EXHIBIT 1

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL and CARMEL LABORATORIES LLC,	)	
Plaintiffs,	)	C.A. No. 17-868-CFC-SRF
v.	)	
L'ORÉAL USA, INC.,	)	
Defendant.	)	

[PROPOSED] ORDER

THIS MATTER having been brought before the Court on Motion by Defendant L'Oréal USA seeking supplementation of Plaintiffs' infringement contentions and production of related testing information; and the Court having considered the parties' positions as set forth in the letters submitted on December 4 and December 5, 2019, and during the December 9, 2019 hearing;

IT IS on this _____ day of December, 2019, hereby:

ORDERED that L'Oréal USA's Motion is hereby GRANTED; and it is further

ORDERED that Plaintiffs shall serve amended infringement contentions by December 20, 2019, specifically identifying which information and/or documents provide the basis for how the Accused Products allegedly meet the claim language "wherein the adenosine concentration applied to the dermal cells is [recited amount]" and "without increasing dermal cell proliferation";[1] and it is further

ORDERED that Plaintiffs shall produce by December 20, 2019, documents and information on which they are relying for their infringement contentions, including documents

[1] To the extent Plaintiffs contend that testing of one product provides the basis for their claim of infringement for another product, they must specify which tested product provides the basis of their claim of infringement for each untested product.

regarding any underlying testing (*e.g.*, the "[redacted]"), testing conditions and protocols, underlying data, other results, and laboratory notebooks.

_____

Hon. Sherry R. Fallon, U.S.M.J.

EXHIBIT 2

US006423327B1

(12) **United States Patent**
Dobson, Jr. et al.

(10) **Patent No.: US 6,423,327 B1**
(45) **Date of Patent: Jul. 23, 2002**

(54) **TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG**

(75) Inventors: **James G. Dobson, Jr.**, Auburn; **Michael F. Ethier**, Grafton, both of MA (US)

(73) Assignee: **University of Massachusetts**, Boston, MA (US)

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

(21) Appl. No.: **09/672,348**

(22) Filed: **Sep. 28, 2000**

Related U.S. Application Data

(63) Continuation of application No. 09/179,006, filed on Oct. 26, 1998, now abandoned.

(51) **Int. Cl.**[7] **A61K 7/00**

(52) **U.S. Cl.** **424/401**; 424/447; 424/448; 424/449; 514/46

(58) **Field of Search** 424/407, 447, 424/448, 449; 514/46

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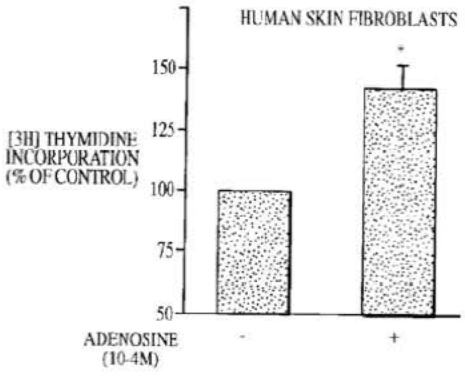
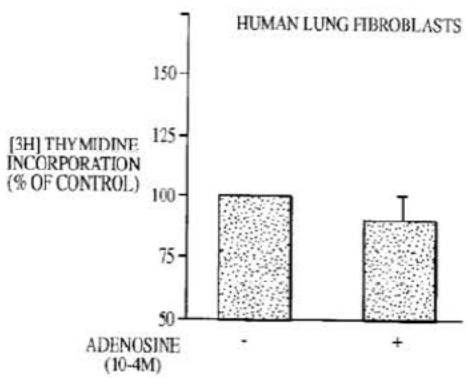
Primary Examiner—Thurman K. Page
Assistant Examiner—Lakshmi Channavajjala
(74) *Attorney, Agent, or Firm*—Fish & Richardson P.C.

(57) **ABSTRACT**

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.

10 Claims, 2 Drawing Sheets





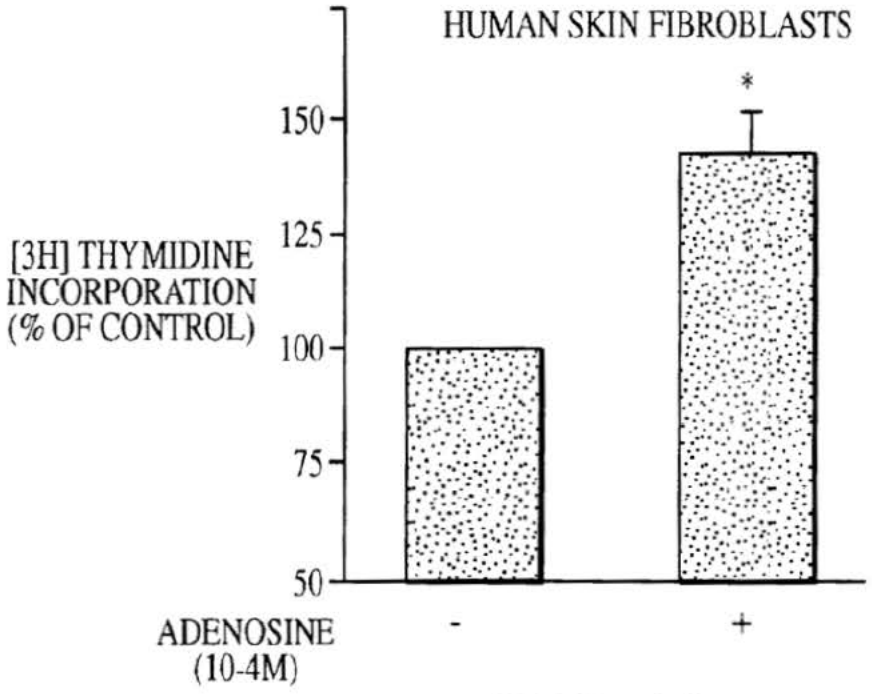
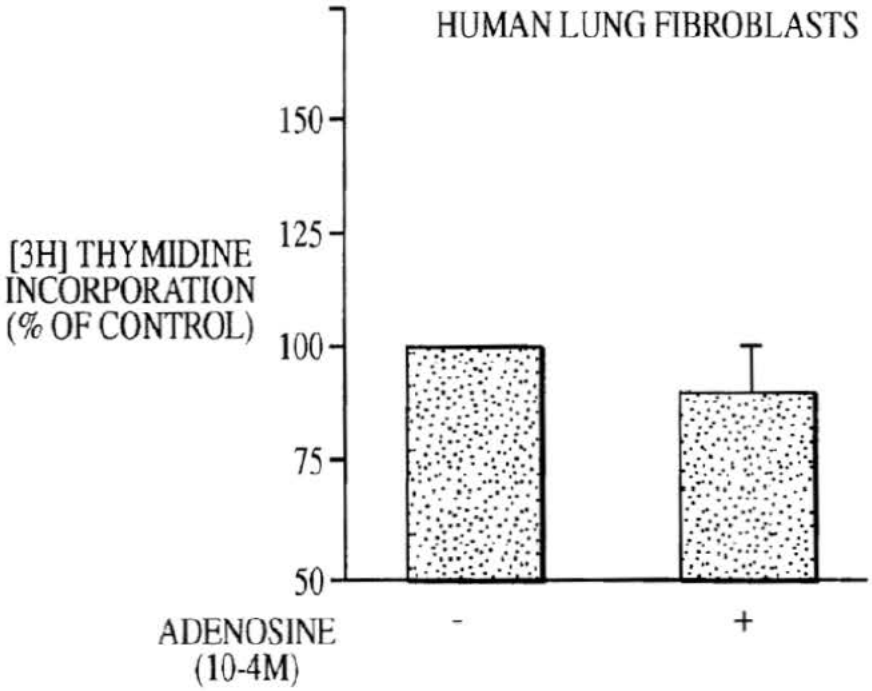

HUMAN SKIN FIBROBLASTS
[3H] THYMIDINE INCORPORATION (% OF CONTROL)
150
125
100
75
50
*
ADENOSINE (10-4M)
-
+

FIG. 1A


HUMAN LUNG FIBROBLASTS
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150
125
100
75
50
ADENOSINE (10-4M)
-
+

FIG. 1B

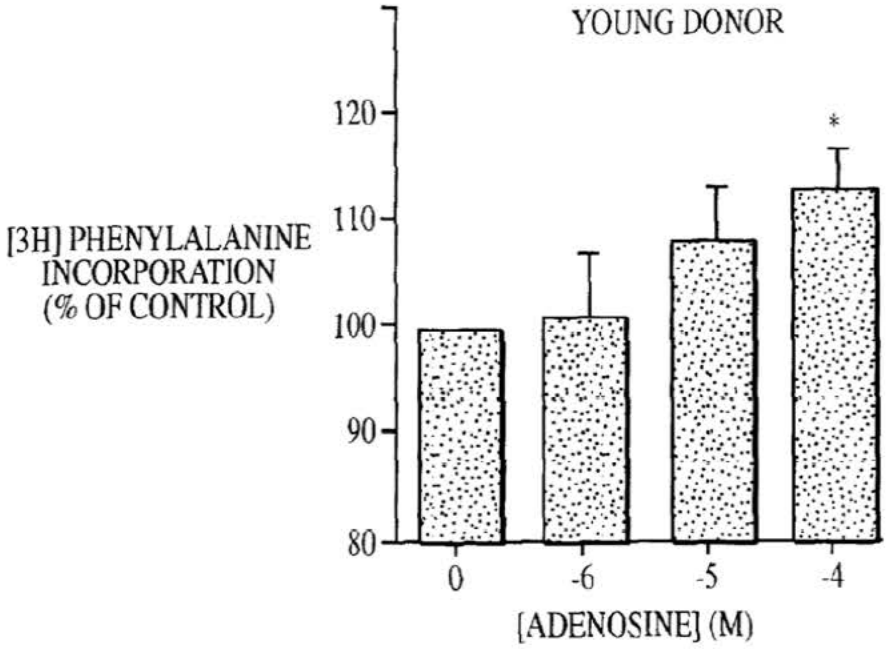
YOUNG DONOR
[3H] PHENYLALANINE INCORPORATION (% OF CONTROL)
120
110
100
90
80
*
0
-6
-5
-4
[ADENOSINE] (M)

FIG. 2A

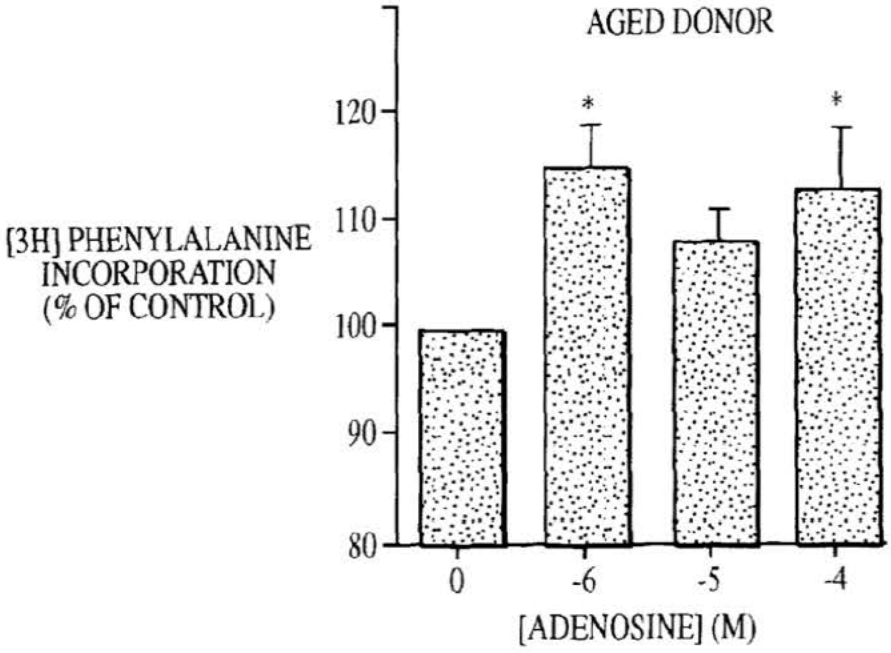
AGED DONOR
[3H] PHENYLALANINE INCORPORATION (% OF CONTROL)
120
110
100
90
80
*
*
0
-6
-5
-4
[ADENOSINE] (M)

FIG. 2B

TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

This application is a continuation of application Ser. No. 09/179,006, filed Oct. 26, 1998, now abandoned.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

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

FIELD OF THE INVENTION

This invention relates to dermatology and cell biology.

BACKGROUND OF THE INVENTION

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

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

SUMMARY OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

The invention also provides a composition including about 10^{-3} M to about 10^{-7} M adenosine and a therapeutically effective amount of an angiogenesis factor. In some embodiments, the composition of the adenosine is about 10^{-4} M.

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1A** and **1B** are histograms showing the effect of adenosine on [^{3}H]thymidine incorporation in cultures of

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

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

DETAILED DESCRIPTION

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

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

Agonists of adenosine include 2'-deoxyadenosine; 2', 3'-isopropoylidene adenosine; toyocamycin; 1-methyladenosine; N-6-methyladenosine; adenosine N-oxide; 6-methylmercaptopurine riboside; 6-chloropurine riboside, 5'adenosine monophosphate, 5'-adenosine diphosphate, or 5'-adenosine triphosphate. Adenosine receptor agonists include phenylisopropyl-adenosine ("PIA"), 1-Methylisoguanosine, ENBA (S(-), N^6-Cyclohexyladenosine (CHA), N^6-Cyclopentyladenosine (CPA), 2-Chloro-N6-cyclopentyladenosine, 2-chloroadenosine, and adenosine amine congener (ADAC), all of which are agonists for the adenosine A_1 receptor. Other receptor agonists include 2-p-(2-carboxy-ethyl) phenethyl-amino-5'-N-ethylcarboxamido-adenosine (CGS-21680), N-ethylcarboxamido-adenosine (NECA) and napthyl-substituted aralkoxyadenosine (SHA-082), 5' (N-Cyclopropyl)-carboxamidoadenosine, DPMA (PD 129, 944), Metrifudil, which are agonists for the adenosine A_2 receptor. Other adenosine receptor agonists include those which preferentially bind the A_1 receptor relative to the A_2 receptor, such as 2-Chloroadenosine, N_6-Phenyladenosine, and N^6-Phenylethyladenosine; and those which preferentially bind the A_2 receptor relative to the A_1 receptor, such as 2-Phenylaminoadenosine and MECA.

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

Adenosine can be also be administered with a second compound. The second compound can enhance the action of adenosine or the adenosine analog, e.g., by enhancing binding of adenosine or an adenosine analog to an adenosine receptor. An example of such a compound is PD 81, 728, which is described in Kollias-Baker et al. J. Pharmacol. Exp. Ther. 281:761–68. Alternatively, the second agent can itself act to enhance skin condition. Examples of these types of agents include tretinoin, a recognized skin conditioning agent (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 37:217–26, 1997), an angiogenic factor such as vascular endothelial cell growth factor (VEGF) or basic fibroblast growth factor (BFGF), or a conditioning agent.

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

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

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

The pharmaceutical composition may be formulated using conventional methods to prepare pharmaceutically useful compositions. Such compositions preferably include at least one pharmaceutically acceptable carrier, such as those described in Remington's Pharmaceutical Sciences (E. W. Martin). In addition, the compositions preferably include a pharmaceutically acceptable buffer, preferably phosphate buffered saline, together with a pharmaceutically acceptable compound for adjusting isotonic pressure, such as, for example, sodium chloride, mannitol, or sorbitol.

