EXHIBIT B

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

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3-15-02

Commissioner for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132

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

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

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

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

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February 13, 2002
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proliferation of a major type of dermal cells, i.e., skin fibroblasts. In this testing, we cultured skin fibroblasts from two subjects, a 30 year-old female and an 84 year-old male. For each experiment, we used 35 mm culture dishes plated with fibroblasts at a density of 1×10^4 cells/cm^2. Adenosine was added to dishes the following day. For each adenosine-treated dish, a matching control dish was treated with vehicle. After 5 days in culture, we counted the total number of cells in the control dish, and then in the test dish. For each pair of culture dishes, the number of cells in the control dish was designated as 100% and the number of cells in the adenosine-treated dish was expressed as a percentage of the control dish. In each experiment, the mean and standard error for adenosine-treated dishes was generated from the total number of samples (n = 6 or 7) for each test and expressed as a percent of the control. The adenosine concentrations and results are listed in Table 1 attached to this declaration as Exhibit A. As shown, adenosine concentrations of both 10 ☒M (10^{-5} M) and 100 ☒M (10^{-4} M) caused no significant change in cell proliferation, i.e., the number of cells did not change. Based on these results, we believe that lower adenosine concentrations, e.g., 10^{-6} M and 10^{-7} M, would also not increase cell proliferation.

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

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

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

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

Date: 02/11/02

James G. Dobson, Jr., Ph.D

Date: 2/11/02

Michael F. Ethier, Ph.D

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