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**Datasheet for the decision
of 9 April 2009**

Case Number: T 1031/06 - 3.3.04

Application Number: 01986261.4

Publication Number: 1322318

IPC: A61K 35/74

Language of the proceedings: EN

Title of invention:

Use of probiotic lactic acid bacteria for balancing the skin's immune system

Applicant:

Société des Produits Nestlé S.A.

Opponent:

-

Headword:

Probiotic lactic acid bacteria/NESTLÉ

Relevant legal provisions:

EPC Art. 54, 56, 84, 123(2)

Relevant legal provisions (EPC 1973):

-

Keyword:

"Main request: - added matter (no) - clarity (yes) - novelty (yes) - inventive step (yes)"

Decisions cited:

G 0005/83, T 0939/92, T 0435/04

Catchword:

-



Case Number: T 1031/06 - 3.3.04

DECISION
of the Technical Board of Appeal 3.3.04
of 9 April 2009

Appellant: Société des Produits Nestlé S.A.
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 16 February 2006
refusing European application No. 01986261.4
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: U. Kinkeldey
Members: R. Gramaglia
F. Blumer

Summary of Facts and Submissions

- I. European patent application No. 01 986 261.4 was published as international application WO-A-02/28402 with the title "Use of probiotic lactic acid bacteria for balancing the skin's immune system".
- II. At the oral proceedings held on 7 June 2005 before the examining division, the applicant wished to proceed with claims 1-10 of the main request filed on 6 May 2005 and the claims of the 1st to 6th auxiliary requests filed with fax on 6 June 2005 (see the "Minutes", paragraph 2). The examining division accepted the claims of the 5th auxiliary request (renamed "3rd auxiliary request" during the oral proceedings). Claim 1 of this request read as follows:
- "1. Use of a probiotic lactic acid bacterium selected from CNCM I-1225 or CNCM I-2116, or a culture supernatant thereof for preparing a carrier for preventing ultraviolet radiation induced immunosuppression in the skin."
- III. With letter dated 27 January 2006 the applicant expressed its disagreement to the text as proposed for grant and requested the grant of a patent on the basis of the main request filed on 28 October 2005 (which was identical to the 2nd auxiliary request filed with the fax of 6 June 2005).
- IV. However, since claim 1 of this 2nd auxiliary request had been found during the previous oral proceedings held on 7 June 2005 not to be acceptable for lack of compliance with the requirements of Article 123(2) EPC,

the examining division refused the application under Article 97(1) EPC.

- V. The applicant (appellant) filed an appeal against the decision of the examining division.

- VI. The board sent a communication pursuant to Article 17 of the Rules of Procedure of the Boards of Appeal (RPBA) indicating its preliminary non-binding opinion.

- VII. Submissions in reply to the board's communication were filed on 3 November 2008 with a main request and an auxiliary request. In this letter, the appellant also clarified that his request for oral proceedings did not apply if the board, on the basis of the written submissions on file, were to come to a positive decision. Subsequently, the board did not consider oral proceedings to be necessary.

- VIII. Further to a phone interview, a new main request was submitted by facsimile on 26 March 2009 in replacement of any previous claim requests. Claim 1 of the main request read as follows:

"1. Use of probiotic lactic acid bacteria or a culture supernatant thereof for preparing an ingestible carrier for down-regulating inflammatory or allergic reaction in the skin induced by UV irradiation of the skin and up-regulating the immune system in the skin during an immuno-suppressive condition induced by UV irradiation of the skin."

Dependent claims 2 to 6 related to specific embodiments of the use according to claim 1.

IX. The following documents are cited in the present decision:

D1 FR-A-2 682 596;

D2 WO-A-99/17788;

D3 FR-A-2 718 752;

D4 Derwent Publication, Week 199711 and Patent Abstracts of Japan JP-A-09002959;

A1 FR-A-2 750 298;

A3 DE-A-199 09 820;

A5 US-A-5,902,743;

A6 WO-A-98/27824;

A8 EP-A-1 034 788.

