE OR PROTEIN SYNTHESIS)
L3         18979 SEA ABB=ON  PLU=ON  L1 (P) (DNA (A) SYNTHESIS OR MITOSIS OR
                 MITOGENESIS OR THYMIDINE (5A) UPTAKE OR PROTEIN (A) SYNTHESIS)

L4            24 SEA ABB=ON  PLU=ON  L3 (P) (SKIN (A) CELLS OR DERMAL (A) CELLS
                 OR DERMAL (A) FIBROBLASTS)
L5            12 SEA ABB=ON  PLU=ON  L3 (P) (SKIN (A) CELLS OR DERMAL (A) CELLS
                 OR DERMAL (A) FIBROBLASTS) (P) (MULITPLICATION OR PROLIFERATION
                  OR CELL (A) NUMBERS)
L6             4 DUP REM L5 (8 DUPLICATES REMOVED)
                 D L6 IBIB KWIC 1-
L7             3 SEA ABB=ON  PLU=ON  L1 (5A) (SKIN (A) CELLS OR DERMAL (A)
                 CELLS OR DERMAL (A) FIBROBLASTS) (5A) (MULITPLICATION OR
                 PROLIFERATION OR CELL (A) NUMBERS)
                 D L7 IBIB KWIC 1-
L8          4405 SEA ABB=ON  PLU=ON  L1 (5A) (DNA (A) SYNTHESIS OR MITOSIS OR
                 MITOGENESIS OR THYMIDINE (5A) UPTAKE OR PROTEIN (A) SYNTHESIS)

L9             1 SEA ABB=ON  PLU=ON  L1 (5A) (DNA (A) SYNTHESIS OR MITOSIS OR
                 MITOGENESIS OR THYMIDINE (5A) UPTAKE OR PROTEIN (A) SYNTHESIS)
                 (P) (DERMAL (A) CELLS OR DERMAL (5A) FIBROBLASTS OR SKIN (2A)
                 CELLS)
```

=> d l8 ibib kwic

L8 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
ACCESSION NUMBER: 2001:610985 CAPLUS
TITLE: Age dependence of signal transduction and cell signaling as a major factor of intervention into the aging process
AUTHOR(S): Niedermuller, H.; Basota, I.; Strasser, A.; Hofecker, G.
CORPORATE SOURCE: Institut fur Physiologie und Ludwig Boltzmann-Institut fur Experimentelle Gerontologie der Veterinarmedizinischen, Universitat Wien, Vienna, A-1210, Austria
SOURCE: Arch. Gerontol. Geriatr. (2001), 33(2), 151-161
CODEN: AGGEDL; ISSN: 0167-4943
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nowadays, it has become necessary to investigate the mechanisms underlying **aging** changes and their modulation. Of particular interest are the cellular and mol. level cell-cell and cell-matrix interactions. Thus, we partly detd. in rats aged 9 and 31 mo (a) the concns. and the activities of signal mols., such as G-proteins, cyclic **adenosine** monophosphate (cAMP) and kinases (cellular) and collagens, proteoglycans (PG) and fibronectin (extracellular) in vivo in the skin of the back, as well as in isolated fibroblasts and keratinocytes; (b) the cell proliferation and (c) we tried to retard the **aging** process in the skin by **topical** application (or by addn. to cell cultures) of fetal mesenchymal cells, PGs, and soya matrix and we compared the above mentioned parameters with those obtained by stimulation of skin cells with growth factors. There are indications that there is (a) no change in the quantity of Gs-proteins but a redn. of the binding capacity. We found lower concns. of cAMP, a reduced activity of protein kinase C in vivo, a higher collagen crosslinking, a lower PG concn. and no change of the amt. of fibronectin in the old rat's skin and (b) there is a more or less extensive restoration of these parameters by all the above mentioned stimuli. So, we conclude that all the above mentioned influences modulate the **aging** process of the skin and its cells by intervention into the signaling pathways, by mediating new signals to the cells and hence by readjusting damaged feedforward systems in the cells.

=> d l8 ibib kwic 2-8

L8 ANSWER 2 OF 8 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001220114 MEDLINE
DOCUMENT NUMBER: 21209817 PubMed ID: 11314862
TITLE: Mitochondrial medicine--molecular pathology of defective oxidative phosphorylation.
AUTHOR: Fosslien E
CORPORATE SOURCE: Department of Pathology, College of Medicine, University of Illinois at Chicago, 60612, USA.. efosslie@uic.edu
SOURCE: ANNALS OF CLINICAL AND LABORATORY SCIENCE, (2001 Jan) 31 (1) 25-67. Ref: 322
Journal code: 532; 0410247. ISSN: 0091-7370.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517
AB . . . evidence that defective OXPHOS plays an important role in atherogenesis, in the pathogenesis of Alzheimer's disease, Parkinson's

disease, diabetes, and **aging**. Defective OXPHOS may be caused by abnormal mitochondrial biosynthesis due to inherited or acquired mutations in the nuclear (n) or. . . mitochondrial (mt) deoxyribonucleic acid (DNA). For instance, the presence of a mutation of the mtDNA in the pancreatic beta-cell impairs **adenosine** triphosphate (ATP) generation and insulin synthesis. The nuclear genome controls mitochondrial biosynthesis, but mtDNA has a much higher mutation rate. . . ATP causes cell death. Many agents affect OXPHOS. Several nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit or uncouple OXPHOS and induce the '**topical**' phase of gastrointestinal ulcer formation. Uncoupled mitochondria reduce cell viability. The Helicobacter pylori induces uncoupling. The uncoupling that opens the. . .

L8 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:675442 CAPLUS
DOCUMENT NUMBER: 130:7299
TITLE: Antiaging cosmetics containing lignan glycosides and cell activators and/or moisturizers
INVENTOR(S): Kuriyama, Kenichi; Hisano, Noriyasu; Watanabe, Yoichi; Takisada, Mikimasa; Imoo, Masami; Kameyama, Kumi
PATENT ASSIGNEE(S): Nisshin Oil Mills Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 15 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 10279463	A2	19981020	JP 1997-99814	19970401

OTHER SOURCE(S): MARPAT 130:7299
IT 50-28-2, Estra-1,3,5(10)-triene-3,17-diol (17.beta.)-, biological studies 56-65-5, **Adenosine** triphosphate, biological studies 57-13-6, Urea, biological studies 81-13-0, D-Panthenol 99-20-7, Trehalose 506-26-3, .gamma.-Linolenic acid 9007-28-7, Chondroitin sulfate
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(antiaging **cosmetics** contg. lignan glycosides and cell activators and/or **moisturizers**)

L8 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:405929 CAPLUS
DOCUMENT NUMBER: 127:39497
TITLE: Use of adenosine against skin aging
INVENTOR(S): Schoenrock, Uwe; Pollet, Dieter; Schreiner, Volker; Maerker, Uwe; Kruse, Inge
PATENT ASSIGNEE(S): Beiersdorf A.-G., Germany
SOURCE: Ger. Offen., 8 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19545107	A1	19970605	DE 1995-19545107	19951204

AB **Adenosine** is useful in **cosmetic** and dermatol. prepns. for treatment of natural, chem. induced, or UV-induced skin **aging** and its sequelae by stimulation of cell proliferation in the skin. Thus, an oil-in-water sunscreen cream contained stearic acid 3.50, octyldodecanol 1.00, iso-Pr palmitate 5.00, cyclomethicone 4.00, methylbenzylidenecamphor 1.00, butylmethoxydibenzoylmethane 3.00, cetyl alc. 1.00, tri-Na HEDTA 5.00, 45% NaOH 1.00, glycerin 0.40, **adenosine** 0.10, preservative, perfume, and water to 100.00 wt.%.