Adenosine or an adenosine agonist can also be provided in carriers and adjuvants such as ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances, such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen

phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances and polyethylene glycol. Adjuvants for topical or gel base forms of adenosine or adenosine analogs may, for example, be selected from the group consisting of sodium carboxymethylcellulose, polyacrylates, polyoxythylene-polyoxypropylene-block polymers, polyethylene glycol and wood wax alcohols. For all administrations, conventional depot forms may be used.

The adenosine or adenosine analog-containing compositions may be in any pharmaceutically acceptable dosage form. They are preferably applied by topical routes to exert local therapeutic effects. For topical application, the penetration of the adenosine into skin tissue may be enhanced by a variety of methods known to those of ordinary skill in the art. For example, adenosine may be applied directly and mechanically rubbed into the skin. Alternatively, adenosine or adenosine analogs may be incorporated into a transdermal patch that is applied to the skin. Preferably, the penetration resulting from these methods is enhanced with a chemical transdermal delivery agent such as dimethyl sulfoxide (DMSO) or the nonionic surfactant, n-decylmethyl sulfoxide (NDMS), as described in Choi et al., Pharmaceutical Res., 7(11):1099, 1990.

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

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

Adenosine or an adenosine analog enhances skin condition when there is a noticeable decrease in noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling of the treated skin. Methods of measuring improvements in skin condition are well known in the art (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 26:215–24, 1992), and can include subjective evaluations by the patient or a second party, e.g., a treating physician. Objective methods can include skin topography measurements, such as those described in Grove et al., J. Amer. Acad. Dermatol. 21:631–37 (1989). In skin topography measurements, silicone rubber replicas are made of a small area of skin, e.g., a 1 cm diameter circular area. The silicone rubber replicas capture fine lines and wrinkles on the skin. These specimens are then analyzed using computerized digital image processing to provide an objective measurement of the skin's topography. Skin topography measurements generated following digital-image processing can be measured using the values R_a and R_z as described in Olsen et al., J. Amer. Acad. Dermatol. 37:217–26, 1997, where R_a represents the area of deviation of skin surface features above and below an average central line, and R_z represents the difference between the maximum and minimum heights in five equal segments of the skin surface profile. A statistically significant decline (e.g., $P<0.05$) in R_a and R_z values in skin treated with adenosine or an adenosine analog compared to untreated skin indicates an enhancement of skin condition.

Fibroblasts treated with adenosine or adenosine analogs can also be incorporated into a matrix and implanted in the body, e.g., as part of a skin graft. In addition, fibroblasts can be genetically engineered ex vivo to increase the amount of intracellular adenosine levels and then re-introduced into a human patient. (See, for example, Anderson et al. U.S. Pat. No. 5,399,349; and Mulligan & Wilson, U.S. Pat. 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, N.J.). For skin fibroblasts, primary cultures had been initiated from explants obtained from a 3 mm punch biopsy of the mesial aspect of the upper left arm. Human lung fibroblasts (IMR-90) were established from a 16-week normal female fetus. All cells displayed a normal diploid karyotype and all cells tested negative for bacteria, fungi and mycoplasma contamination.

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

Incorporation of [^{3}H]Thymidine

As an index of DNA synthesis incorporation of [^{3}H] thymidine was measured as described in Ethier et al., Am. J. Physiol. 272:H1470–79 (1997). Confluent monolayers of human skin fibroblasts in MEM plus 10% FBS were seeded into 16 mm diameter culture wells (24-well plates) at a density of 1×10^4 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 lmCi/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, 2 μCi/ml

[^{3}H]phenylalanine was added to the cultures. Unlabeled phenylalanine (0.36 mM) was also added to equalize concentrations of intracellular and extracellular phenylalanine. After 8 hours, medium was removed and the cells were washed twice with cold (4° C.) HBSS and incubated for 20 minutes in cold 10% (w/v) TCA. Cells were then incubated 5 minutes in 95% ethanol (4° C.) and the TCA-insoluble material was solubilized with a solution of 0.2M NaOH and 0.2% SDS. The radioactivity of this fraction was determined by standard liquid scintillation spectrometric techniques.

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

Determination of Cell Size

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

Experimental Materials

MEM, FBS, penicillin, streptomycin, trypsin, and HBSS were obtained from GIBCO (Grand Island, N.Y.), [^{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, Mass.). Adenosine was from Boehringer Mannheim, SDS was from National Diagnostics, (Highland Park, N.J.) 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 10–4M 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. **1**A. In contrast, adenosine (10^{-4}M) had no effect on [^{3}H] thymidine incorporation in cultures of human lung fibroblasts (IMR-90) (FIG. **1**B). 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 Age	Donor Sex	[^{3}H] thymidine incorporation (% of control)	n
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 Age	Donor Sex	[^{3}H] thymidine incorporation (% of control)	n
AG11728	–	67	F	100	6
	+			91 ± 6	6
AG12949	–	70	M	100	11
	+			150 + 31*	11
AG11730	–	84	M	100	10
	+			154 ± 22*	10

Protein Synthesis

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

Cell Size

The effect of adenosine on cell size was determined on human skin fibroblasts from young and aged donors by measuring forward light scatter in a FACS analyzer. Cultures made quiescent by serum removal were exposed to adenosine for 18 hours, removed by trypsinization, and diluted in 4° C. HBSS. A minimum of 1×10^4 cells were measured for each experiment. The results are shown in Table 2. Values are mean +SEM for relative cell size determined by forward light scatter (FLS) in a fluorescence-activated cell sorter, and

n=number of cells measured. The asterisk denotes the measurement is significantly different from corresponding control.

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

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

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

TABLE 3

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

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

TABLE 4

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

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

Other Embodiments

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention. For example, while the invention has been described using adenosine and adenosine agonists, other compounds structurally similar to adenosine can also be used, e.g., purine-containing compounds and compounds having a ribosyl moiety. Other aspects, advantages, and modifications of the invention are within the scope of the following claims.

We claim:

1. 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.

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

3. The method of claim **1**, wherein the adenosine concentration is 10^{-4} M to 10^{-6} M.

4. The method of claim **1**, wherein the adenosine concentration is about 10^{-4} M.

5. The method of claim **1**, wherein the composition further comprises a conditioning agent.

6. The method of claim **5**, wherein the conditioning agent is a humectant, an emollient, or an occlusive agent.

7. The method of claim **1**, wherein the mammal is a human.

8. The method of claim **1**, wherein the skin comprises a skin graft.

9. The method of claim **1**, wherein the composition further comprises a transdermal delivery agent.

10. The method of claim **1**, wherein the composition is in a transdermal patch and the composition is topically applied by contacting the patch to the skin.

* * * * *

EXHIBIT 3

US006645513B2

(12) **United States Patent**
Dobson, Jr. et al.

(10) **Patent No.: US 6,645,513 B2**
(45) **Date of Patent: *Nov. 11, 2003**

(54) **TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG**

(75) Inventors: **James G. Dobson, Jr.**, Auburn, MA (US); **Michael F. Ethier**, Grafton, MA (US)

(73) Assignee: **University of Massachusetts**, Boston, MA (US)

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

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/184,810**

(22) Filed: **Jun. 28, 2002**

(65) **Prior Publication Data**

US 2003/0044439 A1 Mar. 6, 2003

Related U.S. Application Data

(63) Continuation of application No. 09/672,348, filed on Sep. 28, 2000, now Pat. No. 6,423,327, which is a continuation of application No. 09/179,006, filed on Oct. 26, 1998, now abandoned.

(51) **Int. Cl.**[7] **A61K 7/00**; A61K 31/7076

(52) **U.S. Cl.** **424/401**; 424/447; 424/448; 424/449; 514/46

(58) **Field of Search** 424/401, 447, 424/448, 449; 514/46

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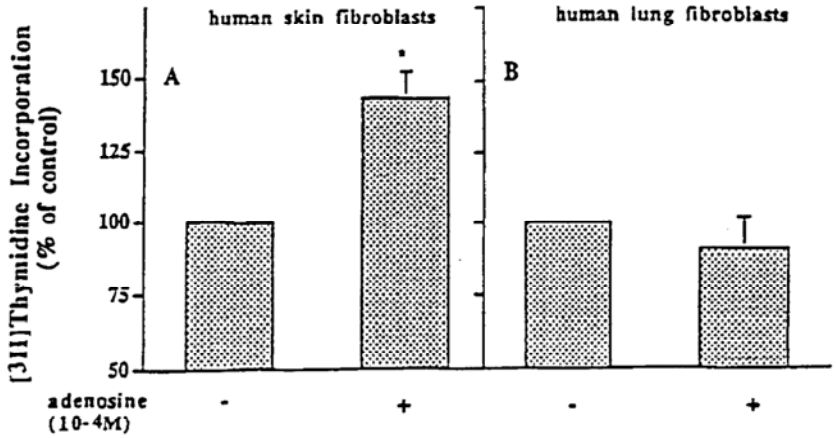
(74) *Attorney, Agent, or Firm*—Fish & Richardson P.C.

(57) **ABSTRACT**

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.

10 Claims, 2 Drawing Sheets



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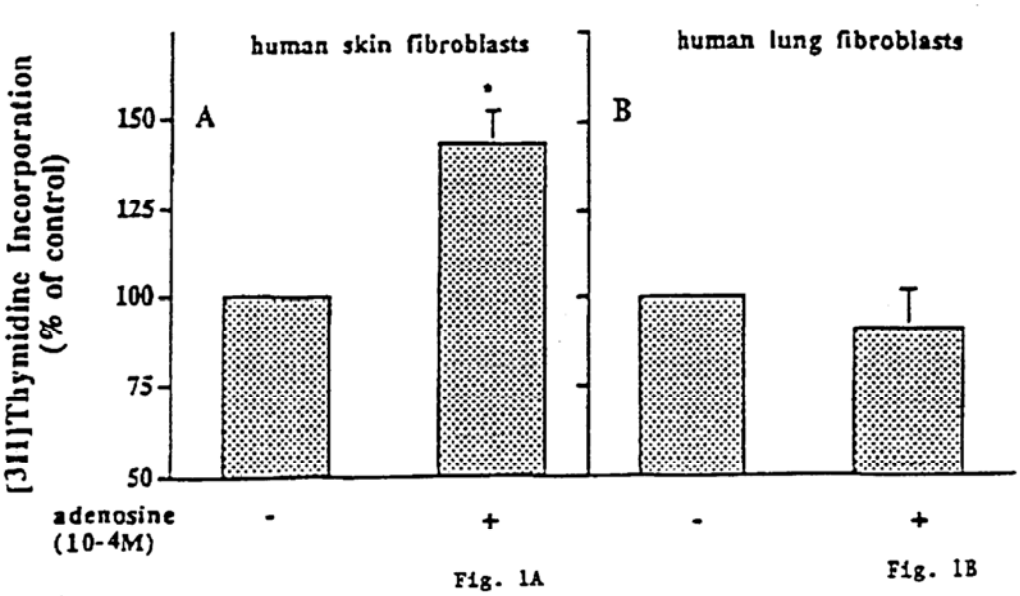

human skin fibroblasts
human lung fibroblasts
[311]Thymidine Incorporation
(% of control)
150
125
100
75
50
A
B
*
adenosine
(10-4M)
-
+
-
+

Fig. 1A Fig. 1B

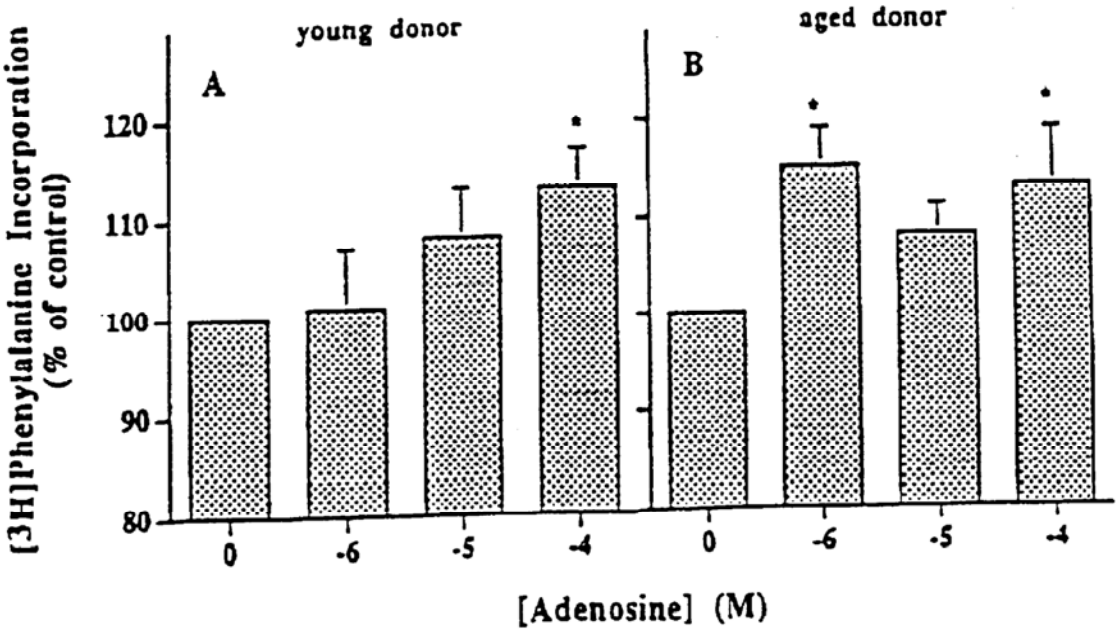

young donor
aged donor
A
B
[3H]Phenylalanine Incorporation (% of control)
120
110
100
90
80
*
*
*
0
-6
-5
-4
0
-6
-5
-4
[Adenosine] (M)

Fig. 2A

Fig. 2B

TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 09/672,348, filed on Sep. 28, 2000, now U.S. Pat. No. 6,423,327, which is a continuation of U.S. patent application Ser. No. 09/179,006, filed on Oct. 26, 1998, now abandoned, which are incorporated herein by reference in their entirety.

STATEMENT AS TO FERDERALLY SPONSORED RESEARCH

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

FIELD OF THE INVENTION

This invention relates to dermatology and cell biology.

BACKGROUND OF THE INVENTION

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

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

SUMMARY OF THE INVENTION

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

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

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

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

The invention also features a method of increasing protein synthesis in a dermal cell of non-diseased skin of a mammal.

The method includes topically administering a composition including a therapeutically effective amount of adenosine or an adenosine analog to a region of skin of the mammal containing the dermal cell. The adenosine or adenosine analog does not cause proliferation of the dermal cell.

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

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

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

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

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

The invention also provides a composition including about 10^{-3} M to about 10^{-7} M adenosine and a therapeutically effective amount of an angiogenesis factor. In some embodiments, the composition of the adenosine is about 10^{-4} M.

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

DETAILED DESCRIPTION

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

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

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

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

Adenosine can be also be administered with a second compound. The second compound can enhance the action of adenosine or the adenosine analog, e.g., by enhancing binding of adenosine or an adenosine analog to an adenosine receptor. An example of such a compound is PD 81,728, which is described in Kollias-Baker et al. J. Pharmacol. Exp. Ther. 281:761–68. Alternatively, the second agent can itself act to enhance skin condition. Examples of these types of agents include tretinoin, a recognized skin conditioning agent (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 37:217–26, 1997), an angiogenic factor such as vascular endothelial cell growth factor (VEGF) or basic fibroblast growth factor (BFGF), or a conditioning agent.