X. The submissions by the appellant (applicant), insofar as they are relevant to the present decision, can be summarized as follows:

Clarity (Article 84 EPC)

- The exposure of skin to UV irradiation could induce an immunosuppressive effect as well as an inflammatory and irritant or allergic effect. The use according to present claim 1 acted on both components of the resulting effects of UV

irradiations on the skin, namely immunosuppressive effect and inflammatory/allergic effect. This twofold therapeutic effect clearly stood out from the wording of present claim 1.

Article 123(2) EPC

- Support for the terms in claim 1 "down-regulating inflammatory or allergic reaction in the skin induced by UV irradiation of the skin" and "up-regulating the immune system in the skin during an immuno-suppressive condition induced by UV irradiation of the skin" could be found in the published WO application on page 5, second paragraph and on page 6, third to fifth paragraph.
- Support for the term "ingestable (carrier)" in claim 1 could be found in claim 2 of the published WO application.

Novelty (Article 54 EPC)

- Document D1 related to cosmetic compositions acting on the skin, not to "ingestable carriers". Additionally, this document was silent with respect to possible beneficial influences on the skin subject to UV irradiation.
- Document D2 described a composition for the treatment of candidiasis and further to a method for enhancing the immune system of an animal. These were situations different from simultaneously up-regulating the immune system in the skin and down-regulating inflammatory and/or allergic reaction

during an immuno-suppressive condition induced by UV irradiation of the skin.

- Document D3 pertained to compositions having an effect on the amount of sebum and on the hydration of skin and provided no information with respect to the subject-matter of claim 1.
- Document D4 referred to the use of lactobacilli as an anti-allergic agent, as shown by their capacity to reduce the IgE-production and provided no information with respect to the subject-matter of claim 1.
- Documents A1 to A8 were not relevant with respect to the subject-matter of claim 1.

Inventive step (Article 56 EPC)

- The problem underlying the present invention was to provide an agent which could reduce the skin's tendency to develop hyper-reactions and reduce the suppression of the skin's immune system, both occurring when the skin was irradiated by ultraviolet radiations.
- All the above-mentioned documents of the prior art related to solving different problems, when compared with the present invention, as none of them was concerned with alleviating the effects of ultraviolet radiation on the skin.
- Therefore, neither document D3 nor anyone of documents D1, D2 or D4 gave any indication to a

skilled person that the use of lactic acid bacteria might have a positive effect on the skin subjected to ultraviolet irradiation in terms of reduction of the skin's tendency to develop hyper-reactions and in terms of reduction of the suppression of the skin's immune system.

- XI. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request submitted by facsimile on 26 March 2009.

Reasons for the Decision

Main request

Clarity (Article 84 EPC)

1. The exposure of skin to a stress condition caused by UV irradiation may induce an immunosuppressive effect as well as an inflammatory and irritant or allergic effect (see published WO application, page 2, third paragraph). The use according to present claim 1 acts on both components of the resulting deleterious effects of UV irradiations on the skin, i.e. the immunosuppressive effect and the inflammatory or allergic effect (see published WO application; page 5, third paragraph and page 6, fifth paragraph).

This twofold therapeutic effect clearly stands out from the wording of present claim 1.

Article 123(2) EPC

2. The examining division refused the application because the wording "having the capability to stimulate the immune system" in claim 1 of the first auxiliary request filed with fax on 6 June 2005 had been found during the oral proceedings not to be acceptable for lack of compliance with the requirements of Article 123(2) EPC (see paragraph IV supra). Present claim 1 no longer includes the above wording found by the examining division to introduce added subject-matter.

The wordings in claim 1 "for down-regulating inflammatory or allergic reaction in the skin induced by UV irradiation of the skin" and "up-regulating the immune system during an immuno-suppressive condition in the skin induced by UV irradiation of the skin" are based on page 6, lines 7 to 13 of the published WO application, taken in combination with page 2, third paragraph thereof.

The feature "ingestable" has been taken from claim 2 of the published WO application.

Dependent claims 2 to 5 correspond to claims 3, 4, 8 and 9 as filed.

Dependent claim 6 is based on claim 10 as filed; the wording thereof has been adapted to present independent claim 1.

