

# EXHIBIT 1

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

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- (54) **TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG**
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- (\*) 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.<sup>7</sup>** ..... **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

**References Cited**

**U.S. PATENT DOCUMENTS**

4,088,756 A	5/1978	Voorhees .....	424/180
4,454,122 A	6/1984	Stramentionoli et al. ...	424/180
5,399,349 A	3/1995	Paunescu et al. ....	424/195.1
5,460,959 A	10/1995	Mulligan et al. ....	435/172.3
5,618,544 A *	4/1997	Brown .....	424/401
5,770,582 A	6/1998	Von Borstel et al. ....	514/45
5,785,978 A *	7/1998	Porter et al. ....	424/401
5,821,237 A	10/1998	Bissett et al. ....	514/75
5,932,558 A	8/1999	Crostein et al. ....	514/46
5,998,423 A	12/1999	Manneth et al. ....	514/260

**FOREIGN PATENT DOCUMENTS**

DE 19545107 \* 6/1997

**OTHER PUBLICATIONS**

Hartzstark et al. The use of indentometry to study the effect of agents known to increase skin cAMP content. *Experientia*. 41(3), 378-379, 1985.\*

Adair et al., "Vascular development in chick embryos: a possible role for adenosine" *American Physiological Society*; 0363-6135/89 1989.

Ahmed et al., "Presence of Both A<sub>1</sub> and A<sub>2</sub> Adenosine Receptors in Human Cells and Their Interaction," *Biochemical and Biophysical Research Communications*, 208:871-878, 1995.

Ethier et al., "Adenosine Stimulation of DNA Synthesis in Human Endothelial Cells," *The American Physiological Society*, 272:H1470-H1479, 1997.

Grove et al., "Optical profilometry: An objective method for quantification of facial wrinkles," *Journal of the American Academy of Dermatology*, 21:631-637, 1989.

Gruber et al., "Increased Adenosine Concentration in Blood From Ischemic Myocardium by AICA Riboside," *Circulation*, 80:1400-1411, 1989.

Kollias-Baker et al., *Journal Pharmacology and Experimental Therapeutics*, 281: 761-768, 1997.

Newby et al., *Critical Evaluation of the Role of Ecto—and Cytosolic 5' Nucleotidase in Adenosine Formation Topics and Perspectives in Adenosine Research*, 155-168, 1987.

Olsen et al., "Tretinoin emollient cream: a new therapy for photodamaged skin," *Journal of the American Academy of Dermatology*, 26:215-224, 1992.

Olsen et al., "Tretinoin emollient cream for photodamaged skin: Results of 48-week, multicenter, double-blind studies," *Journal of the American Academy of Dermatology*, 37:217-226, 1997.

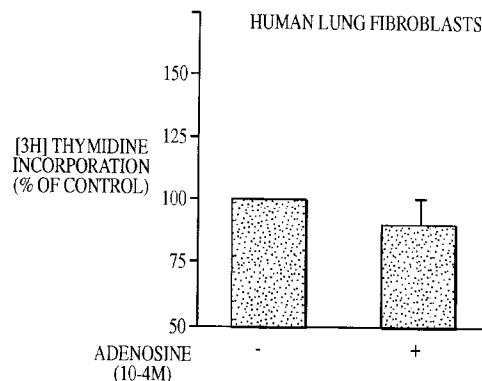
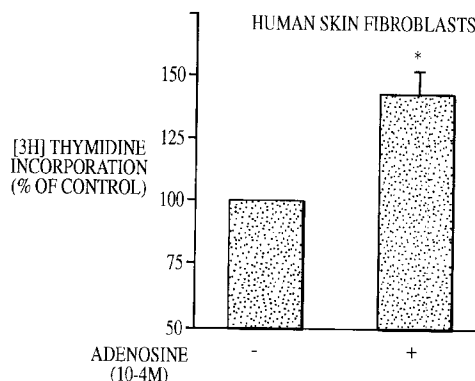
\* cited by examiner

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(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**