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

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

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

The pharmaceutical composition may be formulated using conventional methods to prepare pharmaceutically useful compositions. Such compositions preferably include at least one pharmaceutically acceptable carrier, such as those described in Remington's Pharmaceutical Sciences (E. W. Martin). In addition, the compositions preferably include a pharmaceutically acceptable buffer, preferably phosphate buffered saline, together with a pharmaceutically acceptable compound for adjusting isotonic pressure, such as, for example, sodium chloride, mannitol, or sorbitol.

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

The adenosine or adenosine analog-containing compositions may be in any pharmaceutically acceptable dosage form. They are preferably applied by topical routes to exert local therapeutic effects. For topical application, the penetration of the adenosine into skin tissue may be enhanced by a variety of methods known to those of ordinary skill in the art. For example, adenosine may be applied directly and mechanically rubbed into the skin. Alternatively, adenosine or adenosine analogs may be incorporated into a transdermal patch that is applied to the skin. Preferably, the penetration resulting from these methods is enhanced with a chemical transdermal delivery agent such as dimethyl sulfoxide (DMSO) or the nonionic surfactant, n-decylmethyl sulfoxide (NDMS), as described in Choi et al., Pharmaceutical Res., 7(11):1099, 1990.

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

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

Adenosine or an adenosine analog enhances skin condition when there is a noticeable decrease in noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling of the treated skin. Methods of measuring improvements in skin condition are well known in the art (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 26:215–24, 1992), and can include subjective evaluations by the patient or a second party, e.g., a treating physician. Objective methods can include skin topography measurements, such as those described in Grove et al., J. Amer. Acad. Dermatol. 21:631–37 (1989). In skin topography measurements, silicone rubber replicas are made of a small area of skin, e.g., a 1 cm diameter circular area. The silicone rubber replicas capture fine lines and wrinkles on the skin. These specimens are then analyzed using computerized digital image processing to provide an objective measurement of the skin's topography. Skin topography measurements generated following digital-image processing can be measured using the values R_a and R_z as described in Olsen et al., J. Amer. Acad. Dermatol. 37:217–26, 1997, where R_a represents the area of deviation of skin surface features above and below an average central line, and R_z represents the difference between the maximum and minimum heights in five equal segments of the skin surface profile. A statistically significant decline (e.g., $P<0.05$) in R_a and R_z values in skin treated with adenosine or an adenosine analog compared to untreated skin indicates an enhancement of skin condition.

Fibroblasts treated with adenosine or adenosine analogs can also be incorporated into a matrix and implanted in the body, e.g., as part of a skin graft. In addition, fibroblasts can be genetically engineered ex vivo to increase the amount of intracellular adenosine levels and then re-introduced into a human patient. (See, for example, Anderson et al. U.S. Pat. No. 5,399,349; and Mulligan & Wilson, U.S. Pat. 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, N.J.). For skin fibroblasts, primary cultures had been initiated from explants obtained from a 3 mm punch biopsy of the mesial aspect of the upper left arm. Human lung fibroblasts (IMR-90) were established from a 16-week normal female fetus. All cells displayed a normal diploid karyotype and all cells tested negative for bacteria, fungi and mycoplasma contamination.

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

Incorporation of [^{3}H]Thymidine

As an index of DNA synthesis incorporation of [^{3}H] thymidine was measured as described in Ethier et al., Am. J. Physiol. 272:H1470–79 (1997). Confluent monolayers of human skin fibroblasts in MEM plus 10% FBS were seeded into 16 mm diameter culture wells (24-well plates) at a density of 1×10^4 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 1 mCi/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, 2 μCi/ml [^{3}H]phenylalanine was added to the cultures. Unlabeled phenylalanine (0.36 mM) was also added to equalize concentrations of intracellular and extracellular phenylalanine. After 8 hours, medium was removed and the cells were washed twice with cold (4° C.) HBSS and incubated for 20 minutes in cold 10% (w/v) TCA. Cells were then incubated 5 minutes in 95% ethanol (4° C.) and the TCA-insoluble material was solubilized with a solution of 0.2M NaOH and 0.2% SDS. The radioactivity of this fraction was determined by standard liquid scintillation spectrometric techniques.

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

Determination of Cell Size

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

Experimental Materials

MEM, FBS, penicillin, streptomycin, trypsin, and HBSS were obtained from GIBCO (Grand Island, N.Y.), [^{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, Mass.). Adenosine was from Boehringer Mannheim, SDS was from National Diagnostics, (Highland Park, N.J.) 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. **1**A. In contrast, adenosine (10^{-4}M) had no effect on [^{3}H]thymidine incorporation in cultures of human lung fibroblasts (IMR-90) (FIG. **1**B). 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 Age	Donor Sex	[^{3}H] thymidine incorporation (% of control)	n
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 Age	Donor Sex	[^{3}H] thymidine incorporation (% of control)	n
AG11728	–	67	F	100	6
	+			91 ± 6	6
AG12949	–	70	M	100	11
	+			150 ± 31*	11
AG11730	–	84	M	100	10
	+			154 ± 22*	10

Protein Synthesis

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

Cell Size

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

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

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

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

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

TABLE 3

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

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

TABLE 4

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

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

Other Embodiments

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention. For example, while the invention has been described using adenosine and adenosine agonists, other compounds structurally similar to adenosine can also be used, e.g., purine-containing compounds and compounds having a ribosyl moiety. Other aspects, advantages, and modifications of the invention are within the scope of the following claims.

We claim:

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

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

3. The method of claim **1**, wherein the adenosine concentration is 10^{-1} M to 10^{-6} M.

4. The method of claim **1**, wherein the adenosine concentration is about 10^{-3} M.

5. The method of claim **1**, wherein the composition further comprises a conditioning agent.

6. The method of claim **5**, wherein the conditioning agent is a humectant, an emollient, or an occlusive agent.

7. The method of claim **6**, wherein the mammal is a human.

8. The method of claim **1**, wherein the skin comprises a skin graft.

9. The method of claim **1**, wherein the composition further comprises a transdermal delivery agent.

10. The method of claim **1**, wherein the composition is in a transdermal patch and the composition is topically applied by contacting the patch to the skin.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

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

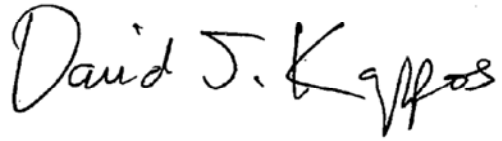
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 10, claim 3, line 2:

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

Signed and Sealed this

Twenty-second Day of June, 2010



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

EXHIBIT 4

Exhibit 169

U.S. Patent No. 6,423,327 vs. L'Oréal Paris Wrinkle Expert 55+ Moisturizer

The following claim chart includes illustrations and references relating to this accused product, which includes but is not limited to the product listed in the title above, as well as other substantially identical products sold under other names with substantially identical ingredients, formulations, and marketing and/or advertising and/or website materials that L'Oréal designs, produces, sells, and disseminates, including but not limited to L'Oréal Paris Wrinkle Expert 55+ Anti-Wrinkle Eye Treatment. Various sources cited herein are intended to illustrate theories of infringement, and are not intended to exclude other allegations of infringement.

Claim	Claim Element	Evidence of Infringement
1[a]	A method for enhancing the condition of unbroken skin of a mammal	Using L'Oréal Paris Wrinkle Expert 55+ Moisturizer comprises a method for enhancing the condition of unbroken skin of a mammal. For example, using L'Oréal Paris Wrinkle Expert 55+ Moisturizer enhances the condition of unbroken skin. L'Oréal Paris Wrinkle Expert 55+ Moisturizer is intended to be used on human, i.e. mammalian skin. *See, e.g.*, ADENOSINE_00003141-3201 • "Reduces wrinkles. Improves contours. 24 hour hydration." • "Wrinkle Expert is L'Oréal Paris' first daily anti-wrinkle skincare line for all of life's stages featuring formulas, with selected ingredients, for younger looking skin at every age. Our anti-wrinkle face cream for ages 55+ with Calcium works to strengthen thinning skin and improve smoothness for a more youthful appearance. Visibly reduces signs of aging including wrinkles, sagging contours, and density loss." • "HOW TO Every morning and night, smooth gently over the face and neck until thoroughly absorbed. For best results, use in conjunction with other L'Oréal Paris products."

1[b]	by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin,	Using L'Oréal Paris Wrinkle Expert 55+ Moisturizer reduces one or more of wrinkling, roughness, dryness, or laxity of the skin. *See, e.g.*, ADENOSINE_00003141-3201 • "Reduces wrinkles. Improves contours. 24 hour hydration." • "Wrinkle Expert is L'Oréal Paris' first daily anti-wrinkle skincare line for all of life's stages featuring formulas, with selected ingredients, for younger looking skin at every age. Our anti-wrinkle face cream for ages 55+ with Calcium works to strengthen thinning skin and improve smoothness for a more youthful appearance. Visibly reduces signs of aging including wrinkles, sagging contours, and density loss." • "HOW TO Every morning and night, smooth gently over the face and neck until thoroughly absorbed. For best results, use in conjunction with other L'Oréal Paris products."
1[c]	without increasing dermal cell proliferation,	L'Oréal Paris Wrinkle Expert 55+ Moisturizer contains adenosine in an amount that does not increase dermal cell proliferation. *See* forthcoming expert disclosures and/or defendants' internal, to-be-produced documents.
1[d]	the method comprising topically applying to the skin a composition	Using L'Oréal Paris Wrinkle Expert 55+ Moisturizer is a method comprising topically applying to the skin a composition. L'Oréal directs and/or controls its customers topically applying L'Oréal Paris Wrinkle Expert 55+ Moisturizer. *See, e.g.*, ADENOSINE_00003141-3201 • "Reduces wrinkles. Improves contours. 24 hour hydration." • "Wrinkle Expert is L'Oréal Paris' first daily anti-wrinkle skincare line for all of life's stages featuring formulas, with selected ingredients, for younger looking skin

		at every age. Our anti-wrinkle face cream for ages 55+ with Calcium works to strengthen thinning skin and improve smoothness for a more youthful appearance. Visibly reduces signs of aging including wrinkles, sagging contours, and density loss." • "HOW TO Every morning and night, smooth gently over the face and neck until thoroughly absorbed. For best results, use in conjunction with other L'Oréal Paris products."
1[e]	comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation,	L'Oréal Paris Wrinkle Expert 55+ Moisturizer contains a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation. Using L'Oréal Paris Wrinkle Expert 55+ Moisturizer enhances the condition of the skin. *See* claim element 1[a]. L'Oréal Paris Wrinkle Expert 55+ Moisturizer contains adenosine in an amount that enhances skin condition. *See, e.g.*, ADENOSINE_00003141-3201. • Ingredients: "Adenosine" *See also* https://www.lorealparisusa.com/ingredient-library/adenosine.aspx (*See* ADENOSINE_00001443-1448.) • "Adenosine is the nucleoside that is most commonly associated with the body's energy-transferring processes. It is present in adenosine triphosphate (ATP), an essential biological and chemical signaling molecule. Due to its high-biological profile, adenosine uses in skincare have grabbed the attention of cosmetic companies. As a result, studies have shown the use of adenosine for skin can be an effective method for providing anti-aging benefits. When applied topically,

		adenosine-containing products showed significant improvements in the visible signs of aging as well as improving skin smoothness. 1 For this reason, adenosine can most commonly be found in moisturizing skincare products such as creams or serums." *See also* Abella, M. L. Evaluation of anti-wrinkle efficacy of adenosine-containing products using the FOITS technique. International journal of cosmetic science 28.6, 447-451 (2006). (*See* ADENOSINE_00001450-1454.) • "Both adenosine-containing products led to significant improvements in skin smoothness in the periorbital area. Improvements were evidenced after 3 weeks of product application as measured by Ra and Rz parameters using the FOITS technique, and were steadily confirmed after 2 months, despite severe climatic conditions and independently of the analysis technique that was used with the FOITS data. Adenosine-containing cream also significantly improved glabellar frowns. This study demonstrates the potential beneficial effects of adenosine-containing products on crow's feet and glabellar facial wrinkles." *See also* Legendre, J.Y. Formulation, characterization, and efficacy of an adenosine-containing dissolvable film for localized anti-wrinkle effect. Journal of cosmetic science 58.2, 147-155 (2007). (*See* ADENOSINE_00001449.) • "A randomized, placebo-controlled, investigator-blind study was conducted in female volunteers to assess the efficacy of the 1% adenosine-containing dissolvable film. After three weeks and eight weeks, a twice daily application led to a significant decrease in the skin roughness parameters as observed using fast optical in vivo topometry (FOITS)." *See also* U.S. Patent No. 9,023,826. (*See* ADENOSINE_00001479-1484.) • "In the cosmetic domain, adenosine and its analogs are important active compounds for skin anti-aging due to its function on increasing DNA/protein synthesis in dermal cells."

		See also U.S. Patent Application No. 2004/0146474. (*See* ADENOSINE_00001455-1461.) • "[A]denosine and its analogs can satisfy the . . . need for effective compounds for relaxing the skin with a view to smoothing or toning down expression lines, relaxing the skin, relaxing facial features, decreasing wrinkles, reducing laugh lines, reducing frown lines, etc." *See also* U.S. Patent Application No. 2010/0168049. (*See* ADENOSINE_00001462-1478.) • Use of a compound containing, among other ingredients, adenosine or an adenosine analog "leads to a complementarity of action both on the microrelief of the skin, making it possible especially to combat the formation of expression wrinkles, and also on the stimulation of dermal and/or epidermal regeneration by stimulating the metabolism and the process of epidermal renewal, leading to a reduction in the appearance of the signs of chronological ageing and photoageing." *See also* forthcoming expert disclosures and/or defendants' internal, to-be-produced documents. L'Oréal Paris Wrinkle Expert 55+ Moisturizer contains adenosine in an amount that does not increase dermal cell proliferation. *See* claim element 1[c].
1[f]	wherein the adenosine concentration applied to the dermal cells is 10^{-4} to 10^{-7} M.	Using L'Oréal Paris Wrinkle Expert 55+ Moisturizer entails applying to the dermal cells a concentration of adenosine of approximately 10^{-4} to 10^{-7} M. *See* forthcoming expert disclosures.
3	The method of claim 1, wherein the adenosine concentration is 10^{-4} to 10^{-6} M.	*See* claim 1.

		Using L'Oréal Paris Wrinkle Expert 55+ Moisturizer entails applying to the dermal cells a concentration of adenosine of approximately 10^{-4} to 10^{-6} M. *See* forthcoming expert disclosures.
5	The method of claim 1, wherein the composition further comprises a conditioning agent.	*See* claim 1. L'Oréal Paris Wrinkle Expert 55+ Moisturizer contains at least one conditioning agent. For example, L'Oréal Paris Wrinkle Expert 55+ Moisturizer contains GLYCERIN, DIMETHICONE, CETYL ALCOHOL, and CAPRYLYL GLYCOL. *See, e.g.*, ADENOSINE_00003141-3201
6	The method of claim 5, wherein the conditioning agent is a humectant, an emollient, or an occlusive agent.	*See* claim 5. For example, L'Oréal Paris Wrinkle Expert 55+ Moisturizer contains GLYCERIN, DIMETHICONE, CETYL ALCOHOL, and CAPRYLYL GLYCOL. *See, e.g.*, ADENOSINE_00003141-3201
7	The method of claim 1, wherein the mammal is a human.	*See* claim 1 and claim element 1[a].
9	The method of claim 1, wherein the composition further comprises a transdermal delivery agent.	*See* claim 1. L'Oréal Paris Wrinkle Expert 55+ Moisturizer contains at least one transdermal delivery agent. For example, L'Oréal Paris Wrinkle Expert 55+ Moisturizer contains ISOPROPYL ISOSTEARATE, PROPYLENE GLYCOL, OCTYLDODECANOL, CETYL ALCOHOL, PHENOXYETHANOL, PALMITIC ACID, STEARYL ALCOHOL, and T-BUTYL ALCOHOL.