The board thus concludes that the subject matter of claim 1 and dependent claims 2 to 6 satisfies the requirements of Article 123(2) EPC.

Novelty (Article 54 EPC)

3. Claim 1 is directed to the second or further therapeutic application of probiotic lactic acid bacteria or a culture supernatant thereof given orally to a patient (cf. the term "ingestable" in claim 1), said therapeutic application being the simultaneous up-regulation of the immune system in the skin and the down-regulation of the inflammatory/allergic reaction in the skin, both caused by UV irradiation of the skin.
4. This claim is worded accordingly in the form suggested by the Enlarged Board of Appeal when considering the so-called second medical indication (see G 5/83, OJ EPO 1985, 64, point 9 of the reasons) in cases where the therapeutic agent of the claimed use is no different from a known agent.
5. The board observes that the medical application recited in present claim 1 is twofold. Hence a prerequisite for a document of the prior art to affect the novelty of the claimed subject-matter is the disclosure of both therapeutic effects.
6. The question therefore arises whether or not any of the prior art documents presently before the board directly and unambiguously discloses a relationship between, on the one hand, using the therapeutic agent (lactic acid bacteria, or supernatants thereof, given orally) and, on the other hand, obtaining the simultaneous up-

regulation of the immune system in the skin after being affected by UV irradiation **and** the down-regulation of the inflammatory and/or allergic reaction induced by UV irradiation of the skin.

Document D1

7. Document D1 discloses a composition comprising a supernatant from *Lactobacillus* for the topical application on the skin for (i) scavenging active oxygen/radicals deleterious to the skin's DNA (see "Exemple expérimental 1" on page 12); for (ii) strengthening the skin DNA repair system of UV-damaged DNA (see "Exemple expérimental 2" on page 14 and lines 13 and 27 thereof); and for (iii) strengthening the skin immune system against pathogens via the increase of IgG's (see page 3, line 29; page 5, lines 1-5; page 16, line 15 and page 17, lines 8-11).

Document D2

8. This document pertains to an oral composition which includes one or more *Lactobacilli* probiotic microorganisms for the treatment of candidiasis, which may occur on the skin (see page 7, line 9: "epidermal"). The composition is reported to enhance the immune system in general.

Document D3

9. This document relates to an oral preparation comprising whey which has been fermented with at least one *Lactobacillus*, at least one *Streptococcus*, at least one *Leuconostoc* and at least one yeast, and which

optionally may comprise radical scavengers such as vitamins A, E, C, B1 and superoxide dismutase (SOD). This composition is reported to enhance the immune system in general (see page 3, line 25) and to confer on the skin a more gentle and smooth aspect (see page 4, lines 9-12) via an anti-radical (scavenging) effect (see page 4, line 6).

Document D4

10. This document refers to an oral preparation comprising Lactobacilli to be used as an anti-allergic agent against type I allergic diseases such as pollinosis, allergic nasal catarrh, atopic dermatitis and bronchitis (see under "Use/Advantage").

Document A1

11. This document relates to yoghurt products for nutrition containing Lactobacilli (see claim 4), which are capable of improving a host's health and intestinal flora (see page 1, lines 18-20).

Document A3

12. It is stated in this document (see column 1, lines 23-27 that lactic acid bacteria may exert a non-specific stimulation of the immune system via the formation of IgA's (alpha-immunoglobulins) and interferon.

Document A5

13. This document discloses a Bifidobacterium strain isolate and its use as probiotic material achieving "protective health benefits" (see column 1, line 27).

Document A6

14. It is stated on page 1, third paragraph of this document that probiotic lactic acid bacteria such as CNCM 1-1225 act upon the human immune system.

Document A8

15. It is stated in paragraphs [0036] and [0049] of this document that probiotic lactic acid bacteria such as ST-11 (CNCM I-2116) exhibit anti-allergic properties in that said strain has an impact on the synthesis of different immunological mediators, leading to a good anti-Th2 profile.
16. In summary, none of these above-cited effects anticipates any of the specific therapeutic effects recited in claim 1, namely the down-regulation of inflammatory/allergic reaction in the skin and the up-regulation of immuno-suppressive condition in the skin caused UV irradiation of the skin, let alone anticipates the combination of the two effects. The board thus concludes that the subject matter of claim 1 and dependent claims 2 to 6 satisfies the requirements of Article 54 EPC.