IT Cell proliferation

Cosmetics
Skin aging
Sunscreens
Topical drug delivery systems
(use of **adenosine** against skin **aging**)

L8 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:517347 CAPLUS
DOCUMENT NUMBER: 121:117347
TITLE: Anti-aging cosmetics containing plant extracts and skin-whitening agents
INVENTOR(S): Iwanaga, Atsufumi
PATENT ASSIGNEE(S): Sansei Seiyaku Kk, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 27 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 06048934	A2	19940222	JP 1993-78368	19930405

PRIORITY APPLN. INFO.: JP 1992-141571 19920602
IT 50-81-7, Ascorbic acid, biological studies 56-12-2, .gamma.-Aminobutyric acid, biological studies 60-92-4, **Adenosine** -3',5'-cyclicmonophosphate 123-31-9, Hydroquinone, biological studies 302-79-4, Retinoic acid 501-30-4, Kojic acid 551-15-5, Liquiritin 7665-99-8, Guanosine-3',5'-cyclic monophosphate 119588-63-5
RL: BIOL (Biological study)
(anti-**aging cosmetics** contg. plant ext. and)

L8 ANSWER 6 OF 8 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 92242748 MEDLINE
DOCUMENT NUMBER: 92242748 PubMed ID: 1573183
TITLE: Age-related alterations in the arterial microvasculature of skeletal muscle.
AUTHOR: Cook J J; Wailgum T D; Vasthare U S; Mayrovitz H N; Tuma R F
CORPORATE SOURCE: Department of Physiology, Temple University School of Medicine.
CONTRACT NUMBER: AG-0335 (NIA)
SOURCE: JOURNAL OF GERONTOLOGY, (1992 May) 47 (3) B83-8.
Journal code: IAV; 0374762. ISSN: 0022-1422.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199206
ENTRY DATE: Entered STN: 19920619
Last Updated on STN: 19920619
Entered Medline: 19920604

AB This study investigated the possibility that the **aging** process results in alterations in the structure and/or functional reactivity of the microvessels that could contribute to increased resistance to. . . the average diameter was not different between age groups, segmental length (distance between adjacent branches) increased significantly (3rd order) during **aging**. Additionally, in vivo experiments were performed to determine the response of the vessels to the **topical** application of norepinephrine and **adenosine**. There was no increase in vasoconstriction produced by norepinephrine; however, the vasodilation in response to **adenosine** declined dramatically (1st and 2nd order) with advancing age. It can be concluded that the increase in skeletal muscle vascular resistance during contraction in aged male rats could be explained by morphological changes and/or the diminished vasodilation elicited by **adenosine**.

L8 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1989:121100 CAPLUS
DOCUMENT NUMBER: 110:121100
TITLE: Skin cosmetics containing evening primrose oil and radical scavengers and spleen extracts
INVENTOR(S): Marty, Jean Pierre
PATENT ASSIGNEE(S): Roussel-UCLAF, Fr.
SOURCE: Fr. Demande, 8 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2606279	A1	19880513	FR 1986-16154	19861120
FR 2606279	B1	19940218		

AB **Cosmetic** and dermatol. compns. contain evening primrose oil, spleen tissue exts., and .gtoreq.1 radical scavengers and singlet O inhibitors. Radical scavengers are e.g. terpenes, lipid-sol. carrot exts., and .alpha.-tocopherol. These **cosmetics** retard the signs of **aging** of the skin. Evening primrose oil contains essential fatty acids that inhibit dryness of the skin, loss of elasticity, and transdermal loss of water. The formulations may optionally contain **adenosine** phosphate, e.g. ATP, and addnl. caffeine or theophylline that inhibits phosphodiesterase and cAMP degrdn. A **cosmetic** cream contained glucate SS 3, glucamate SSE-20 2, evening primrose oil 10, fatty acid esters 7, plant sterols 5, lipid-sol. carrot ext. 0.2, .alpha.-tocopherol 0.05, UV absorbers 3, Mg Al silicate 1.2, spleen ext. 5, preservatives q.s., Na pyrrolidonecarboxylate 2, hyaluronic acid 0.03, phosphorylated ATP riboside 0.025, cAMP 0.02, perfume 0.3, and H2O to 100% by wt.

L8 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:400614 CAPLUS
DOCUMENT NUMBER: 103:614
TITLE: The use of indentometry to study the effect of agents known to increase skin cAMP content
AUTHOR(S): Hartzshtark, A.; Dikstein, S.
CORPORATE SOURCE: Sch. Pharm., Hebrew Univ., Jerusalem, Israel
SOURCE: Experientia (1985), 41(3), 378-9
CODEN: EXPEAM; ISSN: 0014-4754
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Applied to the skin of human forehead, **adenosine** [58-61-7], isoproterenol bitartarte [59-60-9], terbutaline sulfate [23031-32-5], papaverine [58-74-2], and N6-O2-dibutyryl cAMP [362-74-3] reduced the degree of skin indentation resulting from application of standardized wt. It seems that this change (indicative of a firmer, younger skin) involves cAMP [60-92-4], since the decrease in identability occurs at those drug concns. known to increase cAMP concns. in skin. These findings may contribute to the development of **cosmetic** and pharmaceutical prepns. for counteracting the **aging** of human skin.

L1 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1980:154767 BIOSIS
DOCUMENT NUMBER: BA69:29763
TITLE: PHYSIOLOGICAL AND GENETIC EFFECTS OF PUROMYCIN AMINO NUCLEOSIDE ON UV IRRADIATED ESCHERICHIA-COLI STRAINS.
AUTHOR(S): SIDEROPOULOS A S
CORPORATE SOURCE: DEP. BIOL. SCI., DUQUESNE UNIV., PITTSBURGH, PA. 15219, USA.
SOURCE: MUTAT RES, (1979) 62 (3), 439-450.