		See, e.g., ADENOSINE_00003141-3201

EXHIBIT 5

Exhibit 268

U.S. Patent No. 6,645,513 vs. Easeamine Day Crème

The following claim chart includes illustrations and references relating to this product. Various sources cited herein are intended to illustrate theories of infringement, and are not intended to exclude other allegations of infringement.

Claim	Claim Element	Evidence of Infringement
1[a]	A method for enhancing the condition of unbroken skin of a mammal	Using Easeamine Day Crème comprises a method for enhancing the condition of unbroken skin of a mammal. For example, using Easeamine Day Crème enhances the condition of unbroken skin. Easeamine Day Crème is intended to be used on human, i.e. mammalian skin. *See, e.g.*, https://www.easeamine.com/Easeamine-Day-Creme-p/4.htm (ADENOSINE_00001421-1425) • "Imagine skin that's been reborn with the fresh glow of youth. Skin that's saturated with moisture from within, so it's soft, firm, vital. With Easeamine Day Crème this is your skin. Formulated with Adenosine, this delicate Day Crème is more than an anti-aging treatment, it's also a powerful protector that helps to replenish vital moisture and rehydrate and recondition skin. Enriched with powerful anti-oxidant Vitamins A and E, it protects against environmental and free radical damage that ages skin. In just twelve weeks, lines and wrinkles appear less prominent, texture is smoother, skin color is brightened and skin tone is evened out for skin that's healthier and more radiant than you ever thought possible." • Easeamine Day Crème formulated with Adenosine, penetrates deep into the skin's layers, helping hydrate and replenish the natural vital moisture barrier, promoting cell regeneration, strengthening firmness and tone. Anti-oxidant Vitamins A, C and E protect against environmental and free radical damage that ages skin. Anti-aging

		Adenosine reduces fine lines and wrinkles, while increasing the healthy appearance of your skin." • "Product Application After treating your skin with Easeamine Gel Cleanser and Easeamine Day Crème, lightly apply Easeamine Day Crème—massaging thoroughly into face, throat and décolleté. Apply every morning. Avoid direct contact with eye area." • "Product Benefits Helps reduce fine lines and wrinkles Delivering vital moisturizers and hydrators Promotes skin elasticity and smooth texture Promotes stimulation of collagen and elastin at cellular level helping to restore appearance of volume and firmness to skin Enriched with powerful anti-oxidant Vitamins A and E preserving anti-aging gains and protection against environmental stress and free radical damage • "Formula Profile Patented anti-aging Adenosine Skin Technology Patented Hydroxysomes® calcium-based delivery system Free of artificial colors, dyes and mineral oil Paraben and fragrance-free Natural botanical preservative No animal testing"
1[b]	by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin,	Using Easeamine Day Crème reduces one or more of wrinkling, roughness, dryness, or laxity of the skin. *See, e.g.*, https://www.easeamine.com/Easeamine-Day-Creme-p/4.htm(ADENOSINE_00001421-1425)

		• "Imagine skin that's been reborn with the fresh glow of youth. Skin that's saturated with moisture from within, so it's soft, firm, vital. With Easeamine Day Crème this is your skin. Formulated with Adenosine, this delicate Day Crème is more than an anti-aging treatment, it's also a powerful protector that helps to replenish vital moisture and rehydrate and recondition skin. Enriched with powerful anti-oxidant Vitamins A and E, it protects against environmental and free radical damage that ages skin. In just twelve weeks, lines and wrinkles appear less prominent, texture is smoother, skin color is brightened and skin tone is evened out for skin that's healthier and more radiant than you ever thought possible." • Easeamine Day Crème formulated with Adenosine, penetrates deep into the skin's layers, helping hydrate and replenish the natural vital moisture barrier, promoting cell regeneration, strengthening firmness and tone. Anti-oxidant Vitamins A, C and E protect against environmental and free radical damage that ages skin. Anti-aging Adenosine reduces fine lines and wrinkles, while increasing the healthy appearance of your skin." • "Product Application After treating your skin with Easeamine Gel Cleanser and Easeamine Day Crème, lightly apply Easeamine Day Crème—massaging thoroughly into face, throat and décolleté. Apply every morning. Avoid direct contact with eye area." • "Product Benefits Helps reduce fine lines and wrinkles Delivering vital moisturizers and hydrators Promotes skin elasticity and smooth texture Promotes stimulation of collagen and elastin at cellular level helping to restore appearance of volume and firmness to skin Enriched with powerful anti-oxidant Vitamins A and E preserving anti-aging gains and protection against environmental stress and free radical damage

		• "Formula Profile Patented anti-aging Adenosine Skin Technology Patented Hydroxysomes® calcium-based delivery system Free of artificial colors, dyes and mineral oil Paraben and fragrance-free Natural botanical preservative No animal testing"
1[c]	without increasing dermal cell proliferation,	Easeamine Day Crème contains adenosine in an amount that does not increase dermal cell proliferation. *See* forthcoming expert disclosures and/or defendants' internal, to-be-produced documents.
1[d]	the method comprising topically applying to the skin a composition	Using Easeamine Day Crème is a method comprising topically applying to the skin a composition. *See, e.g.*, https://www.easeamine.com/Easeamine-Day-Creme-p/4.htm(ADENOSINE_00001421-1425) • "Imagine skin that's been reborn with the fresh glow of youth. Skin that's saturated with moisture from within, so it's soft, firm, vital. With Easeamine Day Crème this is your skin. Formulated with Adenosine, this delicate Day Crème is more than an anti-aging treatment, it's also a powerful protector that helps to replenish vital moisture and rehydrate and recondition skin. Enriched with powerful anti-oxidant Vitamins A and E, it protects against environmental and free radical damage that ages skin. In just twelve weeks, lines and wrinkles appear less prominent, texture is smoother, skin color is brightened and skin tone is evened out for skin that's healthier and more radiant than you ever thought possible."

		• Easeamine Day Crème formulated with Adenosine, penetrates deep into the skin's layers, helping hydrate and replenish the natural vital moisture barrier, promoting cell regeneration, strengthening firmness and tone. Anti-oxidant Vitamins A, C and E protect against environmental and free radical damage that ages skin. Anti-aging Adenosine reduces fine lines and wrinkles, while increasing the healthy appearance of your skin." • "Product Application After treating your skin with Easeamine Gel Cleanser and Easeamine Day Crème, lightly apply Easeamine Day Crème—massaging thoroughly into face, throat and décolleté. Apply every morning. Avoid direct contact with eye area." • "Product Benefits Helps reduce fine lines and wrinkles Delivering vital moisturizers and hydrators Promotes skin elasticity and smooth texture Promotes stimulation of collagen and elastin at cellular level helping to restore appearance of volume and firmness to skin Enriched with powerful anti-oxidant Vitamins A and E preserving anti-aging gains and protection against environmental stress and free radical damage • "Formula Profile Patented anti-aging Adenosine Skin Technology Patented Hydroxysomes® calcium-based delivery system Free of artificial colors, dyes and mineral oil Paraben and fragrance-free Natural botanical preservative No animal testing"
1[e]	comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without	Easeamine Day Crème contains a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation. Using Easeamine Day Crème enhances the condition of the skin.

	increasing dermal cell proliferation,	*See* claim element 1[a]. Easeamine Day Crème contains adenosine in an amount that enhances skin condition. *See, e.g.*, https://www.easeamine.com/Easeamine-Day-Creme-p/4.htm(ADENOSINE_00001421-1425) • Key Ingredients: "Adenosine" *See also* https://www.lorealparisusa.com/ingredient-library/adenosine.aspx (*See* ADENOSINE_00001443-1448.) • "Adenosine is the nucleoside that is most commonly associated with the body's energy-transferring processes. It is present in adenosine triphosphate (ATP), an essential biological and chemical signaling molecule. Due to its high-biological profile, adenosine uses in skincare have grabbed the attention of cosmetic companies. As a result, studies have shown the use of adenosine for skin can be an effective method for providing anti-aging benefits. When applied topically, adenosine-containing products showed significant improvements in the visible signs of aging as well as improving skin smoothness. 1 For this reason, adenosine can most commonly be found in moisturizing skincare products such as creams or serums." *See also* Abella, M. L. Evaluation of anti-wrinkle efficacy of adenosine-containing products using the FOITS technique. International journal of cosmetic science 28.6, 447-451 (2006). (*See* ADENOSINE_00001450-1454.) • "Both adenosine-containing products led to significant improvements in skin smoothness in the periorbital area. Improvements were evidenced after 3 weeks of product application as measured by Ra and Rz parameters using the FOITS

		technique, and were steadily confirmed after 2 months, despite severe climatic conditions and independently of the analysis technique that was used with the FOITS data. Adenosine-containing cream also significantly improved glabellar frowns. This study demonstrates the potential beneficial effects of adenosine-containing products on crow's feet and glabellar facial wrinkles." *See also* Legendre, J.Y. Formulation, characterization, and efficacy of an adenosine-containing dissolvable film for localized anti-wrinkle effect. Journal of cosmetic science 58.2, 147-155 (2007). (*See* ADENOSINE_00001449.) • "A randomized, placebo-controlled, investigator-blind study was conducted in female volunteers to assess the efficacy of the 1% adenosine-containing dissolvable film. After three weeks and eight weeks, a twice daily application led to a significant decrease in the skin roughness parameters as observed using fast optical in vivo topometry (FOITS)." *See also* U.S. Patent No. 9,023,826. (*See* ADENOSINE_00001479-1484.) • "In the cosmetic domain, adenosine and its analogs are important active compounds for skin anti-aging due to its function on increasing DNA/protein synthesis in dermal cells." *See also* U.S. Patent Application No. 2004/0146474. (*See* ADENOSINE_00001455-1461.) • "[A]denosine and its analogs can satisfy the . . . need for effective compounds for relaxing the skin with a view to smoothing or toning down expression lines, relaxing the skin, relaxing facial features, decreasing wrinkles, reducing laugh lines, reducing frown lines, etc." *See also* U.S. Patent Application No. 2010/0168049. (*See* ADENOSINE_00001462-1478.)

		• Use of a compound containing, among other ingredients, adenosine or an adenosine analog "leads to a complementarity of action both on the microrelief of the skin, making it possible especially to combat the formation of expression wrinkles, and also on the stimulation of dermal and/or epidermal regeneration by stimulating the metabolism and the process of epidermal renewal, leading to a reduction in the appearance of the signs of chronological ageing and photoageing." *See also* forthcoming expert disclosures and/or defendants' internal, to-be-produced documents. Easeamine Day Crème contains adenosine in an amount that does not increase dermal cell proliferation. *See* claim element 1[c].
1[f]	wherein the adenosine concentration applied to the dermal cells is 10^{-3} to 10^{-7} M.	Using Easeamine Day Crème entails applying to the dermal cells a concentration of adenosine of approximately 10^{-3} to 10^{-7} M. *See* forthcoming expert disclosures.
3	The method of claim 1, wherein the adenosine concentration is 10^{-3} to 10^{-6} M.	Using Easeamine Day Crème entails applying to the dermal cells a concentration of adenosine of approximately 10^{-3} to 10^{-6} M. *See* forthcoming expert disclosures.
5	The method of claim 1, wherein the composition further comprises a conditioning agent.	*See* claim 1. Easeamine Day Crème contains at least one conditioning agent. For example, Easeamine Day Crème contains glycerin, dimethicone, simmondsia chinensis (jojoba) seed oil, and cetyl alcohol.

		See, e.g., https://www.easeamine.com/Easeamine-Day-Creme-p/4.htm(ADENOSINE_00001421-1425)
6	The method of claim 5, wherein the conditioning agent is a humectant, an emollient, or an occlusive agent.	*See* claim 5. For example, Easeamine Day Crème contains glycerin, dimethicone, simmondsia chinensis (jojoba) seed oil, and cetyl alcohol. *See, e.g.*, https://www.easeamine.com/Easeamine-Day-Creme-p/4.htm(ADENOSINE_00001421-1425)
7	The method of claim 1, wherein the mammal is a human.	*See* claim 1 and claim element 1[a].
9	The method of claim 1, wherein the composition further comprises a transdermal delivery agent.	*See* claim 1. Easeamine Day Crème contains at least one transdermal delivery agent. For example, Easeamine Day Crème contains hydroxyapatite, stearyl alcohol, and cetyl alcohol. *See, e.g.*, https://www.easeamine.com/Easeamine-Day-Creme-p/4.htm (ADENOSINE_00001421-1425)

EXHIBIT 6

From: Murray, Katherine F.
Sent: Monday, October 28, 2019 5:28 PM
To: Tamar Lusztig; Polatoglu, Serli; Ellis, Dennis S.; PH-UMASS v. L'Oreal USDC; 'Frederick Cottrell'; 'Jason Rawnsley'; 'Jeffrey Moyer'; Palys, Joseph E.; 'Katharine Mowery'; Modi, Naveen
Cc: Beatrice Franklin; Bill Carmody; 'Brian Farnan'; Justin A. Nelson; Keeley Lombardo; 'Lucas I. Silva'; 'Matthew Lowrie'; Rodney Polanco
Subject: RE: UMass v. L'Oreal

Counsel:

We write regarding Plaintiffs' infringement contentions. Plaintiffs have failed to comply with Paragraph 3(c) of the Scheduling Order (D.I. 46), which requires a "chart identifying specifically where and how each limitation of each asserted claim is found within each Accused Instrumentality." Despite this requirement, with respect to at least the claim limitations "without increasing dermal cell proliferation" and "wherein the adenosine concentration applied to the dermal cells is [recited amount]," Plaintiffs have merely parroted the claim language without providing any further explanation and refer to "forthcoming expert disclosures and/or defendants' internal, to-be produced documents." The same is also true for Plaintiffs' Paragraph 3(g) charts regarding their own products. This fails to comply with the Court's Scheduling Order and local rules. Defendants reserve the right to raise additional deficiencies in Plaintiffs' infringement contentions at a later time.

Please confirm by Wednesday, October 30th that, to avoid any further prejudice to Defendants, Plaintiffs will remedy their non-compliant contentions by November 4th, including by providing the basis on which Plaintiffs contend that the accused products as well as their own products meet these limitations. If Plaintiffs do not so agree, please let us know your availability for a meet and confer this week.

In addition, we also need to discuss Plaintiffs' deficient responses to L'Oréal USA's First Set of Requests for Production. As you know, Plaintiffs have refused to produce documents responsive to 35 Requests. This is improper and fails to comply with Federal Rule of Civil Procedure 34. For instance, Request Nos. 11, 17, 18, 30-33, 45, 60, 83, 84, 87-90, 92, 94, 95, and 98-103 seek information directly relevant to Plaintiffs' allegations in the First Amended Complaint, including allegations that L'Oréal USA's launch of its Youth Code skincare line created financial hardship for the Teresian Carmelites. (*See, e.g.*, FAC ¶¶ 25-29.) As such, they plainly seek discoverable information. Plaintiffs' boilerplate objections to these Requests are meritless and Plaintiffs' refusal to produce the requested documents is improper.