Inventive step

Closest prior art and problem to be solved

17. The examining division considered document D3 as representing the closest prior art because it dealt with lactic acid bacteria having an effect against radicals on the skin (see the "Minutes of the oral proceedings", paragraph 18). However, given that the claimed subject-matter deals with alleviating UV skin's damages, the board agrees with the appellant's view that a document concerned with alleviating the effects of UV on the skin would represent the best starting point.

One such document is indeed before the board since document D1 describes inter alia (see point 7 supra) the use of a composition comprising a supernatant from *Lactobacillus* for the topical application on the skin for strengthening the skin DNA repair system of UV-damaged DNA (see "Exemple expérimental 2" on page 14 and lines 13 and 27 thereof in combination with page 3, lines 6-10). Document D1 thus represents the closest prior art.

18. The problem to be solved in view of the closest prior art is the provision of an agent capable of reducing further damages, in addition to DNA damages (document D1), occurring to the skin irradiated by UV light, namely the skin's tendency to develop both hyper-reactions and immuno-suppression (see the WO application, page 2, third paragraph and page 3, lines 19-21).

19. The solution to this problem according the invention is the oral administration of probiotic lactic acid bacteria or culture supernatants thereof. Example 1 of the application shows that the probiotic lactic acid bacterium ST-11 (CNCM I-2116) or a culture supernatant thereof taken orally indeed achieves a reduction (see Table I) of the inflammation induced by dinitrochlorobenzene (DNCB) to mice ears, which is a model for measuring the level of an hypersensitivity reaction occurring in the skin. The levels of ICAM-1, IL-10 (pro-inflammatory markers) and TGF- β (anti-inflammatory marker) are also measured and the levels of these markers confirm the results of the "ear thickness test". Example 2 further shows that UV-light induced suppression of the immune response in the animals' skin is restored by oral administration to the animals of probiotic lactic acid bacteria or culture supernatants thereof (see Table V). The board is thus satisfied that the above-formulated problem has indeed been solved.

Has the problem been solved within the whole range of claim 1?

20. Compared with claim 1 accepted by the examining division (see paragraph II supra), claim 1 of this request is no longer restricted to the exemplified lactic acid bacteria strains CNCM I-1225 (see Example 1) and CNCM I-2116 (see Example 2), or a culture supernatant thereof.
21. Relying on decision T 939/92 (OJ EPO 1996, 309), the examining division reasoned that a broader claim referring to any lactic acid bacteria strain or a culture supernatant thereof (such as present claim 1)

was not allowable under Article 56 EPC because it would cover bacterial strains failing to exhibit the required biological effect and hence failing to solve any problem (see communication dated 23 February 2005, paragraph 4.1).

22. However, the board cannot endorse this argumentation. The board regards the principle underlying decision T 939/92 as being that, for the presence of an inventive step to be acknowledged, the purpose according to the invention of all the subject-matter falling within a claim must be plausibly achieved. Although decision T 939/92 was based on a product claim, the rationale of this decision can, in the board's view, also be applied to the present case, where a second medical use is at stake (see point 4 supra). Once the rationale of decision T 939/92 is applied to the present second medical use claim 1, addressing the oral administration of lactic bacterial for the treatment of inflammatory/allergic reaction and immuno-suppressive conditions in the skin caused by the UV irradiation of the skin (see also the problem formulated in point 18 supra), the only question that could arise in connection with the argument put forward by the examining division is therefore whether, by analogy with the principles set out in T 939/92, all the lactic acid bacterial strains or culture supernatants thereof referred to in the claim are suitable for the above defined skin treatment.