CODEN: MUREAV. ISSN: 0027-5107.
FILE SEGMENT: BA; OLD
LANGUAGE: English

=> d l1 ibib kwic 1-
YOU HAVE REQUESTED DATA FROM 2 ANSWERS - CONTINUE? Y/(N):y

L1 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1980:154767 BIOSIS
DOCUMENT NUMBER: BA69:29763
TITLE: PHYSIOLOGICAL AND GENETIC EFFECTS OF PUROMYCIN AMINO NUCLEOSIDE ON UV IRRADIATED ESCHERICHIA-COLI STRAINS.
AUTHOR(S): SIDEROPOULOS A S
CORPORATE SOURCE: DEP. BIOL. SCI., DUQUESNE UNIV., PITTSBURGH, PA. 15219, USA.
SOURCE: MUTAT RES, (1979) 62 (3), 439-450.
CODEN: MUREAV. ISSN: 0027-5107.
FILE SEGMENT: BA; OLD
LANGUAGE: English
IT Miscellaneous Descriptors
PURINE RIBOSIDE **ADENOSINE** ANTIDOTE MUTAGEN RNA SYNTHESIS **DNA SYNTHESIS PROTEIN SYNTHESIS** FEEDBACK MUTATION RATE SYNERGISM STREPTOMYCIN RESISTANCE REPAIR PROFICIENCY

L1 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1976:179448 BIOSIS
DOCUMENT NUMBER: BA62:9448
TITLE: ENHANCEMENT OF 9-BETA-D ARABINO FURANOSYL ADENINE CYTO TOXICITY TO MOUSE LEUKEMIA L-1210 IN-VITRO BY 2 DEOXY COFORMYCIN.
AUTHOR(S): CASS C E; AU-YEUNG T H
SOURCE: CANCER RES, (1976) 36 (4), 1486-1491.
CODEN: CNREA8. ISSN: 0008-5472.
FILE SEGMENT: BA; OLD
LANGUAGE: Unavailable
IT Miscellaneous Descriptors
ANTI NEOPLASTIC-DRUGS METAB-DRUGS **ADENOSINE** DEAMINASE INHIBITOR **DNA SYNTHESIS PROTEIN SYNTHESIS**

=> d l4 ibib 1- kwic
YOU HAVE REQUESTED DATA FROM 9 ANSWERS - CONTINUE? Y/(N):y

L4 ANSWER 1 OF 9 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000272038 MEDLINE
DOCUMENT NUMBER: 20272038 PubMed ID: 10801966
TITLE: The role of zinc in growth and cell proliferation.
AUTHOR: MacDonald R S
CORPORATE SOURCE: Nutritional Sciences Program, University of Missouri, Columbia, MO 65211, USA.
SOURCE: JOURNAL OF NUTRITION, (2000 May) 130 (5S Suppl) 1500S-8S. Ref: 60
Journal code: JEV; 0404243. ISSN: 0022-3166.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000616
Last Updated on STN: 20000616
Entered Medline: 20000608
AB . . . through independent, although well coordinated, mechanisms. Despite the long-term study of zinc metabolism, the first limiting role of zinc in **cell proliferation** remains undefined. Zinc participates in the regulation of **cell proliferation** in several ways; it is essential to enzyme systems that influence cell division and proliferation. Removing zinc from the extracellular milieu results in decreased activity of deoxythymidine kinase and reduced levels of adenosine(5')tetraphosphate(5')-**adenosine**. Hence, zinc may directly regulate **DNA synthesis** through these systems. Zinc also influences hormonal regulation of cell division. Specifically, the pituitary growth hormone (GH)-insulin-like growth factor-I (IGF-I). . . through exogenous administration, which suggests the defect occurs in hormone signaling. Zinc appears to be essential for IGF-I induction of **cell proliferation**; the site of regulation is postreceptor binding. Overall, the evidence suggests that reduced zinc availability affects membrane signaling systems and intracellular second messengers that coordinate **cell proliferation** in response to IGF-I.

L4 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
ACCESSION NUMBER: 1999:400108 CAPLUS
DOCUMENT NUMBER: 131:153920
TITLE: An adenosine receptor agonist-induced modulation of TSH-dependent cell growth in FRTL-5 thyroid cells mediated by inhibitory G protein, Gi
AUTHOR(S): Sho, Kimie; Narita, Torao; Okajima, Fumikazu; Kondo, Yoichi
CORPORATE SOURCE: Laboratory of Signal Transduction, Institute for Molecular and Cellular Regulation, Gunma University, Maebashi, 371-8512, Japan
SOURCE: Biochimie (1999), 81(4), 341-346
CODEN: BICMBE; ISSN: 0300-9084
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 23
REFERENCE(S): (1) Akbar, M; Mol Pharmacol 1994, V45, P1036 CAPLUS
(4) Depoortere, F; J Cell Biol 1998, V140, P1427 CAPLUS
(5) Kimura, T; Endocrinology 1995, V136, P116 CAPLUS
(6) Ledent, C; EMBO J 1992, V11, P537 CAPLUS
(8) Moses, A; Endocrinology 1989, V125, P2758 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Adenosine has been shown to modulate the TSH-induced DNA synthesis in

FRTL-5 thyroid cells. The mechanism of this adenosine action has been somewhat controversial because both A1 adenosine receptor-mediated and non-receptor-mediated mechanisms have been proposed. The authors have now reexamd. the authors' preliminary finding of the inhibitory action of a non-metabolizable adenosine deriv., N6-(L-2-phenylisopropyl) **adenosine** (PIA), on the TSH-induced **DNA synthesis** to clarify the **adenosine**-dependent mechanism of cell growth modulation. PIA dose-dependently inhibited the TSH-induced DNA synthesis expressed by [3H]thymidine incorporation into DNA. This adenosine deriv. also prevented the TSH-induced entry of the cell cycle to the S phase at 24 h of culture and the increase in cell no. at 48 h. These PIA actions on different aspects of TSH-dependent cell growth were abolished by the treatment of the cells with pertussis toxin, suggesting the involvement of Gi in the PIA action mechanism. Dibutyryl cAMP-induced DNA synthesis was not influenced by PIA. In concert with the authors' previous finding that PIA in a similar concn. range inhibited TSH-induced cAMP prodn. through the adenosine A1 receptor, the present results strongly support the idea that the major pathway of adenosine signaling for the inhibition of the TSH-induced **cell proliferation** is through the A1 adenosine receptor-Gi system.

L4 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
ACCESSION NUMBER: 1998:270771 CAPLUS
DOCUMENT NUMBER: 129:14830
TITLE: Mitogenic action of adenosine on osteoblast-like cells, MC3T3-E1
AUTHOR(S): Shimegi, S.