Plaintiffs' objections to Request Nos. 64, 65, 66, 74, 75, 105, 112, 121, 122, and 123 are also not well-taken, as they seek information relevant to infringement and invalidity issues. Similarly, L'Oréal USA is entitled to documents responsive to Request No. 58, which seeks documents relating to non-infringing alternatives to the Patents-in-Suit. Such information is crucial to any claim of lost profits. *See Panduit Corp. v. Stahlin Bros. Fibre Works*, 575 F.2d 1152, 1156 (6th Cir. 1978) (lost profits only available if "acceptable noninfringing substitutes" do not exist).

As with the infringement contentions, please confirm by October 30th that Plaintiffs will be amending their responses to these Requests by November 4th, or let us know your availability to meet and confer this week.

Thank you,
Kathy

Katherine Murray | Of Counsel, Litigation Department
Paul Hastings LLP | 515 South Flower Street, Twenty-Fifth Floor, Los Angeles, CA 90071
Direct: +1.213.683.6273 | Main: +1.213.683.6000 | Fax: +1.213.627.0705 |
katherinemurray@paulhastings.com | www.paulhastings.com

EXHIBIT 7

From: Polatoglu, Serli
Sent: Monday, November 11, 2019 2:39 PM
To: Tamar Lusztig; Murray, Katherine F.; Brian Farnan; Bill Carmody; Beatrice Franklin; cottrell@rlf.com; Ellis, Dennis S.; Justin A. Nelson; Palys, Joseph E.; Keeley Lombardo; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen; PH-UMASS v. L'Oreal USDC
Cc: Michael J. Farnan
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Counsel,

Contrary to Plaintiffs' assertions, during the parties' meet and confer (and as memorialized in our November 6 email), L'Oréal USA explained how Plaintiffs' Infringement Contentions fail to comply with the local rules and the Scheduling Order. That said, we appreciate Plaintiffs' willingness to now attempt to minimize the prejudice to L'Oréal USA and supplement Plaintiffs' Infringement Contentions. With respect to Plaintiffs' offer, we understand that, for the limitations L'Oréal USA identified, Plaintiffs will be providing their bases and theories of infringement, including a production of any documents and data (which will include an identification of any methodologies used to arrive at such data) upon which Plaintiffs are relying. Accordingly, please confirm when Plaintiffs will be supplementing their Infringement Contentions.

We further appreciate Plaintiffs' recognition that the delay in L'Oréal USA's timely receipt of Plaintiffs' Infringement Contentions has impacted the rest of the case schedule. We believe the parties can work together to arrive at an agreed-upon schedule per our November 8 email, and look forward to discussing the schedule with you early this week.

Best,
-Serli

From: Tamar Lusztig <TLusztig@susmangodfrey.com>
Sent: Friday, November 8, 2019 2:24 PM
To: Polatoglu, Serli <serlipolatoglu@paulhastings.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: [EXT] RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Serli,

We've discussed your complaints about our infringement contentions with our clients. As we mentioned on our call earlier this week, we believe our infringement contentions fully comply with the local rules. Although you were unable

to articulate any specific complaints about our infringement contentions yesterday (other than to say vaguely that you believe our disclosure is deficient for unspecified reasons), we are writing to propose a compromise to avoid motion practice. If you can agree it will resolve your issues with our infringement contentions, we would be willing to amend our infringement contentions to further disclose that the basis for plaintiffs' contention that the accused products contain adenosine in an amount that does not increase dermal cell proliferation, and apply adenosine in the claimed ranges to the dermal cells, is a combination of testing and inventor research. As you acknowledged on our call, disclosure of our theories of infringement is not expert discovery, but—in an effort to resolve this dispute—we would also be willing to give you the data that we relied on to form the basis of our belief that these limitations are met.

Let us know if you agree that this proposal would resolve your issues with our infringement contentions. Provided that you do, we would also be happy to discuss moving your invalidity contention deadline.

With respect to Plaintiffs' RFP responses, we are working on revised responses in light of our call on Monday and expect to be able to serve them next week.

-Tamar

From: Polatoglu, Serli <serlipolatoglu@paulhastings.com>
Sent: Wednesday, November 6, 2019 6:44 PM
To: Murray, Katherine F. <katherinemurray@paulhastings.com>; Tamar Lusztig <TLusztig@susmangodfrey.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Counsel,

I write to follow up on our meet and confer Monday afternoon. An overview of our understanding of the discussions is below.

With respect to Plaintiffs' Infringement Contentions, we explained that they are currently deficient, as they do not provide an explanation of the "where and how," *i.e.*, the basis or theory, for Plaintiffs' claims of infringement with respect to the claim language "without increasing dermal cell proliferation" and "wherein the adenosine concentration applied to the dermal cells is [recited amount]." You stated that you would consider the issue further and potentially provide us with amended contentions. Please confirm by Friday, November 8, that Plaintiffs will remedy their non-compliant contentions.

We also discussed the current case schedule. As Plaintiffs refuse to narrow the scope of the Accused Products (which stand at about 170 products total), we explained that some of the current deadlines are unworkable. You stated that you were amenable to continuing at least some of these deadlines, including the upcoming deadline to file our invalidity contentions. We are working on a proposed amended schedule and will circulate it soon.

With respect to Plaintiffs' discovery requests, we confirmed that we will be making a document production this week, and that we will be updating our interrogatory responses to reflect as much. We also confirmed that we have not been able to locate any product samples (aside from those currently sold on the market) to date. Our investigation continues, and we will let you know if anything changes on this front.

With respect to Defendant's Requests for Production, you stated that you would let us know whether you would supplement your responses to Request Nos. 11, 30, 31, 32, 33, 45, 92, 94, and 95, which relate to Plaintiffs' allegations regarding the Teresian Carmelites. We explained that these Requests seek documents supporting Plaintiffs' allegations regarding Teresian Carmelites' financial status before and after the launch of the Accused Products. You also stated that you would get back to us on whether you would supplement your responses to Request Nos. 58, 64, 65, 74, 75, 105, 112, and 121, which seek documents relevant to Plaintiffs' claim for damages and L'Oréal USA's defenses to infringement. Please let us know promptly whether and when you plan to supplement these responses.

During the meet and confer, Plaintiffs stated that Request Nos. 122 and 123 are overly broad. We have considered the scope of these Requests further, and in light of the specific subject matter to which they are directed, we disagree that they are overbroad. Request No. 122 as written is relevant at least to Plaintiffs' claim for lost profits. Request No. 123 concerns a specific limitation of the asserted claims, and is thus relevant at least to the alleged validity of the asserted claims. Please confirm that Plaintiffs will produce documents responsive to these Requests.

You also stated that you would produce documents responsive to Request No. 60, which seeks documents relating to products sold in the same market as Easeamine that either Plaintiff was aware of. You also stated that you would produce documents responsive to Request Nos. 83, 84, 87, 88, 89, 90, 94, 95, 98, 99, and 100-103, which seek documents relating to Plaintiffs' claim for damages (particularly, any request for a reasonable royalty), including documents reflecting the cost of Easeamine, the profits made therefrom, the person(s) financing the products' production, etc.

Best,
-Serli

Serli Polatoglu | **Associate, Litigation Department**
Paul Hastings LLP | 515 South Flower Street, Twenty-Fifth Floor, Los Angeles, CA 90071
Direct: +1.213.683.6106 | Main: +1.213.683.6000 | Fax: +1.213.996.3106 |
serlipolatoglu@paulhastings.com | www.paulhastings.com

From: Murray, Katherine F. <katherinemurray@paulhastings.com>
Sent: Monday, November 4, 2019 10:38 AM
To: Tamar Lusztig <TLusztig@susmangodfrey.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Polatoglu, Serli <serlipolatoglu@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

We can use the following dial in for the 4pm call today:

Within the US and Canada: 1-800-308-2601 Mobile: (tel://1-800-308-2601,*,,2136836273#)
Outside US and Canada: 1-719-955-2367 Mobile: (tel://1-719-955-2367,*,,2136836273#)
Passcode: 2136836273

Audio Conference Star Commands
*0 to reach an operator
*6 to mute or unmute your personal line
*5/*8 to increase or decrease conference volume (for yourself only)

~~*~*~* *~*~*~*~*

From: Tamar Lusztig <TLusztig@susmangodfrey.com>
Sent: Monday, November 4, 2019 8:00 AM
To: Murray, Katherine F. <katherinemurray@paulhastings.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Polatoglu, Serli <serlipolatoglu@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: [EXT] Re: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Kathy, what number should we use for today's call? I don't think I have seen a calendar invite from you.

From: Murray, Katherine F. <katherinemurray@paulhastings.com>
Sent: Friday, November 1, 2019 6:33 PM
To: Tamar Lusztig <TLusztig@susmangodfrey.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com <cottrell@rlf.com>; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com <lsilva@foley.com>; mambros@foley.com <mambros@foley.com>; mlowrie@foley.com <mlowrie@foley.com>; mowery@rlf.com <mowery@rlf.com>; moyer@rlf.com <moyer@rlf.com>; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Polatoglu, Serli <serlipolatoglu@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Counsel:

Thank you for the information regarding Plaintiffs' amended contentions. We are concerned about Plaintiffs' proposed amendments, which propose to further expand the scope of this case, rather than reduce it.

As you know, when Plaintiffs filed suit, they identified only a single specific accused product, L'Oréal Paris' RevitaLift Triple Power Deep-Acting Moisturizer. Thereafter, the Scheduling Order was put in place. Yet when Plaintiffs' served

their Infringement Contentions, they identified more than 180 accused products. The proposed amended contentions propose to add still more.

At this juncture, the unsupported nature of Plaintiffs' infringement allegations, as well as the large number of accused products, have rendered the current case schedule unworkable. We propose that Plaintiffs either agree to significantly reduce the number of accused products or that the parties discuss amending the current scheduling order.

We are available for a meet and confer at your proposed time of 4pm ET on Monday, November 4th, and plan to discuss this issue on the call as well.

Thanks,
Kathy

From: Tamar Lusztig <TLusztig@susmangodfrey.com>
Sent: Wednesday, October 30, 2019 3:13 PM
To: Murray, Katherine F. <katherinemurray@paulhastings.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Polatoglu, Serli <serlipolatoglu@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: [EXT] RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Kathy,

The changes in Plaintiffs' amended contentions are:

- Exhibits 5 and 6:
  - Added Decleor Orexcellence Energy Concentrate Youth Eye and Decleor Orexcellence Energy Concentrate Youth Mask to Exhibit 5, which were already on Exhibit 6, but inadvertently omitted from Exhibit 5.
  - Correct the spelling of Decleor Orexcellence Energy Concentrate Youth Mask on Exhibit 6.
- Exhibits 27 and 28:
  - Removed claim 3 from the charts, which was inadvertently included.
- Exhibits 33 and 34:
  - Corrected the list of transdermal agents in claim 9, which previously contained a typographical error.
- Exhibits 41 and 42:
  - Removed claim 3 from the charts, which was inadvertently included.
- Exhibits 59 and 60:
  - Removed claim 3 from the charts, which was inadvertently included.
- Exhibits 87 and 88:
  - Added claim 3 to the charts, which was inadvertently omitted.
- Exhibit 179 and 180:
  - Added claim 3 to the charts, which was inadvertently omitted.
- Exhibits 193 and 194:
  - Removed claim 3 from the charts, which was inadvertently included.
- Exhibits 225 and 226:
  - Added claim 3 to the charts, which was inadvertently omitted.
- Exhibits 275 and 276:

- These are new exhibits that we inadvertently omitted.

-Tamar

From: Murray, Katherine F. <katherinemurray@paulhastings.com>
Sent: Tuesday, October 29, 2019 4:30 PM
To: Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Polatoglu, Serli <serlipolatoglu@paulhastings.com>; Tamar Lusztig <TLusztig@susmangodfrey.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Counsel:

We are in receipt of Plaintiffs' proposed amended contentions and are considering Plaintiffs' proposal. To facilitate our consideration, please promptly identify what has been corrected in the exhibits to the amended contentions, including providing redlines so that we may see what has changed in each of the documents. L'Oreal USA continues to reserve its rights to challenge the proposed amended contentions, as well as Plaintiffs' previously served contentions.

Thank you,
Kathy

From: Brian Farnan <bfarnan@farnanlaw.com>
Sent: Tuesday, October 29, 2019 8:38 AM
To: bcarmody@susmangodfrey.com; bfranklin@susmangodfrey.com; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; jnelson@susmangodfrey.com; Palys, Joseph E. <josephpalys@paulhastings.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; KLombardo@susmangodfrey.com; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Polatoglu, Serli <serlipolatoglu@paulhastings.com>; tlusztig@susmangodfrey.com
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: [EXT] FW: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

The link below contains Plaintiffs' Amended Disclosure of Asserted Claims and Initial Infringement Contentions (and the notice of service) which contains certain corrected exhibits. The original exhibits remain effective unless a corrected exhibit is provided.

https://farnanlaw.sharefile.com/d-s7591ed517024c529

Please let us know if Defendant opposes the foregoing amendments. If there is no opposition, Plaintiffs agree that Defendant reserves all rights concerning the sufficiency of the contentions.

Thanks,

Brian

From: ded_nefreply@ded.uscourts.gov <ded_nefreply@ded.uscourts.gov>
Sent: Tuesday, October 29, 2019 11:27 AM
To: ded_ecf@ded.uscourts.gov
Subject: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

This is an automatic e-mail message generated by the CM/ECF system. Please DO NOT RESPOND to this e-mail because the mail box is unattended.
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U.S. District Court

District of Delaware

Notice of Electronic Filing

The following transaction was entered by Farnan, Brian on 10/29/2019 at 11:26 AM EDT and filed on 10/29/2019

Case Name: University of Massachusetts et al v. L'Oreal U.S.A., Inc.
Case Number: 1:17-cv-00868-CFC-SRF
Filer: Carmel Laboratories, LLC
University of Massachusetts
Document Number: 59

Docket Text:
NOTICE OF SERVICE of Plaintiffs' Amended Disclosure of Asserted Claims and Initial Infringement Contentions filed by Carmel Laboratories, LLC, University of Massachusetts.(Farnan, Brian)

1:17-cv-00868-CFC-SRF Notice has been electronically mailed to:

Beatrice Franklin bfranklin@susmangodfrey.com

Brian E. Farnan bfarnan@farnanlaw.com, tfarnan@farnanlaw.com

Frederick L. Cottrell , III cottrell@rlf.com, anita-garvey-1560@ecf.pacerpro.com, garvey@rlf.com

Jason James Rawnsley rawnsley@rlf.com, patricianne-stewart-3997@ecf.pacerpro.com, pstewart@rlf.com

Joseph E. Palys josephpalys@paulhastings.com, michellehong@paulhastings.com

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Katherine F. Murray katherinemurray@paulhastings.com, maggieicart@paulhastings.com

Michael J. Farnan mfarnan@farnanlaw.com, tfarnan@farnanlaw.com

Naveen Modi naveenmodi@paulhastings.com, courtneyhsieh@paulhastings.com

Tamar E. Lusztig tlusztig@susmangodfrey.com, josterlof@susmangodfrey.com

William C. Carmody bcarmody@susmangodfrey.com, cdacosta@susmangodfrey.com

1:17-cv-00868-CFC-SRF Filer will deliver document by other means to:

Blaine M. Hackman
UNDELIVERABLE EMAIL 7/9/2018

The following document(s) are associated with this transaction:

Document description: Main Document
Original filename:n/a
Electronic document Stamp:
[STAMP dcecfStamp_ID=1079733196 [Date=10/29/2019] [FileNumber=3997284-0] [298f594c352f0835df8b94a6e47cdc5fa7862df80c657d35a2af9c11b265178c10a1995a17cd65011359e0e09a4601c7daad3bbd1e2b83b8d8639ee1f2a1d41c]]

EXHIBIT 8

From: Polatoglu, Serli
Sent: Tuesday, November 19, 2019 2:18 PM
To: Tamar Lusztig; Murray, Katherine F.; Brian Farnan; Bill Carmody; Beatrice Franklin; cottrell@rlf.com; Ellis, Dennis S.; Justin A. Nelson; Palys, Joseph E.; Keeley Lombardo; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen; PH-UMASS v. L'Oreal USDC
Cc: Michael J. Farnan
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Counsel:

We write further to yesterday's meet and confer, specifically with respect to Plaintiffs' deficient infringement contentions. As we previously explained, Plaintiffs already agreed to produce "the data that we relied on to form the basis of our belief that these limitations are met." *See* Nov. 8, 2019 Email from Plaintiffs. The document provided by Plaintiffs, however, is only a table with numerical values that does not, for example, explain how those numbers were obtained. Moreover, the table does not address a number of the accused products.

