EXHIBIT A



Serial No.: 09/672,348

Filed: September 28, 2000

Title : TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

BOX AF

Commissioner for Patents Washington, D.C. 20231

RESPONSE TO FINAL OFFICE ACTION DATED OCTOBER 10, 2001

ofm 2-11-02

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.

3-8-02

(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.

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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,



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



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 x 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



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