CORPORATE SOURCE: Fac. Health Sport Sci., Osaka Univ., Toyonaka, 560, Japan
SOURCE: Calcif. Tissue Int. (1998), 62(5), 418-425
CODEN: CTINDZ; ISSN: 0171-967X
PUBLISHER: Springer-Verlag New York Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this study was to investigate the mechanisms by which adenosine stimulates proliferation of osteoblast-like cells, MC3T3-E1. Adenosine by itself induces the stimulation of **cell proliferation** and accentuates the mitogenicity of PDGFs (AA and BB homodimers) for the cells. 8-Cyclopentyl-1,3-dimethylxanthine (CPX), a nonselective adenosine receptor antagonist, partially inhibited **adenosine**-induced **DNA synthesis** in a competitive manner, suggesting that the mitogenic action of adenosine is, at least in part, mediated by xanthine-sensitive receptors. In pertussis-toxin (PTX)-pretreated cells, **adenosine**- but not PDGF-BB-stimulated **DNA synthesis** was partially inhibited, and CPX did not exert a further inhibitory effect, suggesting an involvement of PTX-sensitive G-protein downstream of CPX-sensitive receptor. When adenosine uptake was prevented with dipyridamole, the stimulation of proliferation by adenosine was not decreased at all, indicating that the CPX-insensitive part of adenosine action is not assocd. with the uptake of adenosine and subsequent incorporation into the nucleotide pool. Adenosine did not influence the basal level or the PDGF-BB-induced increase in [Ca2+]i. Since it is known that the cAMP pathway acts in inhibiting osteoblast proliferation, the mitogenic action of adenosine would be dependent on neither the cAMP pathway nor the phospholipase C/Ca2+ pathway. It has been concluded that adenosine exerts a mitogenic effect via two pathways at least, one mediated by xanthine-sensitive receptor and PTX-sensitive G-protein and the other through an unknown xanthine- and PTX-insensitive process.

L4 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:544690 CAPLUS
DOCUMENT NUMBER: 129:240268
TITLE: Adenosine stimulation of DNA synthesis in mammary epithelial cells
AUTHOR(S): Yuh, In-Suh; Sheffield, Lewis G.
CORPORATE SOURCE: Endocrinology-Reproductive Physiology Program and

Department of Dairy Science, University of Wisconsin, Madison, WI, 53706, USA
SOURCE: Proc. Soc. Exp. Biol. Med. (1998), 218(4), 341-348
CODEN: PSEBAA; ISSN: 0037-9727
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **Cell proliferation**
DNA formation
Mammary epithelium
S phase
(**adenosine** stimulation of **DNA synthesis** in mammary epithelial cells)

L4 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
ACCESSION NUMBER: 1997:366607 CAPLUS
DOCUMENT NUMBER: 127:76492
TITLE: Adenosine inhibits DNA synthesis stimulated with TSH, insulin, and phorbol 12-myristate 13-acetate in rat thyroid FRTL-5 cells
AUTHOR(S): Vainio, Minna; Saarinen, Pia; Tornquist, Kid
CORPORATE SOURCE: Dep. Biosciences, Div. Animal Physiology, Univ. Helsinki, Finland
SOURCE: J. Cell. Physiol. (1997), 171(3), 336-342
CODEN: JCLLAX; ISSN: 0021-9541
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Adenosine has been shown to modulate **cell proliferation** in FRTL-5 thyroid cells, although the mechanisms by which this interaction occurs is still unclear. In the present study the authors investigated the effects of adenosine on the 3H-thymidine incorporation, cell cycle kinetics, and expression of the transcription factor c-Fos in cells stimulated via three different mitogenic pathways, i.e., by TSH, cAMP, insulin (tyrosine kinase), or phorbol 12-myristate 13-acetate (protein kinase C). Addn. of adenosine to cells grown in medium contg. hormones and serum did not inhibit the incorporation of 3H-thymidine. If adenosine was added hormone-deprived cells together with any of the tested mitogens, the stimulation of the 3H-thymidine incorporation was inhibited in a dose-dependent manner. The inhibition was significantly lower when the cells were preincubated with TSH or insulin for 48 h. Flow cytometric studies showed that adenosine evoked an inhibition of the cells in the G0/G1 phase. Submaximal doses of adenosine (10 nM-10 .mu.M) were able to induce c-Fos expression in FRTL-5 cells. However, the mitogen-induced expression of c-Fos was not reduced by maximal dose of adenosine (100 .mu.M). The effect of **adenosine** on **DNA synthesis** was not dependent on pertussis toxin-sensitive G-proteins. In addn., adenosine A1- or A2-receptor antagonists did not block the effect of adenosine. The effect of adenosine was abolished by treatment of the cells with adenosine deaminase, suggesting that the obsd. effect was not mediated by a metabolite of adenosine. The results suggest that adenosine is an effective blocker of mitogen-evoked DNA synthesis of FRTL-5 cells, provided that adenosine is administered simultaneously with the mitogen.

L4 ANSWER 6 OF 9 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 97057482 MEDLINE
DOCUMENT NUMBER: 97057482 PubMed ID: 8901821
TITLE: Cyclic AMP-adenosine pathway inhibits vascular smooth muscle cell growth.
AUTHOR: Dubey R K; Mi Z; Gillespie D G; Jackson E K
CORPORATE SOURCE: Department of Medicine and Pharmacology, University of Pittsburgh Medical Center, PA 15213-2582, USA.
CONTRACT NUMBER: HL-55314 (NHLBI)
SOURCE: HYPERTENSION, (1996 Nov) 28 (5) 765-71.
Journal code: GK7; 7906255. ISSN: 0194-911X.
PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961206

AB . . . ecto-phosphodiesterase with DPSPX, and of ecto-5'-nucleotidase with AMP-CP. To evaluate the physiological relevance of cAMP-derived adenosine in vascular smooth muscle **cell proliferation**, we studied the inhibitory effects of cAMP (10(-4) mol/L) and 8-bromo-cAMP (10(-4) mol/L) on fetal calf serum-induced DNA synthesis ([3H]thymidine. . . of adenosine deaminase), dipyridamole (a blocker of adenosine transport), KF17837 (a selective A2 adenosine receptor antagonist), and DPSPX (a nonselective **adenosine** receptor antagonist). cAMP inhibited **DNA synthesis**, and both EHNA and dipyridamole enhanced this effect. Both KF17837 and DPSPX significantly reduced the inhibitory effects of cAMP on. . .

L4 ANSWER 7 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V. DUPLICATE 6
ACCESSION NUMBER: 96059509 EMBASE
DOCUMENT NUMBER: 1996059509
TITLE: Glutathione metabolism during Yoshida ascites sarcoma growth.
AUTHOR: Ruggeri P.; Bono A.; Lagana G.; Fimiani V.