Plaintiffs have not denied that they are in possession of other materials concerning, *e.g.*, how the testing was performed, but have refused to provide them. In addition, during the meet and confer, Plaintiffs refused to withdraw their infringement claims for accused products not identified in the table, and were not willing to supplement their contentions to provide the bases for accusing such products.

Consistent with Plaintiffs' prior representations, the Local Rules, and the Scheduling Order, Plaintiffs should provide the testing data and/or other information explaining how these limitations are allegedly met. *See, e.g.*, D.I. 46 at ¶ 3(c); *Intellectual Ventures I LLC v. AT&T Mobility LLC*, No. 13-1668-LPS, 2017 WL 658469 (D. Del. Feb. 14, 2017) ("Infringement contentions . . . serve the purpose of providing notice to the Defendants of infringement theories beyond the mere language of the patent claim" and must provide adequate notice of "***how*** the accused products allegedly meet" the claim limitations) (emphasis added); *Tessenderlo Kerkley, Inc. v. Or-Cal, Inc.*, No. C 11-04100 WHA, 2012 WL 1253178 (N.D. Cal. Apr. 13, 2012) ("Plaintiff must, however, articulate the precise way in which it believes the products to be infringing. To the extent testing data are the basis for this belief, this order finds its disclosure is required under Rule 3-1."). Such information is distinct from any expert opinions and must be provided at this stage. Moreover, to the extent Plaintiffs' claims of infringement for one product are based on testing of another product, Plaintiffs must so state.

Finally, as discussed during the meet and confer, please provide us Plaintiffs' bases for refusing to de-designate the table it produced.

As stated during the meet and confer yesterday, given Plaintiffs' refusal to provide the "where and how" of its infringement allegations, we are at an impasse on these issues and will reach out to the Court. To the extent Plaintiffs are willing to reconsider their positions, please let us know immediately.

Best,
-Serli

From: Polatoglu, Serli
Sent: Monday, November 18, 2019 10:47 PM
To: 'Tamar Lusztig' <TLusztig@susmangodfrey.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; 'Brian Farnan' <bfarnan@farnanlaw.com>; 'Bill Carmody' <bcarmody@SusmanGodfrey.com>; 'Beatrice Franklin'

<BFranklin@susmangodfrey.com>; 'cottrell@rlf.com' <cottrell@rlf.com>; Ellis, Dennis S. <DennisEllis@paulhastings.com>; 'Justin A. Nelson' <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; 'Keeley Lombardo' <KLombardo@susmangodfrey.com>; 'lsilva@foley.com' <lsilva@foley.com>; 'mambros@foley.com' <mambros@foley.com>; 'mlowrie@foley.com' <mlowrie@foley.com>; 'mowery@rlf.com' <mowery@rlf.com>; 'moyer@rlf.com' <moyer@rlf.com>; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>
Cc: 'Michael J. Farnan' <mfarnan@farnanlaw.com>
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Tamar,

Following up on our call earlier today, and as we've explained repeatedly during meet and confer discussions, L'Oréal USA will continue to make rolling productions in this case. We expect to be able to make another production this week. We will also be supplementing our responses to interrogatories for which we have additional information (with content and reference to Bates numbers). We expect to be able to serve these interrogatory responses this week or next week.

Best,
-Serli

From: Polatoglu, Serli
Sent: Friday, November 15, 2019 2:25 PM
To: 'Tamar Lusztig' <TLusztig@susmangodfrey.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Great, I will circulate a calendar invite shortly.

Best,
-Serli

From: Tamar Lusztig <TLusztig@susmangodfrey.com>
Sent: Friday, November 15, 2019 2:14 PM
To: Polatoglu, Serli <serlipolatoglu@paulhastings.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: [EXT] RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Yes, that's fine.

From: Polatoglu, Serli <serlipolatoglu@paulhastings.com>
Sent: Friday, November 15, 2019 4:17 PM
To: Tamar Lusztig <TLusztig@susmangodfrey.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Tamar,

Are Plaintiffs available for a meet and confer between 4:30 and 5:30 PM EST on Monday? If not, we can make 2:00 PM work. Please let me know and I will circulate a dial-in.

Best,
-Serli

From: Tamar Lusztig <TLusztig@susmangodfrey.com>
Sent: Friday, November 15, 2019 6:07 AM
To: Polatoglu, Serli <serlipolatoglu@paulhastings.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: [EXT] Re: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Serli,

We can agree to the extended dates in the email I sent this Wednesday regardless of L'Oreal's agreement on other issues, and would be happy to discuss that and the other issues in your email on a call.

On the same call, we would like to address Plaintiffs' proposed motion to amend our infringement contentions, which we first asked you about on October 29—more than two weeks ago—and you have never responded with your position. We would also like to address the supplementary interrogatory responses (to our interrogatories 1, 2, 3, 5, and 6), which we first emailed you about on September 11—more than two months ago—and which, on our call on October 14, you said you would supplement within 2-3 weeks. Those 2-3 weeks have come and gone without any such supplement, nor does it appear that the documents you served on November 11 are responsive to these issues. We are also waiting for L'Oreal to begin its productions of the marketing documents you told us on October 14 you would begin producing in 3-4 weeks. That time has also come and gone without any such production from L'Oreal.

Let's have a call to discuss all of these issues. We are not available today at 1:30 ET, but could do Monday at 2 ET. Please circulate a dial-in if that works for you.

Thanks,

-Tamar

From: Polatoglu, Serli <serlipolatoglu@paulhastings.com>
Sent: Thursday, November 14, 2019 3:00:47 PM
To: Tamar Lusztig <TLusztig@susmangodfrey.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com <cottrell@rlf.com>; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com <lsilva@foley.com>; mambros@foley.com <mambros@foley.com>; mlowrie@foley.com <mlowrie@foley.com>; mowery@rlf.com <mowery@rlf.com>; moyer@rlf.com <moyer@rlf.com>; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Counsel:

We write further to the emails below regarding Plaintiffs' deficient infringement contentions and potential amendments to the schedule.

With respect to Plaintiffs' infringement contentions, Plaintiffs had previously agreed to produce "the data that we relied on to form the basis of our belief that these limitations are met." *See* Nov. 8, 2019 Email from Plaintiffs. The [redacted] testing document provided by Plaintiffs, however, appears to be a summary document. Plaintiffs must also produce the underlying data (or confirm that there is none) along with relevant documents such as laboratory notebooks and experimental protocols. Such information is distinct from any expert opinions and must be provided at this stage. Please confirm that Plaintiffs will do so without further delay.

Moreover, the summary document provided by Plaintiffs does not contain information for certain accused products (*e.g.*, Giorgio Armani Regenessence 3.R High Lift Eyes, Kiehl's Double Strength Deep Wrinkle Filler, Lancôme Absolue Precious Cells Day Cream, and L'Oréal Paris Collagen Moisture Filler Day Lotion, Biotherm Blue Therapy Night). Please confirm that any products not addressed in the summary document are no longer being accused of infringement.

Finally, we do not see any basis for designating the [redacted] testing of L'Oréal USA's products as Attorneys' Eyes Only. Please confirm that this document does not contain any confidential information of Plaintiffs. To the extent these issues are resolved, we believe that we can avoid motion practice regarding Plaintiffs' infringement contentions.

We appreciate Plaintiffs' willingness to discuss amending the schedule, but it is improper for Plaintiffs to condition this discussion on accepting Plaintiffs' infringement contentions in their current state, which has already prejudiced L'Oréal USA. That is especially true given that L'Oréal USA already provided Plaintiffs with an extension of the deadline for their infringement contentions. We believe it would be productive for the parties to discuss the scheduling issues. Please let us know if you are available for a meet and confer tomorrow at 1:30 PM Eastern time.

Best,
Serli

From: Tamar Lusztig <TLusztig@susmangodfrey.com>
Sent: Wednesday, November 13, 2019 4:05 PM
To: Polatoglu, Serli <serlipolatoglu@paulhastings.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: [EXT] RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Serli,

Although, as we have said, we believe our contentions are more than adequate under the applicable rules, in order to avoid motion practice, we can agree to amend our contentions to cite the attached document, which should be treated as RESTRICTED-ATTORNEYS' EYES ONLY under the protective order, as well as ETHIER_00000041 and CARMEL LABS_00000710, in each chart in place of the statement that currently reads "See forthcoming expert disclosures and/or defendants' internal, to-be-produced documents." This offer is contingent on L'Oreal's agreement that this revision would address L'Oreal's complaints about our contentions, because we cannot agree to amend toward a moving target, and it is also contingent on L'Oreal's agreement to accept the corrections to our infringement contentions. We first sent you those proposed corrections on October 28, but have not yet gotten an answer from you as to whether you agree.

Provided that L'Oreal agrees on both counts, we would also be happy to discuss amending the schedule. We cannot agree to amend the Court-ordered dates, but are amenable to a reasonable compromise with respect to some interim dates:

- Disclosure of invalidity contentions and documents responsive to paragraphs 6(b), (c), and (e) of the scheduling order: 12/13/19
- Disclosure of documents responsive to paragraphs 6(a) and (d) of the scheduling order: 12/20/19
- Deadline to exchange terms for construction: 12/27/19
- Deadline to file joint claim construction chart: 1/8/19
- Service of Plaintiffs' opening claim construction brief: 1/22/19
- Service of Defendants' opening claim construction brief: 2/5/19
- Service of Plaintiffs' reply claim construction brief: 2/19/19
- Service of Defendants' sur-reply claim construction brief: 3/4/19
- Deadline to file joint claim construction brief: 3/6/19

Please let us know if you agree.

-Tamar

From: Polatoglu, Serli <serlipolatoglu@paulhastings.com>
Sent: Wednesday, November 13, 2019 2:02 PM
To: Murray, Katherine F. <katherinemurray@paulhastings.com>; Tamar Lusztig <TLusztig@susmangodfrey.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo

<KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Counsel:

We have not heard back from Plaintiffs in response to either our November 8 email regarding the case schedule or our November 11 email responding to Plaintiffs' proposal regarding supplemental infringement contentions.

Per our November 11 email, please confirm that we have agreement on the scope of Plaintiffs' proposed supplemental contentions and let us know when we will receive them. Please also let us know your availability tomorrow afternoon for a meet and confer regarding the case schedule.

Best,
-Serli

From: Polatoglu, Serli
Sent: Friday, November 8, 2019 3:18 PM
To: Murray, Katherine F. <katherinemurray@paulhastings.com>; 'Tamar Lusztig' <TLusztig@susmangodfrey.com>; 'Brian Farnan' <bfarnan@farnanlaw.com>; 'Bill Carmody' <bcarmody@SusmanGodfrey.com>; 'Beatrice Franklin' <BFranklin@susmangodfrey.com>; 'cottrell@rlf.com' <cottrell@rlf.com>; Ellis, Dennis S. <DennisEllis@paulhastings.com>; 'Justin A. Nelson' <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; 'Keeley Lombardo' <KLombardo@susmangodfrey.com>; 'lsilva@foley.com' <lsilva@foley.com>; 'mambros@foley.com' <mambros@foley.com>; 'mlowrie@foley.com' <mlowrie@foley.com>; 'mowery@rlf.com' <mowery@rlf.com>; 'moyer@rlf.com' <moyer@rlf.com>; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>
Cc: 'Michael J. Farnan' <mfarnan@farnanlaw.com>
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Counsel:

Further to the below and our meet and confer on Monday, attached is a chart with proposed amendments to the schedule. Please let us know if Plaintiffs are amenable to these changes and, if so, we will prepare a stipulation for submission to the Court; otherwise, please let us know your availability for a meet and confer early next week.

Best,
-Serli

From: Polatoglu, Serli
Sent: Wednesday, November 6, 2019 3:44 PM
To: Murray, Katherine F. <katherinemurray@paulhastings.com>; Tamar Lusztig <TLusztig@susmangodfrey.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>

Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Counsel,

I write to follow up on our meet and confer Monday afternoon. An overview of our understanding of the discussions is below.

With respect to Plaintiffs' Infringement Contentions, we explained that they are currently deficient, as they do not provide an explanation of the "where and how," *i.e.*, the basis or theory, for Plaintiffs' claims of infringement with respect to the claim language "without increasing dermal cell proliferation" and "wherein the adenosine concentration applied to the dermal cells is [recited amount]." You stated that you would consider the issue further and potentially provide us with amended contentions. Please confirm by Friday, November 8, that Plaintiffs will remedy their non-compliant contentions.

We also discussed the current case schedule. As Plaintiffs refuse to narrow the scope of the Accused Products (which stand at about 170 products total), we explained that some of the current deadlines are unworkable. You stated that you were amenable to continuing at least some of these deadlines, including the upcoming deadline to file our invalidity contentions. We are working on a proposed amended schedule and will circulate it soon.

With respect to Plaintiffs' discovery requests, we confirmed that we will be making a document production this week, and that we will be updating our interrogatory responses to reflect as much. We also confirmed that we have not been able to locate any product samples (aside from those currently sold on the market) to date. Our investigation continues, and we will let you know if anything changes on this front.

With respect to Defendant's Requests for Production, you stated that you would let us know whether you would supplement your responses to Request Nos. 11, 30, 31, 32, 33, 45, 92, 94, and 95, which relate to Plaintiffs' allegations regarding the Teresian Carmelites. We explained that these Requests seek documents supporting Plaintiffs' allegations regarding Teresian Carmelites' financial status before and after the launch of the Accused Products. You also stated that you would get back to us on whether you would supplement your responses to Request Nos. 58, 64, 65, 74, 75, 105, 112, and 121, which seek documents relevant to Plaintiffs' claim for damages and L'Oréal USA's defenses to infringement. Please let us know promptly whether and when you plan to supplement these responses.