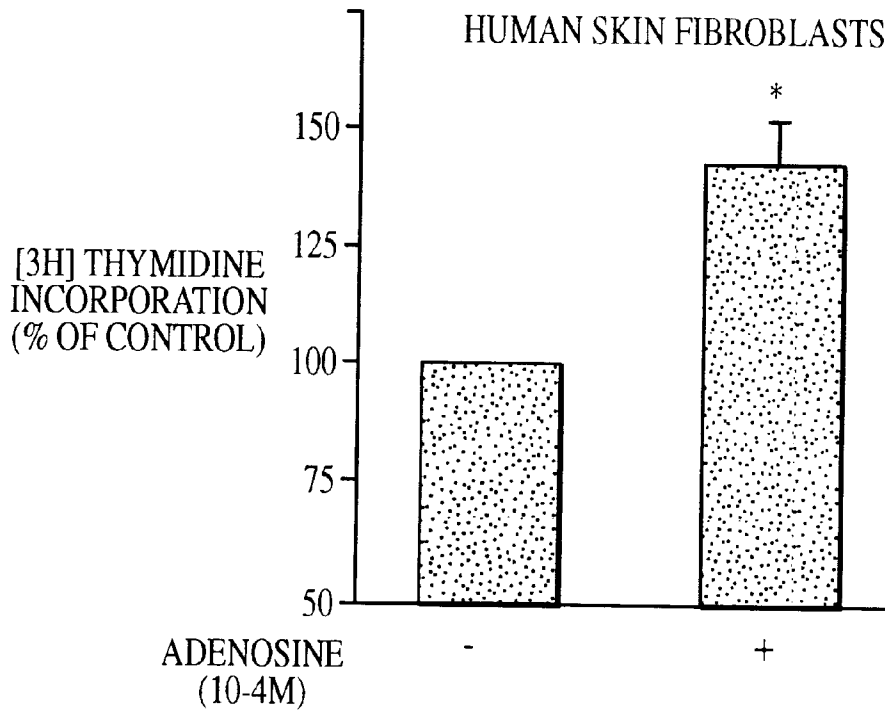


FIG. 1A

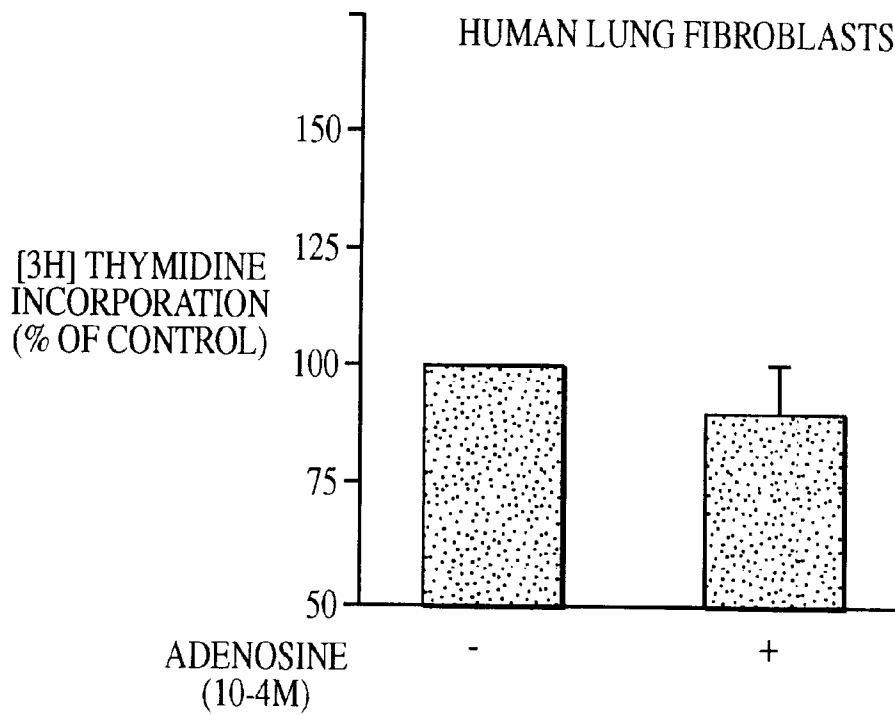


FIG. 1B

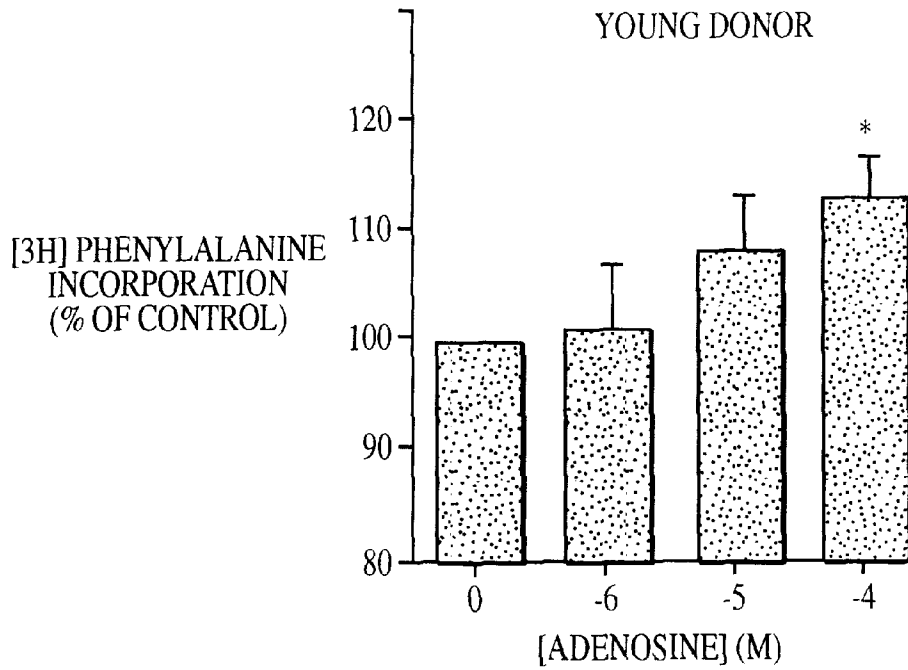


FIG. 2A

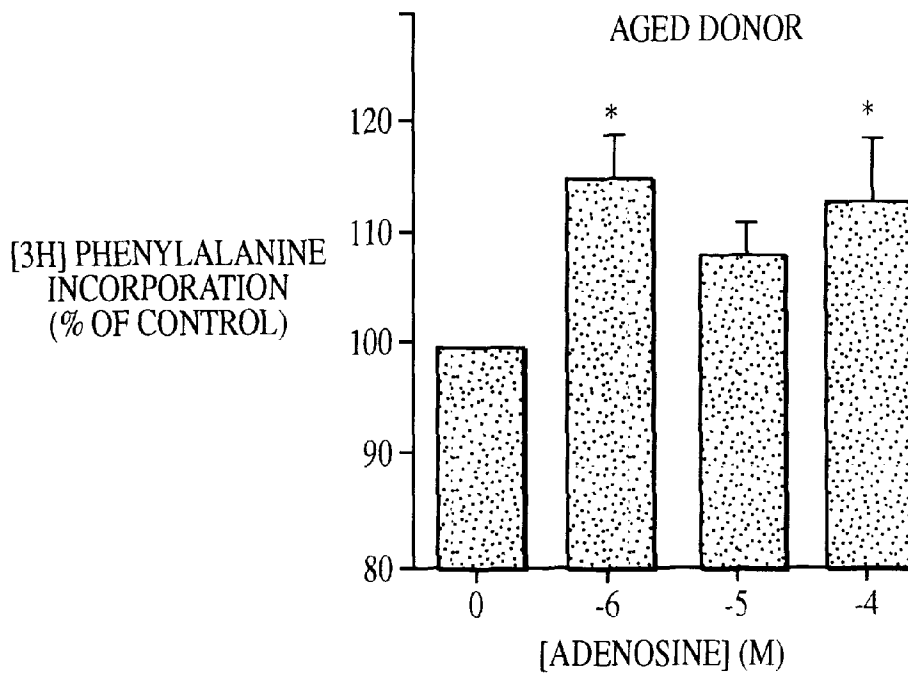


FIG. 2B

## 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 tretinoin 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

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