CORPORATE SOURCE: Institute of General Pathology, Trav. Bivona Bernardi, Via P. Castelli,98122 Messina, Italy
SOURCE: Oncology Reports, (1996) 3/2 (261-264).
ISSN: 1021-335X CODEN: OCRPEW
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English

AB . . . 10 and 13 assumed as 'markers' of different stages of tumor development. During this period the decrease in rate of **cell proliferation** was followed by decrease in **protein synthesis**, GSH, oxidized glutathione (GSSG), **adenosine** triphosphate (ATP), glutathione-S-transferase (GSH-S-transferase) and .gamma.-glutamyl-cysteine synthatase (.gamma.-GCS); by increase in glutathione-peroxidase (GSH-peroxidase); while glutathione-reductase (GSH-reductase) and glucose-6-phosphate-dehydrogenase (G-6-PD) remained. . .

L4 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 7
ACCESSION NUMBER: 1996:368048 CAPLUS
DOCUMENT NUMBER: 125:54646
TITLE: Hypothetical role of extracellular ATP and adenosine in training-induced bone hypertrophy
AUTHOR(S): Shimegi, Satoshi
CORPORATE SOURCE: Fac. Health Sport Sciences, Osaka Univ., Osaka, Japan
SOURCE: Tairyoku Kenkyu (1996), 91, 45-50
CODEN: TAKNAS; ISSN: 0389-9071
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Extracellular ATP and to lesser extent adenosine, an ATP metabolite, stimulated **cell proliferation** in osteoblast-like cells (MC3T3-E1). ATP increased cytosolic Ca2+ due to Ca2+ mobilization from intracellular storage in the same concn. range of the nucleotide as that effective for DNA synthesis, suggesting the mediation of the phospholipase C/Ca2+ system in the mitogenic action. Since adenosine induced no Ca2+ mobilization, P2-purinergic receptor appears to be assocd. with ATP actions. 8-Cyclopentyl-1,3-dimethylxanthine (CPX), a non-selective adenosine receptor antagonist, partially inhibited **adenosine** -induced **DNA synthesis**, suggesting that the mitogenic action of adenosine is, at least in part, mediated by xanthine-sensitive receptor. In pertussis-toxin (PTX)-pretreated cells, **adenosine**

-stimulated **DNA synthesis** was partially inhibited, and CPX did not exert a further inhibitory effect, suggesting the involvement of PTX-sensitive G-protein downstream of CPX-sensitive receptor. Either ATP or adenosine remarkably and synergistically potentiated PDGF-induced DNA synthesis. These findings suggest that extracellular ATP and adenosine may play a physiol. role in the regulation of bone formation in normal bone remodeling and repairs of micro-damaged bone tissue.

L4 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 8
ACCESSION NUMBER: 1994:505135 CAPLUS
DOCUMENT NUMBER: 121:105135
TITLE: Effects of adenine nucleotides on the proliferation of aortic endothelial cells
AUTHOR(S): Van Daele, P.; Van Coevorden, A.; Roger, P. P.; Boeynaems, J. M.
CORPORATE SOURCE: Sch. Med., Free Univ. Brussels, Brussels, B-1070, Belg.
SOURCE: Circ. Res. (1992), 70(1), 82-90
CODEN: CIRUAL; ISSN: 0009-7330
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of adenine nucleotides and **adenosine** on **DNA synthesis** and cell growth were studied in bovine aortic endothelial cells (BAECs). ATP produced a small but significant (+44%) increase of the fraction of BAECs whose nuclei are labeled by [3H]thymidine. This mitogenic effect was mimicked by ADP, the phosphorothioate analogs ATP.gamma.S and ADP.beta.S, and the nonhydrolyzable analog adenosine 5'-(.beta.,.gamma.-imido)triphosphate (APPNP), whereas adenosine 5'-(.alpha.,.beta.-methylene)triphosphate (APCPP), a selective agonist of P2x-purinoceptors, had no effect at 10 .mu.M and a small one at 100 .mu.M; this profile is consistent with the involvement of P2y-receptors. Adenosine induced a mitogenic response of a magnitude similar to that of ATP. This effect was not reproduced by R-phenylisopropyl adenosine, by 5'-N-ethylcarboxamide adenosine, or by 2',5'-dideoxyadenosine, selective ligands of the A1- and A2-receptors and the P site, resp., nor was it inhibited by 8-phenyltheophylline, an antagonist of both A1- and A2-receptors. The mechanism of this adenosine action thus remains unclear. ATP and ATP.gamma.S did not enhance the proliferation of BAECs cultured in the presence of fetal calf serum concns. ranging 0.5-10%. They inhibited the growth-promoting effect of basic fibroblast growth factor; among the various nucleotides tested, APCPP was the least effective to reproduce the action of ATP, suggesting the possible involvement of P2y-receptors. In conclusion, the action of ATP on the proliferation of BAECs is complex: an increase in the fraction of cells synthesizing DNA, no effect on the **cell proliferation** in the presence of serum, and inhibition of the growth-promoting effect of basic fibroblast growth factor.

L6 ANSWER 1 OF 12 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000272038 MEDLINE
DOCUMENT NUMBER: 20272038 PubMed ID: 10801966
TITLE: The role of zinc in growth and cell proliferation.
AUTHOR: MacDonald R S
CORPORATE SOURCE: Nutritional Sciences Program, University of Missouri, Columbia, MO 65211, USA.
SOURCE: JOURNAL OF NUTRITION, (2000 May) 130 (5S Suppl) 1500S-8S. Ref: 60
Journal code: JEV; 0404243. ISSN: 0022-3166.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000616
Last Updated on STN: 20000616
Entered Medline: 20000608

AB . . . through independent, although well coordinated, mechanisms. Despite the long-term study of zinc metabolism, the first limiting role of zinc in **cell proliferation** remains undefined. Zinc participates in the regulation of **cell proliferation** in several ways; it is essential to enzyme systems that influence cell division and proliferation. Removing zinc from the extracellular milieu results in decreased activity of deoxythymidine kinase and reduced levels of adenosine(5')tetraphosphate(5')-**adenosine**. Hence, zinc may directly regulate **DNA synthesis** through these systems. Zinc also influences hormonal regulation of cell division. Specifically, the pituitary growth hormone (GH)-insulin-like growth factor-I (IGF-I). . . through exogenous administration, which suggests the defect occurs in hormone signaling. Zinc appears to be essential for IGF-I induction of **cell proliferation**; the site of regulation is postreceptor binding. Overall, the evidence suggests that reduced zinc availability affects membrane signaling systems and intracellular second messengers that coordinate **cell proliferation** in response to IGF-I.