During the meet and confer, Plaintiffs stated that Request Nos. 122 and 123 are overly broad. We have considered the scope of these Requests further, and in light of the specific subject matter to which they are directed, we disagree that they are overbroad. Request No. 122 as written is relevant at least to Plaintiffs' claim for lost profits. Request No. 123 concerns a specific limitation of the asserted claims, and is thus relevant at least to the alleged validity of the asserted claims. Please confirm that Plaintiffs will produce documents responsive to these Requests.

You also stated that you would produce documents responsive to Request No. 60, which seeks documents relating to products sold in the same market as Easeamine that either Plaintiff was aware of. You also stated that you would produce documents responsive to Request Nos. 83, 84, 87, 88, 89, 90, 94, 95, 98, 99, and 100-103, which seek documents relating to Plaintiffs' claim for damages (particularly, any request for a reasonable royalty), including documents reflecting the cost of Easeamine, the profits made therefrom, the person(s) financing the products' production, etc.

Best,
-Serli

Serli Polatoglu | Associate, Litigation Department
Paul Hastings LLP | 515 South Flower Street, Twenty-Fifth Floor, Los Angeles, CA 90071
Direct: +1.213.683.6106 | Main: +1.213.683.6000 | Fax: +1.213.996.3106 |
serlipolatoglu@paulhastings.com | www.paulhastings.com

From: Murray, Katherine F. <katherinemurray@paulhastings.com>
Sent: Monday, November 4, 2019 10:38 AM
To: Tamar Lusztig <TLusztig@susmangodfrey.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Polatoglu, Serli <serlipolatoglu@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

We can use the following dial in for the 4pm call today:

Within the US and Canada: 1-800-308-2601 Mobile: (tel://1-800-308-2601,*,,2136836273#)
Outside US and Canada: 1-719-955-2367 Mobile: (tel://1-719-955-2367,*,,2136836273#)
Passcode: 2136836273

Audio Conference Star Commands
*0 to reach an operator
*6 to mute or unmute your personal line
*5/*8 to increase or decrease conference volume (for yourself only)

~~*~*~* *~*~*~*~*

From: Tamar Lusztig <TLusztig@susmangodfrey.com>
Sent: Monday, November 4, 2019 8:00 AM
To: Murray, Katherine F. <katherinemurray@paulhastings.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Polatoglu, Serli <serlipolatoglu@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>

Subject: [EXT] Re: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Kathy, what number should we use for today's call? I don't think I have seen a calendar invite from you.

From: Murray, Katherine F. <katherinemurray@paulhastings.com>
Sent: Friday, November 1, 2019 6:33 PM
To: Tamar Lusztig <TLusztig@susmangodfrey.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com <cottrell@rlf.com>; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com <lsilva@foley.com>; mambros@foley.com <mambros@foley.com>; mlowrie@foley.com <mlowrie@foley.com>; mowery@rlf.com <mowery@rlf.com>; moyer@rlf.com <moyer@rlf.com>; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Polatoglu, Serli <serlipolatoglu@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Counsel:

Thank you for the information regarding Plaintiffs' amended contentions. We are concerned about Plaintiffs' proposed amendments, which propose to further expand the scope of this case, rather than reduce it.

As you know, when Plaintiffs filed suit, they identified only a single specific accused product, L'Oréal Paris' RevitaLift Triple Power Deep-Acting Moisturizer. Thereafter, the Scheduling Order was put in place. Yet when Plaintiffs' served their Infringement Contentions, they identified more than 180 accused products. The proposed amended contentions propose to add still more.

At this juncture, the unsupported nature of Plaintiffs' infringement allegations, as well as the large number of accused products, have rendered the current case schedule unworkable. We propose that Plaintiffs either agree to significantly reduce the number of accused products or that the parties discuss amending the current scheduling order.

We are available for a meet and confer at your proposed time of 4pm ET on Monday, November 4th, and plan to discuss this issue on the call as well.

Thanks,
Kathy

From: Tamar Lusztig <TLusztig@susmangodfrey.com>
Sent: Wednesday, October 30, 2019 3:13 PM
To: Murray, Katherine F. <katherinemurray@paulhastings.com>; Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Polatoglu, Serli <serlipolatoglu@paulhastings.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: [EXT] RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Kathy,

The changes in Plaintiffs' amended contentions are:

- Exhibits 5 and 6:
  - Added Decleor Orexcellence Energy Concentrate Youth Eye and Decleor Orexcellence Energy Concentrate Youth Mask to Exhibit 5, which were already on Exhibit 6, but inadvertently omitted from Exhibit 5.
  - Correct the spelling of Decleor Orexcellence Energy Concentrate Youth Mask on Exhibit 6.
- Exhibits 27 and 28:
  - Removed claim 3 from the charts, which was inadvertently included.
- Exhibits 33 and 34:
  - Corrected the list of transdermal agents in claim 9, which previously contained a typographical error.
- Exhibits 41 and 42:
  - Removed claim 3 from the charts, which was inadvertently included.
- Exhibits 59 and 60:
  - Removed claim 3 from the charts, which was inadvertently included.
- Exhibits 87 and 88:
  - Added claim 3 to the charts, which was inadvertently omitted.
- Exhibit 179 and 180:
  - Added claim 3 to the charts, which was inadvertently omitted.
- Exhibits 193 and 194:
  - Removed claim 3 from the charts, which was inadvertently included.
- Exhibits 225 and 226:
  - Added claim 3 to the charts, which was inadvertently omitted.
- Exhibits 275 and 276:
  - These are new exhibits that we inadvertently omitted.

-Tamar

From: Murray, Katherine F. <katherinemurray@paulhastings.com>
Sent: Tuesday, October 29, 2019 4:30 PM
To: Brian Farnan <bfarnan@farnanlaw.com>; Bill Carmody <bcarmody@SusmanGodfrey.com>; Beatrice Franklin <BFranklin@susmangodfrey.com>; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; Justin A. Nelson <jnelson@SusmanGodfrey.com>; Palys, Joseph E. <josephpalys@paulhastings.com>; Keeley Lombardo <KLombardo@susmangodfrey.com>; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Polatoglu, Serli <serlipolatoglu@paulhastings.com>; Tamar Lusztig <TLusztig@susmangodfrey.com>
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: RE: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

Counsel:

We are in receipt of Plaintiffs' proposed amended contentions and are considering Plaintiffs' proposal. To facilitate our consideration, please promptly identify what has been corrected in the exhibits to the amended contentions, including providing redlines so that we may see what has changed in each of the documents. L'Oreal USA continues to reserve its rights to challenge the proposed amended contentions, as well as Plaintiffs' previously served contentions.

Thank you,

Kathy

From: Brian Farnan <bfarnan@farnanlaw.com>
Sent: Tuesday, October 29, 2019 8:38 AM
To: bcarmody@susmangodfrey.com; bfranklin@susmangodfrey.com; cottrell@rlf.com; Ellis, Dennis S. <DennisEllis@paulhastings.com>; jnelson@susmangodfrey.com; Palys, Joseph E. <josephpalys@paulhastings.com>; Murray, Katherine F. <katherinemurray@paulhastings.com>; KLombardo@susmangodfrey.com; lsilva@foley.com; mambros@foley.com; mlowrie@foley.com; mowery@rlf.com; moyer@rlf.com; Modi, Naveen <naveenmodi@paulhastings.com>; PH-UMASS v. L'Oreal USDC <PH-UMass-LOreal-USDC@paulhastings.com>; Polatoglu, Serli <serlipolatoglu@paulhastings.com>; tlusztig@susmangodfrey.com
Cc: Michael J. Farnan <mfarnan@farnanlaw.com>
Subject: [EXT] FW: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

The link below contains Plaintiffs' Amended Disclosure of Asserted Claims and Initial Infringement Contentions (and the notice of service) which contains certain corrected exhibits. The original exhibits remain effective unless a corrected exhibit is provided.

https://farnanlaw.sharefile.com/d-s7591ed517024c529

Please let us know if Defendant opposes the foregoing amendments. If there is no opposition, Plaintiffs agree that Defendant reserves all rights concerning the sufficiency of the contentions.

Thanks,
Brian

From: ded_nefreply@ded.uscourts.gov <ded_nefreply@ded.uscourts.gov>
Sent: Tuesday, October 29, 2019 11:27 AM
To: ded_ecf@ded.uscourts.gov
Subject: Activity in Case 1:17-cv-00868-CFC-SRF University of Massachusetts et al v. L'Oreal U.S.A., Inc. Notice of Service

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U.S. District Court

District of Delaware

Notice of Electronic Filing

The following transaction was entered by Farnan, Brian on 10/29/2019 at 11:26 AM EDT and filed on 10/29/2019

Case Name: University of Massachusetts et al v. L'Oreal U.S.A., Inc.
Case Number: 1:17-cv-00868-CFC-SRF

Filer: Carmel Laboratories, LLC
University of Massachusetts

Document Number: 59

Docket Text:

NOTICE OF SERVICE of Plaintiffs' Amended Disclosure of Asserted Claims and Initial Infringement Contentions filed by Carmel Laboratories, LLC, University of Massachusetts.(Farnan, Brian)

1:17-cv-00868-CFC-SRF Notice has been electronically mailed to:

Beatrice Franklin bfranklin@susmangodfrey.com

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1:17-cv-00868-CFC-SRF Filer will deliver document by other means to:

Blaine M. Hackman
UNDELIVERABLE EMAIL 7/9/2018

The following document(s) are associated with this transaction:

Document description: Main Document
Original filename:n/a
Electronic document Stamp:
[STAMP dcecfStamp_ID=1079733196 [Date=10/29/2019] [FileNumber=3997284-0] [298f594c352f0835df8b94a6e47cdc5fa7862df80c657d35a2af9c11b265178c10a1995a17cd65011359e0e09a4601c7daad3bbd1e2b83b8d8639ee1f2a1d41c]]

EXHIBIT 9

EXHIBIT 10

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

HSM PORTFOLIO LLC, et al.,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	Civil Action No. 11-770-RGA
	:	
FUJITSU LIMITED, et al.,	:	
	:	
Defendants.	:	

ORDER

I have received objections, and an opposition to the objections, relating to an oral ruling of the Special Master. (D.I. 615, 639). The oral ruling in question occurred on February 21, 2014. (D.I. 598 at 63-75; *see* D.I. 615, p.1).

There is some disagreement about whether this is a ruling I review *de novo*. I assume for the sake of argument that I do review it *de novo.*

The issue in dispute is what Plaintiffs need to do to comply with their duty to supply infringement contentions to Defendants Micron and Sony. Plaintiffs provided "initial infringement contentions" as required by the scheduling order. (*See* D.I. 228, at 2 ¶ 2(c)). Plaintiffs provided the Special Master with more than one such chart. (*E.g.,* D.I. 616-2). The particular point of dispute is that one or more of the claims of the '853 patent have a limitation that includes "a predetermined factor." For example, claim 1 contains the limitation that "the N-channel field effect transistor in each inverter stage having a channel width which is less than a predetermined factor times the width of the N-channel of the immediately preceding inverter stage." (D.I. 1-2 at 36-37; D.I. 661-2 at 10). As Plaintiffs state, their initial infringement contentions include colored lines, charts, and boxes. For example, for a Micron product, the

initial infringement contentions are colorful, including green, olive, red, blue, and black. (*Id.*). "Predetermined factor" is in red, and there are two red arrows pointing at Wn for two consecutive inverter stages. There is a lot about this that I do not understand, but one thing I do understand is that the cited infringement contention says nothing about what Plaintiffs think "predetermined factor" means, or why it is present in the Micron product.

Plaintiffs object to the Special Master's ruling on various grounds. Plaintiffs state that the Special Master wanted them to use Defendants' formula for what "predetermined factor" means (D.I. 615, pp. 3-4). I do not see that in the Special Master's ruling, but, if it is there and I missed it, I would modify the ruling to be that Plaintiffs can use their construction of "predetermined factor." If I understand Plaintiffs' claim construction brief (D.I. 616-7), it appears that they define "predetermined factor" to be "K" where "K" is "a defined value that governs the maximum increase in channel width of the N-channel transistors in succeeding inverter stages such that the capacitive load can be driven with a specific signal rise time." It appears that Plaintiffs state that K may be determined by multiple different equations. (*Id.* at 5-6). If that is Plaintiffs' theory, then they should have used those equations in the initial claim charts.[1]

Plaintiffs also complain about deficiencies in Defendants' production of technical documents. Issues about Defendants' production are not before me. Thus, Plaintiffs will need to supplement the infringement contentions. If the formulas or values for "predetermined factor" under Plaintiffs' claim construction have not been provided by Defendants, and are otherwise unknown to Plaintiffs, Plaintiffs need to provide what they have and indicate what they do not

[1] Plaintiffs state that they have twice supplemented the initial infringement contentions (D.I. 615, pp. 2-3), but since they are not cited to, I assume that they do not provide any further detail on "predetermined factor."

know.

NOW, THEREFORE, this 7th day of May, 2014, Plaintiffs are to provide supplemental infringement contentions that contain Plaintiffs' contentions about why the accused products of Defendants Micron and Sony infringe the "predetermined factor" limitation. The Court ORDERS Plaintiffs to do so no later than May 15, 2014.[2]

Richard G. Andrews
United States District Judge

[2] Should this date be unreasonable, and the parties are not able to mutually agree on a different date, the matter should be taken up with the Special Master.

EXHIBIT 11

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

THE GILLETTE COMPANY, Plaintiff, v. DOLLAR SHAVE CLUB, INC., *et al.*, Defendants.	)	C.A. No. 15-1158-LPS

LETTER TO THE HONORABLE LEONARD P. STARK FROM KAREN E. KELLER

John W. Shaw (No. 3362)
Karen E. Keller (No. 4489)
David M. Fry (No. 5486)
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William C. Price
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Los Angeles, CA 90017
(213) 443-3000

Dated: October 6, 2017

SHAW KELLER LLP

Karen E. Keller
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1105 North Market Street, 12th Floor
Wilmington, DE 19801
(302) 298-0702 - Direct
kkeller@shawkeller.com

October 6, 2017

BY CM/ECF AND HAND DELIVERY
The Honorable Leonard P. Stark
J. Caleb Boggs Federal Building
844 N. King Street
Wilmington, DE 19801

Re: *The Gillette Co. v. Dollar Shave Club, Inc.*, et al, C.A. No. 15-1158-LPS-CJB

Dear Chief Judge Stark:

I write on behalf of Defendants regarding Gillette's refusal to provide relevant discovery and Gillette's unfounded objections to Defendants' disclosed expert. Defendants respectfully request that the Court compel Gillette to produce the relevant discovery and overrule Gillette's objection.

1. Documents that Form the Basis of Gillette's Infringement Contentions: Gillette's infringement contentions rely on select images and results from tests of Defendants' products. *See, e.g.*, Ex. 1, 1/11/17, 2nd Amended Initial Claim Charts, Att. A at 1-6; *id*. Atts. B, C, D, E, F, and G at 1-6; Ex. 2, 9/11/17 Final Infr. Cont. ("FIC") at Apps. 1 & 2. Yet, Gillette refuses to produce documents regarding those tests, such as those regarding the testing conditions and protocols, the underlying data, other images, or test reports. Gillette does not dispute that these documents exist but instead claims they are work product and non-testifying expert work. Ex. 3, 8/7/17 Albert Ltr. Gillette bears the burden of proving the applicability of either protection, which it cannot do.