L6 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
ACCESSION NUMBER: 1999:400108 CAPLUS
DOCUMENT NUMBER: 131:153920
TITLE: An adenosine receptor agonist-induced modulation of TSH-dependent cell growth in FRTL-5 thyroid cells mediated by inhibitory G protein, Gi
AUTHOR(S): Sho, Kimie; Narita, Torao; Okajima, Fumikazu; Kondo, Yoichi
CORPORATE SOURCE: Laboratory of Signal Transduction, Institute for Molecular and Cellular Regulation, Gunma University, Maebashi, 371-8512, Japan
SOURCE: Biochimie (1999), 81(4), 341-346
CODEN: BICMBE; ISSN: 0300-9084
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 23
REFERENCE(S): (1) Akbar, M; Mol Pharmacol 1994, V45, P1036 CAPLUS
(4) Depoortere, F; J Cell Biol 1998, V140, P1427 CAPLUS
(5) Kimura, T; Endocrinology 1995, V136, P116 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Adenosine has been shown to modulate the TSH-induced DNA synthesis in FRTL-5 thyroid cells. The mechanism of this adenosine action has been somewhat controversial because both A1 adenosine receptor-mediated and non-receptor-mediated mechanisms have been proposed. The authors have now

reexamd. the authors' preliminary finding of the inhibitory action of a non-metabolizable adenosine deriv., N6-(L-2-phenylisopropyl) **adenosine** (PIA), on the TSH-induced **DNA synthesis** to clarify the **adenosine**-dependent mechanism of cell growth modulation. PIA dose-dependently inhibited the TSH-induced DNA synthesis expressed by [3H]thymidine incorporation into DNA. This adenosine deriv. also prevented the TSH-induced entry of the cell cycle to the S phase at 24 h of culture and the increase in cell no. at 48 h. These PIA actions on different aspects of TSH-dependent cell growth were abolished by the treatment of the cells with pertussis toxin, suggesting the involvement of Gi in the PIA action mechanism. Dibutyryl cAMP-induced DNA synthesis was not influenced by PIA. In concert with the authors' previous finding that PIA in a similar concn. range inhibited TSH-induced cAMP prodn. through the adenosine A1 receptor, the present results strongly support the idea that the major pathway of adenosine signaling for the inhibition of the TSH-induced **cell proliferation** is through the A1 adenosine receptor-Gi system.

L6 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
ACCESSION NUMBER: 1998:270771 CAPLUS
DOCUMENT NUMBER: 129:14830
TITLE: Mitogenic action of adenosine on osteoblast-like cells, MC3T3-E1
AUTHOR(S): Shimegi, S.
CORPORATE SOURCE: Fac. Health Sport Sci., Osaka Univ., Toyonaka, 560, Japan
SOURCE: Calcif. Tissue Int. (1998), 62(5), 418-425
CODEN: CTINDZ; ISSN: 0171-967X
PUBLISHER: Springer-Verlag New York Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The purpose of this study was to investigate the mechanisms by which adenosine stimulates proliferation of osteoblast-like cells, MC3T3-E1. Adenosine by itself induces the stimulation of **cell proliferation** and accentuates the mitogenicity of PDGFs (AA and BB homodimers) for the cells. 8-Cyclopentyl-1,3-dimethylxanthine (CPX), a nonselective adenosine receptor antagonist, partially inhibited **adenosine**-induced **DNA synthesis** in a competitive manner, suggesting that the mitogenic action of adenosine is, at least in part, mediated by xanthine-sensitive receptors. In pertussis-toxin (PTX)-pretreated cells, **adenosine**- but not PDGF-BB-stimulated **DNA synthesis** was partially inhibited, and CPX did not exert a further inhibitory effect, suggesting an involvement of PTX-sensitive G-protein downstream of CPX-sensitive receptor. When adenosine uptake was prevented with dipyridamole, the stimulation of proliferation by adenosine was not decreased at all, indicating that the CPX-insensitive part of adenosine action is not assocd. with the uptake of adenosine and subsequent incorporation into the nucleotide pool. Adenosine did not influence the basal level or the PDGF-BB-induced increase in [Ca2+]i. Since it is known that the cAMP pathway acts in inhibiting osteoblast proliferation, the mitogenic action of adenosine would be dependent on neither the cAMP pathway nor the phospholipase C/Ca2+ pathway. It has been concluded that adenosine exerts a mitogenic effect via two pathways at least, one mediated by xanthine-sensitive receptor and PTX-sensitive G-protein and the other through an unknown xanthine- and PTX-insensitive process.

L6 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:544690 CAPLUS
DOCUMENT NUMBER: 129:240268
TITLE: Adenosine stimulation of DNA synthesis in mammary epithelial cells
AUTHOR(S): Yuh, In-Suh; Sheffield, Lewis G.
CORPORATE SOURCE: Endocrinology-Reproductive Physiology Program and Department of Dairy Science, University of Wisconsin, Madison, WI, 53706, USA
SOURCE: Proc. Soc. Exp. Biol. Med. (1998), 218(4), 341-348

CODEN: PSEBAA; ISSN: 0037-9727
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **Cell proliferation**
DNA formation
Mammary epithelium
S phase
(**adenosine** stimulation of **DNA synthesis** in mammary epithelial cells)

L6 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
ACCESSION NUMBER: 1997:366607 CAPLUS
DOCUMENT NUMBER: 127:76492
TITLE: Adenosine inhibits DNA synthesis stimulated with TSH, insulin, and phorbol 12-myristate 13-acetate in rat thyroid FRTL-5 cells
AUTHOR(S): Vainio, Minna; Saarinen, Pia; Tornquist, Kid
CORPORATE SOURCE: Dep. Biosciences, Div. Animal Physiology, Univ. Helsinki, Finland
SOURCE: J. Cell. Physiol. (1997), 171(3), 336-342
CODEN: JCLLAX; ISSN: 0021-9541
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Adenosine has been shown to modulate **cell proliferation** in FRTL-5 thyroid cells, although the mechanisms by which this interaction occurs is still unclear. In the present study the authors investigated the effects of adenosine on the 3H-thymidine incorporation, cell cycle kinetics, and expression of the transcription factor c-Fos in cells stimulated via three different mitogenic pathways, i.e., by TSH, cAMP, insulin (tyrosine kinase), or phorbol 12-myristate 13-acetate (protein kinase C). Addn. of adenosine to cells grown in medium contg. hormones and serum did not inhibit the incorporation of 3H-thymidine. If adenosine was added hormone-deprived cells together with any of the tested mitogens, the stimulation of the 3H-thymidine incorporation was inhibited in a dose-dependent manner. The inhibition was significantly lower when the cells were preincubated with TSH or insulin for 48 h. Flow cytometric studies showed that adenosine evoked an inhibition of the cells in the G0/G1 phase. Submaximal doses of adenosine (10 nM-10 .mu.M) were able to induce c-Fos expression in FRTL-5 cells. However, the mitogen-induced expression of c-Fos was not reduced by maximal dose of adenosine (100 .mu.M). The effect of **adenosine** on **DNA synthesis** was not dependent on pertussis toxin-sensitive G-proteins. In addn., adenosine A1- or A2-receptor antagonists did not block the effect of adenosine. The effect of adenosine was abolished by treatment of the cells with adenosine deaminase, suggesting that the obsd. effect was not mediated by a metabolite of adenosine. The results suggest that adenosine is an effective blocker of mitogen-evoked DNA synthesis of FRTL-5 cells, provided that adenosine is administered simultaneously with the mitogen.

L6 ANSWER 6 OF 12 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 97057482 MEDLINE
DOCUMENT NUMBER: 97057482 PubMed ID: 8901821
TITLE: Cyclic AMP-adenosine pathway inhibits vascular smooth muscle cell growth.
AUTHOR: Dubey R K; Mi Z; Gillespie D G; Jackson E K
CORPORATE SOURCE: Department of Medicine and Pharmacology, University of Pittsburgh Medical Center, PA 15213-2582, USA.
CONTRACT NUMBER: HL-55314 (NHLBI)
SOURCE: HYPERTENSION, (1996 Nov) 28 (5) 765-71.
Journal code: GK7; 7906255. ISSN: 0194-911X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961206

AB . . . ecto-phosphodiesterase with DPSPX, and of ecto-5'-nucleotidase with AMP-CP. To evaluate the physiological relevance of cAMP-derived adenosine in vascular smooth muscle **cell proliferation**, we studied the inhibitory effects of cAMP (10(-4) mol/L) and 8-bromo-cAMP (10(-4) mol/L) on fetal calf serum-induced DNA synthesis ([3H]thymidine. . . of adenosine deaminase), dipyridamole (a blocker of adenosine transport), KF17837 (a selective A2 adenosine receptor antagonist), and DPSPX (a nonselective **adenosine** receptor antagonist). cAMP inhibited **DNA synthesis**, and both EHNA and dipyridamole enhanced this effect. Both KF17837 and DPSPX significantly reduced the inhibitory effects of cAMP on. . .

L6 ANSWER 7 OF 12 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V. DUPLICATE 6
ACCESSION NUMBER: 96059509 EMBASE
DOCUMENT NUMBER: 1996059509
TITLE: Glutathione metabolism during Yoshida ascites sarcoma growth.
AUTHOR: Ruggeri P.; Bono A.; Lagana G.; Fimiani V.
CORPORATE SOURCE: Institute of General Pathology, Trav. Bivona Bernardi, Via P. Castelli,98122 Messina, Italy
SOURCE: Oncology Reports, (1996) 3/2 (261-264).
ISSN: 1021-335X CODEN: OCRPEW
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
LANGUAGE: English
SUMMARY LANGUAGE: English

AB . . . 10 and 13 assumed as 'markers' of different stages of tumor development. During this period the decrease in rate of **cell proliferation** was followed by decrease in **protein synthesis**, GSH, oxidized glutathione (GSSG), **adenosine** triphosphate (ATP), glutathione-S-transferase (GSH-S-transferase) and .gamma.-glutamyl-cysteine synthatase (.gamma.-GCS); by increase in glutathione-peroxidase (GSH-peroxidase); while glutathione-reductase (GSH-reductase) and glucose-6-phosphate-dehydrogenase (G-6-PD) remained. . .

L6 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 7
ACCESSION NUMBER: 1996:368048 CAPLUS
DOCUMENT NUMBER: 125:54646
TITLE: Hypothetical role of extracellular ATP and adenosine in training-induced bone hypertrophy
AUTHOR(S): Shimegi, Satoshi
CORPORATE SOURCE: Fac. Health Sport Sciences, Osaka Univ., Osaka, Japan
SOURCE: Tairyoku Kenkyu (1996), 91, 45-50
CODEN: TAKNAS; ISSN: 0389-9071
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Extracellular ATP and to lesser extent adenosine, an ATP metabolite, stimulated **cell proliferation** in osteoblast-like cells (MC3T3-E1). ATP increased cytosolic Ca2+ due to Ca2+ mobilization from intracellular storage in the same concn. range of the nucleotide as that effective for DNA synthesis, suggesting the mediation of the phospholipase C/Ca2+ system in the mitogenic action. Since adenosine induced no Ca2+ mobilization, P2-purinergic receptor appears to be assocd. with ATP actions. 8-Cyclopentyl-1,3-dimethylxanthine (CPX), a non-selective adenosine receptor antagonist, partially inhibited **adenosine** -induced **DNA synthesis**, suggesting that the mitogenic action of adenosine is, at least in part, mediated by xanthine-sensitive receptor. In pertussis-toxin (PTX)-pretreated cells, **adenosine** -stimulated **DNA synthesis** was partially inhibited, and CPX did not exert a further inhibitory effect, suggesting the involvement of PTX-sensitive G-protein downstream of CPX-sensitive receptor. Either

ATP or adenosine remarkably and synergistically potentiated PDGF-induced DNA synthesis. These findings suggest that extracellular ATP and adenosine may play a physiol. role in the regulation of bone formation in normal bone remodeling and repairs of micro-damaged bone tissue.

L6 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 8
ACCESSION NUMBER: 1994:505135 CAPLUS
DOCUMENT NUMBER: 121:105135
TITLE: Effects of adenine nucleotides on the proliferation of aortic endothelial cells
AUTHOR(S): Van Daele, P.; Van Coevorden, A.; Roger, P. P.; Boeynaems, J. M.
CORPORATE SOURCE: Sch. Med., Free Univ. Brussels, Brussels, B-1070, Belg.
SOURCE: Circ. Res. (1992), 70(1), 82-90
CODEN: CIRUAL; ISSN: 0009-7330
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of adenine nucleotides and **adenosine** on **DNA synthesis** and cell growth were studied in bovine aortic endothelial cells (BAECs). ATP produced a small but significant (+44%) increase of the fraction of BAECs whose nuclei are labeled by [3H]thymidine. This mitogenic effect was mimicked by ADP, the phosphorothioate analogs ATP.gamma.S and ADP.beta.S, and the nonhydrolyzable analog adenosine 5'-(.beta.,.gamma.-imido)triphosphate (APPNP), whereas adenosine 5'-(.alpha.,.beta.-methylene)triphosphate (APCPP), a selective agonist of P2x-purinoceptors, had no effect at 10 .mu.M and a small one at 100 .mu.M; this profile is consistent with the involvement of P2y-receptors. Adenosine induced a mitogenic response of a magnitude similar to that of ATP. This effect was not reproduced by R-phenylisopropyl adenosine, by 5'-N-ethylcarboxamide adenosine, or by 2',5'-dideoxyadenosine, selective ligands of the A1- and A2-receptors and the P site, resp., nor was it inhibited by 8-phenyltheophylline, an antagonist of both A1- and A2-receptors. The mechanism of this adenosine action thus remains unclear. ATP and ATP.gamma.S did not enhance the proliferation of BAECs cultured in the presence of fetal calf serum concns. ranging 0.5-10%. They inhibited the growth-promoting effect of basic fibroblast growth factor; among the various nucleotides tested, APCPP was the least effective to reproduce the action of ATP, suggesting the possible involvement of P2y-receptors. In conclusion, the action of ATP on the proliferation of BAECs is complex: an increase in the fraction of cells synthesizing DNA, no effect on the **cell proliferation** in the presence of serum, and inhibition of the growth-promoting effect of basic fibroblast growth factor.