Even if the requested documents were work product, Gillette's purposeful disclosure of the test results waived any protection. *See Princeton Digital Image Corp. v. Office Depot Inc.*, 2017 WL 3264068, *2 (D. Del. Aug. 1, 2017) (Stark, J.). The same is true for FRCP 26(b)(4)(D)'s non-testifying expert protection. *In re Intel Corp.*, 2008 WL 11233766, *7 (D. Del. Mar. 6, 2008); *Vasudevan Software, Inc. v. IBM*, 09-cv-05897, 2011 WL 13153991, *3 (N.D. Cal. June 15, 2011) (26(b)(4)(D) did not prevent production of information on testing cited in infringement contentions). Gillette argues that preliminary infringement contentions are not evidence and do not waive 26(b)(4)(D). Ex. 3, 8/7/17 Albert Ltr. But even were that true in this district, the parties are well past preliminary contentions—fact discovery closes in two weeks, and Gillette incorporated its contentions into its interrogatory response. Ex. 4, Gillette's 3rd Supp. Resp. to Interrog. No. 4.

The requested information is critical to understanding the basis for Gillette's infringement contentions. Despite the late stage of the litigation, Defendants still do not know how Gillette performed the testing that it alleges shows infringement—prejudicing Defendants' ability to defend against Gillette's baseless claims that the accused blades have three coating layers when, in fact, they have only two. Gillette cannot withhold these facts given its purposeful disclosure of test results.

2. Gillette's Deficient Infringement Contentions: Despite having received extensive technical discovery, Gillette's infringement contentions fail to give adequate notice of how the products allegedly practice the claims. *See Intellectual Ventures I LLC v. AT&T Mobility LLC*, 2017 WL 658469, at *1 (D. Del. Feb. 14, 2017) (Stark, J.). Yet Gillette refuses to supplement or withdraw its

deficient contentions, prejudicing Defendants' ability to respond and warranting an order to either compel more detailed contentions or strike the deficient contentions. *See id.* at *2-3.

Dorco's [redacted] *Products*: For all asserted claims, Gillette contends Dorco's "process conditions" create *two* separate layers from [redacted]. Ex. 2, FIC, Att. B at 11; Ex. 5, 9/13/2017 Murray Ltr. But Gillette does not explain *how* any process condition creates two layers or identify the basis for its "process conditions" allegations.

Doctrine of Equivalents: Despite having represented to this Court that it has "never taken the position that a two layer blade coating can satisfy the claim," 4/3/2017 Hr'g Tr. at 7:22-25, Gillette now alleges that two layers infringe under the doctrine of equivalents. Ex. 2, FIC, Att. A at 32 (contending single layer is two layers because of different "morphology and/or structure"). But, Gillette cites no evidence beyond a reference to its claim chart for literal infringement, fails to identify the alleged "morphology" and "structure[s]," and fails to consider this Court's construction requiring "a chromium containing layer ***between*** a [hard coating (for claims 1, 20, 24)/hard carbon containing material (for claims 28, 35))] and a PTFE layer." *See* D.I. 380 at 8.

"Doped": This Court construed the "doped" limitation as "another element is introduced into the material in small amounts to modify certain properties of the material." D.I. 380 at 10. Gillette relies on [redacted] *See, e.g.*, Ex. 2, FIC, App. 2 at 7. Gillette fails to explain how [redacted] meets the Court's claim construction beyond a conclusory assertion. *See Intellectual Ventures I LLC,* 2017 WL 658469, at *2-3.

<u>*3. Discovery Regarding Gillette's Manufacturing*</u>: Despite having demanded (and received) detailed and fulsome discovery regarding Dorco's manufacturing—including documents, a facility inspection, and Rule 30(b)(6) deposition—Gillette refuses to provide similar discovery regarding its own manufacturing process. Ex. 6, 9/7/2016 DSC's Request for Production ("RFP") No. 45-47, 49; Ex. 7 Resp. to Interrog. No. 21; Ex. 8, 10/14/2016 Smith Ltr. at 5-6; Ex. 9, 7/27/2017 Kiepura Ltr.; Ex. 10, 8/7/2017 Kiepura Ltr. Gillette initially agreed to produce such information, Ex. 11, Resp. to RFP 47, but now asserts that it is irrelevant. Gillette is incorrect—its manufacturing processes will show whether its products practice the asserted claims, which is relevant to at least non-infringement, secondary considerations, and Gillette's demand for lost profits and an injunction. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 305 n.42 (Fed. Cir. 1985) (products "not covered" by the asserted patent do "not have any relevance" to secondary considerations); *Wechsler v. Macke Int'l Trade, Inc.*, 486 F.3d 1286, 1293 (Fed. Cir. 2007) (to receive lost profits, the "burden on a patentee who has not begun to manufacture the patented product is commensurately heavy"); *Ricoh Co., Ltd. v. Quanta Comp., Inc.*, 06-cv-462, 2010 WL 1607908, *1 (E.D. Wis. 2010) (denying injunction and finding plaintiff's failure to practice patent mitigated any irreparable harm). Indeed, as just one example, Gillette incorrectly alleges that Dorco's products have two metal coating layers because [redacted]; yet Gillette itself [redacted]. Notably, Gillette won a motion to compel Dorco to produce the *very same information* Gillette refuses to produce. D.I. 382.

Gillette appears to contend that its manufacturing documents are not relevant to the apparatus

claims, and that it might, at some point, withdraw assertion of the method-of-manufacturing claims. Ex. 12, 8/23/2017 Abate to Kiepura. But those method claims are *still* a part of this case; indeed, in its FICs, Gillette added two more. Ex. 2, FIC at 6 (adding method claims 25 & 26). And, in any event, Gillette itself cites [redacted] *See, e.g.* Ex. 2, FICs, Att. A at 30-31; *id*. at FIC, Att. B at 11 (contending [redacted] create an infringing apparatus). In fact, for the method claims, Gillette's contentions cite to *the same evidence* as for its apparatus contentions. *Compare id*. at 25-26, *with id.* at 5-6. In short, Gillette's manufacturing processes is highly relevant to *all* asserted claims. *Alloc, Inc. v. Unilin Beheer B.V.*, 03-cv-1266, 2006 WL 757871, *3 (E.D. Wis. Mar. 24, 2006)) (granting motion to compel manufacturing documents as relevant to apparatus claims as they "may lead to the discovery of admissible evidence since product features are defined during the manufacturing process").

Further, Gillette cannot dispute that this discovery is "proportional to the needs of the case," given that the scope of Defendants' requests are commensurate with Gillette's. *Compare, e.g.*, Ex. 13, Request for Dorco Inspection, *with* Ex. 14, Request for Gillette Inspection. Gillette should be compelled to produce the requested documents, respond to Defendants' manufacturing interrogatories, provide a corporate witness, and permit the inspection of its manufacturing facilities.

4. Interrogatory No. 16: Gillette refuses to provide its validity contentions, even though its response addresses only a few prior art references and fails to address non-prior art invalidity. Ex. 15, Resp. to Interrog. No 16. Gillette's refusal is baseless—Defendants' contentions do not cite "over 60 allegedly anticipatory references." D.I. 525 at 3-4; Ex. 16, Defs. Invalid. Cont. Defendants' citation of 18 anticipatory references is reasonable, given the breadth of the asserted claims and of Gillette's (deficient) infringement contentions. Nor does that excuse Gillette's refusal to address other invalidity arguments. Gillette cannot sandbag until expert discovery; it must provide fair notice of its validity contentions at the fact discovery stage.

5. Interrogatory Nos. 20, 22: Gillette refuses to provide fulsome information about its manufacture and testing of its own razors, [redacted] Ex. 7, Resp. to Interrog. Nos. 20, 22. Instead of providing a proper narrative response, Gillette cites hundreds of pages of documents under Rule 33(d). But here, the burden of deriving the answer is not substantially the same for either party—instead, Gillette is the one with full knowledge and control of information about its own manufacturing and testing of razor blades. Fed. R. Civ. P. 33(d); *see also Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 2005 WL 8136574, at *1 (D. Del. Oct. 11, 2005). For example, none of the documents [redacted] (No. 22). Gillette must be compelled to properly disclose this information.

6. Attachments to responsive emails: Gillette has withheld allegedly "non-responsive" attachments to responsive emails. Ex. 17, 9/21/17 DeJong Ltr. Gillette's practice runs afoul of the requirement that parties "must produce documents as they are kept in the usual course of business," Fed. R. Civ. P. 34(b)(2)(E)(i)—which, for emails, means producing with their attachments. *See*

Consolidated Rail Corp. v. Grand Trunk Western Railroad Co., 2009 WL 5151745, at *3 (E.D. Mich. Dec. 18, 2009); *U & I Corp. v. Advanced Med. Design, Inc.*, 251 F.R.D. 667, 675 n.14 (M.D. Fla. 2008). In addition, by withholding attachments, Gillette has not "preserve[d] the integrity of the underlying ESI, i.e., the original formatting [and] the metadata" as required by the Delaware Default Standard for Discovery. Gillette's practice is also inconsistent with this Court's order that Gillette could not redact its documents for alleged non-responsiveness. D.I. 419. Gillette must produce the attachments to its already-produced responsive emails.

7. Gillette's Objection to Defendants' Expert: Gillette has improperly objected to the disclosure under the protective order ("PO") of Highly Confidential information to Defendants' invalidity expert, David Tressel. Mr. Tressel has signed the PO and agreed to its stringent terms, including its prosecution bar. Gillette thus must show "good cause" to prevent disclosure to Mr. Tressel, D.I. 27 ¶ 9, such as a real risk of inadvertent disclosure. *Streck, Inc. v. Research & Diagnostic Sys., Inc.*, 250 F.R.D 426, 430 (D. Neb. 2008); *see Xerox Corp. v. Google, Inc.*, 270 F.R.D. 182, 183 n.4 (D. Del. 2010). Gillette cannot do so.

Courts must balance Defendants' "interest in electing the experts most beneficial to [their] case with [Gillette's] interest in protecting its trade secrets from disclosure to competitors." *Advanced Semiconductor Materials Am. Inc. v. Applied Materials Inc.*, 95-cv-20169, 1996 WL 908654, *3 (N.D. Cal. Oct. 28, 1996). In doing so, courts look to see if the expert has an *on-going* relationship with a competitor—a *former* relationship is insufficient, as that would prevent a party from using any expert with industry experience. *Id*. A "party is owed some degree of deference in retaining and preparing an expert with the relevant industry experience and availability." *GPNE Corp. v. Apple Inc.*, 5:12-cv-2885, 2014 WL 1027948, *2 (N.D. Cal. Mar. 13, 2014).

Mr. Tressel has *no on-going relationship* with any competitor of Gillette, including his *former* employer Schick, from whom he retired over a year ago. Ex. 18, Decl. ¶ 2. The sole basis for Gillette's objection is that Mr. Tressel is an inventor on patent applications from his time at Schick, and Gillette speculates he might assist in prosecuting those applications. *See* Ex. 19, 9/29/17 Email from J. Albert. But Mr. Tressel has *agreed to* the Protective Order's prosecution bar (Decl. ¶ 5; D.I. 27 ¶ 21)[1], thus preventing any possibility of inadvertent disclosure during prosecution. *GPNE*, 2014 WL 1027948, *2. And he already assigned all rights to the applications to Schick, has not participated in prosecution, and is not aware of any obligation to do so. Ex. 18, Decl. ¶¶ 3-4.

Gillette's illusory worries cannot outweigh the substantial harm to Defendants should they be deprived the expert of their choice. Mr. Tressel has significant and unique industry experience in the subject matter of the asserted patent. Ex. 18, Decl. ¶ 1. His industry experience is unmatched, including by other retained experts. And, as an invalidity expert, Defendants expect Mr. Tressel will require access to little confidential information—namely, documents from 1997-2000 concerning Gillette's assertion of an earlier invention date, inventor testimony, and confidential documents Gillette cites for secondary considerations. The competitive importance of such stale information is questionable at best, *Procter & Gamble Co. v. Nabisco Brands, Inc.*, 111 F.R.D. 326, 331 (D. Del. 1986), and in any event is not at risk of inadvertent disclosure.

[1] While the prosecution bar does not otherwise apply to Schick, Mr. Tressel has stated he is willing to abide by its terms with respect to Schick. Ex. 18, Decl. ¶ 5.

Respectfully submitted,

/s/ Karen E. Keller

Karen E. Keller (No. 4489)

cc: Clerk of the Court (via hand delivery)
All Counsel of Record (via CM/ECF and e-mail)

EXHIBIT 12

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNIVERSITY OF MASSACHUSETTS and CARMEL LABORATORIES, LLC, Plaintiffs, v. L'ORÉAL USA, INC., Defendant.	Case No. 17-cv-868-CFC-SRF

PLAINTIFFS' SUPPLEMENTAL OBJECTIONS AND RESPONSES TO DEFENDANT L'ORÉAL USA, INC.'S FIRST SET OF REQUESTS FOR THE PRODUCTION OF DOCUMENTS AND THINGS TO PLAINTIFFS (NOS. 1-131)

Pursuant to Federal Rule of Civil Procedure 34 and the Local Rules of this Court, Plaintiffs University of Massachusetts ("UMass") and Carmel Laboratories, LLC ("Carmel Labs" and, together, "Plaintiffs") submit supplemental objections and responses to certain of the First Set of Requests for Production ("Requests") of Defendant L'Oréal USA, Inc., dated September 11, 2019.

PRELIMINARY STATEMENT

1. These answers are made solely for the purpose of this action. Each answer is subject to all objections, as to competence, relevance, materiality, propriety, and admissibility, and to any and all other objections on any grounds that would require the exclusion of any statements contained herein if such interrogatory were asked of, or statements contained herein were made by a witness present and testifying in Court, all of which objections and grounds are expressly reserved and may be interposed at the time of trial.

2. Plaintiffs' responses are based upon information presently available to and located

encompass public documents that are not in Plaintiffs' possession.

DOCUMENT REQUEST NO. 121

All documents Concerning any testing or analysis of any Accused Product by You or by anyone on Your behalf.

RESPONSE TO NO. 121:

Plaintiffs object to this Request to the extent it seeks information protected from disclosure by the attorney-client privilege, the attorney work product doctrine, the joint defense or common-interest privilege, or any other privilege or immunity. Plaintiffs further object to this Request as overbroad and unduly burdensome insofar as it calls for "All documents" concerning "any testing or analysis." Plaintiffs further object to this Request as seeking documents or things that are not relevant to any claims or defenses in this case, and not proportional to the needs of the case. Plaintiffs further object to the Request to the extent that it seeks draft expert reports or expert work product, or service of final expert reports in advance of the deadline set forth in the Court's scheduling order. Plaintiffs will serve their expert reports on the date set forth in the scheduling order. Plaintiffs further object to this Request insofar as it uses "Your" indiscriminately, without any indication whether it refers to UMass, Carmel Labs, or both.

Subject to and without waiver of the foregoing objections, Plaintiffs are willing to meet and confer with Defendant regarding this Request.

SUPPLEMENTAL RESPONSE TO NO. 121:

Plaintiffs reincorporate all previous objections by reference, and respond additionally as follows: Plaintiffs will produce relevant and non-privileged documents reasonably related to this Request, to the extent such documents exist, can be located upon a reasonable search, and are within Plaintiffs' possession, custody, or control.

adenosine analogs, to the extent such documents exist, can be located upon a reasonable search, and are within Plaintiffs' possession, custody, or control.

DATED: November 15, 2019

Respectfully submitted,

FARNAN LLP

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EXHIBIT 13

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

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

J. Peter Fasse
Reg. No. 32,983

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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.