L6 ANSWER 10 OF 12 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 83001867 MEDLINE
DOCUMENT NUMBER: 83001867 PubMed ID: 7116424
TITLE: The influence of the cell cycle on structure and number of nucleoli in cultured human lymphocytes.
AUTHOR: Wachtler F; Schwarzacher H G; Ellinger A
SOURCE: CELL AND TISSUE RESEARCH, (1982) 225 (1) 155-63.
Journal code: CQD; 0417625. ISSN: 0302-766X.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198212
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19900317
Entered Medline: 19821202
AB . . . sequence of structural changes after stimulation by phytohaemagglutinin. These changes are independent of the cell cycle. Neither the inhibition of **DNA-synthesis** (by **adenosine** and methotrexate), nor the elimination of postmitotic interphase nuclei (by a colchicine block of **mitoses**), nor the release from such blocks has a noticeable effect on nucleolar structure or

on the sequence of nucleolar changes. The number of nucleoli per cell is clearly influenced by the cell cycle. **Mitosis** leads to a marked increase in the number of nucleoli, whereas in all stages of interphase a decrease occurs.

L6 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 10
ACCESSION NUMBER: 1977:495866 CAPLUS
DOCUMENT NUMBER: 87:95866
TITLE: Antiproliferative effects of 9-.beta.-D-arabinofuranosyladenine in a mammalian cell line devoid of adenosine deaminase activity
AUTHOR(S): Drach, John C.; Sandberg, Jean N.; Shipman, Charles, Jr.
CORPORATE SOURCE: Sch. Dent., Univ. Michigan, Ann Arbor, Mich., USA
SOURCE: J. Dent. Res. (1977), 56(3), 275-88
CODEN: JDREAF
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The antiviral drug 9-.beta.-D-arabinofuranosyladenine (I) [5536-17-4] inhibited cellular growth and **DNA synthesis** in an **adenosine** deaminase [9026-93-1]-neg. rat embryo transformed cell line (B-mix K-44/6). Use of adenosine deaminase-contg. calf serum in the culture medium reversed the drug-induced inhibition and resulted in a recovery of both **mitosis** and the rate of DNA synthesis.

L6 ANSWER 12 OF 12 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 75151505 MEDLINE
DOCUMENT NUMBER: 75151505 PubMed ID: 165178
TITLE: Cyclic adenosine 3':5'-monophosphate and the induction of deoxyribonucleic acid synthesis in liver.
AUTHOR: Short J; Tsukada K; Rudert W A; Lieberman I
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1975 May 25) 250 (10) 3602-6.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197507
ENTRY DATE: Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19750724
AB A mixture containing glucagon and thyroid hormone was previously devised that enhances markedly nuclear DNA replication and **mitosis** in the parenchymal liver cells of the unoperated rat. It is now shown that the glucagon of the stimulatory solution. . . is raised during most of the prereplicative period after 70% hepatectomy is confirmed. The evidence supports a positive role for **adenosine** 3':5-monophosphate in regulating **DNA synthesis** in the liver.

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=> d his full

     (FILE 'HOME' ENTERED AT 10:23:14 ON 01 OCT 2001)

     FILE 'CAPLUS, MEDLINE, EMBASE, BIOSIS' ENTERED AT 10:23:32 ON 01 OCT 2001
L1             2 SEA ABB=ON  PLU=ON  ADENOSINE (5A) (DNA SYNTHESIS) (5A)
                 (PROTEIN SYNTHESIS)
                 D UP
                 D L1 IBIB KWIC 1-
L2           535 SEA ABB=ON  PLU=ON  ADENOSINE (5A) (DNA SYNTHESIS OR PROTEIN
                 SYNTHESIS)
L3            28 SEA ABB=ON  PLU=ON  ADENOSINE (5A) (DNA SYNTHESIS OR PROTEIN
                 SYNTHESIS) (P) (CELL PROLIFERAT? OR CELL MULTIPLICAT? OR CELL
                 NUMBER)
L4             9 DUP REM L3 (19 DUPLICATES REMOVED)
                 D L4 IBIB 1- KWIC
L5            34 SEA ABB=ON  PLU=ON  ADENOSINE (5A) (DNA SYNTHESIS OR PROTEIN
                 SYNTHESIS) (P) (CELL PROLIFERAT? OR CELL MULTIPLICAT? OR CELL
                 NUMBER OR MITOSIS OR MITOGENSIS)
L6            12 DUP REM L5 (22 DUPLICATES REMOVED)
                 D L6 IBIB KWIC 1-
L7            12 SEA ABB=ON  PLU=ON  ADENOSINE (P) (COSMETIC OR TOPICAL) (P)
                 (WRINKLES OR DRY SKIN OR MOISTURIZ? OR AGING)
L8             8 DUP REM L7 (4 DUPLICATES REMOVED)
                 D L8 IBIB KWIC 1-
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PATENT APPLICATION FEE DETERMINATION RECORD
Effective December 29, 1999

Application or Docket Number: 09/672348

CLAIMS AS FILED - PART I

	(Column 1) NUMBER FILED		(Column 2) NUMBER EXTRA
BASIC FEE			
TOTAL CLAIMS	1	minus 20=	*
INDEPENDENT CLAIMS	1	minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT			

SMALL ENTITY TYPE ☐			OTHER THAN SMALL ENTITY	
RATE	FEE	OR	RATE	FEE
	345.00	OR		690.00
X$ 9=		OR	X$18=	
X39=		OR	X78=	
+130=		OR	+260=	
TOTAL	345	OR	TOTAL	

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

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	* 26	Minus	** 20	=
Independent	* 3	Minus	*** 3	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY			OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X39=		OR	X78=	
+130=		OR	+260=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

C

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 10	Minus	** 26	=
Independent	* 1	Minus	*** 3	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY			OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X39=		OR	X78=	
+130=		OR	+260=	
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				

SMALL ENTITY			OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE	OR	RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X39=		OR	X78=	
+130=		OR	+260=	
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.