23. However, this question does not arise, because, unlike the product claim underlying the cited decision, the statement of purpose ("...for preparing an ingestible carrier for down-regulating inflammatory or allergic

reaction in the skin induced by UV irradiation of the skin and up-regulating the immune system in the skin during an immuno-suppressive condition induced by UV irradiation of the skin") in the present second medical use claim is an explicit feature of the claim that has a limiting effect (see decision T 435/04 of 13 March 2007, points 29 to 31 of the reasons). Therefore, present claim 1 only refers to those lactic acid bacterial strains or culture supernatants thereof with which the above-mentioned skin diseases caused by UV irradiation can actually be treated successfully. In conclusion, the fact that an ineffective lactic acid bacterial strain might theoretically fall within the frame of present claim 1 does not provide a basis for an attack according to the principles formulated in decision T 939/92.

24. When assessing the inventive step, the question arises whether or not the skilled person would have derived the solution of the above-formulated problem in an obvious way from the closest prior art document D1 on its own, or from document D1 taken in combination with other documents of the prior art.

25. The in vitro experiments described in "Exemple expérimental 2" on page 14 of document D1 deal with measuring the number of thymine dimers formed by UV irradiation and reflecting DNA damage. Therefore, in the board's judgement, this test pertaining to skin DNA repair is predictive neither of the down-regulation of the inflammatory/allergic reaction in the UV irradiated skin, nor of the up-regulation of the immuno-suppressive condition in the UV irradiated skin. Moreover, it should be noted that the lactic acid

bacteria-based agent described in document D1 is applied topically, whereas the agent referred to in present claim 1 is an "ingestable carrier".

26. Therefore, in view of the above differences, the board concludes that the skilled person would derive from document D1 nothing more than the teaching that lactic acid bacteria applied topically to the skin are able to strengthen the skin repair system of UV-damaged DNA, and would not draw any conclusion as to a possible reduction of further damages occurring to the skin irradiated by UV light, namely the skin's tendency to develop both hyper-reactions and immuno-suppression. This is even more true once the skilled person realises that the agent according to the invention is taken orally rather than applied topically according to document D1.

27. The board observes that document D1 also refers to a further technical effect, namely the strengthening of the skin immune system against pathogens (see page 3, line 29; page 5, lines 1-5 and page 17, lines 8-11). The question thus arises whether the knowledge of this additional effect would partially direct the skilled person towards the present invention, at least insofar as the "immunological arm" is concerned. However, this therapeutic effect directed against pathogens is not predictive of the up-regulation of the immuno-suppressive condition in the skin caused by UV irradiation of the skin, given the different aetiology underlying these two pathological situations, as reflected by the divergence between the test used in document D1 (measure of IgG's: see page 16, line 15)

and that used in the present application (measure of % inhibition of HSC by irradiation: see Table V).

28. The board further observes that documents D2, D3, A3 and A6 teach that lactic acid bacteria behave as enhancers of the immune response, whereas documents D4 and A8 relate to the anti-allergic properties thereof. The question thus also arises whether or not the skilled person would have derived the solution of the above-formulated problem in an obvious way from document D1 taken in combination with one or more of these documents.

29. Document D2 pertains to an oral composition which includes one or more Lactobacilli probiotic microorganisms for enhancing the immune system during the treatment of candidiasis, which may occur on the skin (see page 7, line 9: "epidermal"). Document D3 teaches that a composition comprising lactic acid bacteria enhances the immune system in general (see page 3, line 26) via the activation of PKC (protein kinase C: see page 24, lines 22-25). Document A3 (see column 1, lines 23-27) teaches that lactic acid bacteria may exert a non-specific stimulation of the immune system via the formation of IgA's (alpha-immunoglobulins) and interferon. Document A6 (see page 1, third paragraph) teaches that probiotic lactic acid bacteria such as CNCM 1-1225 act upon the human immune system. Document D4 is concerned with treating with lactic acid bacteria a series of type I allergic pathologies including atopic dermatitis. Finally, document A8 states in paragraphs [0036] and [0049] that probiotic lactic acid bacteria such as ST-11 (CNCM I-2116) exhibit anti-allergic properties in that said

strain has an impact on the synthesis of different immunological mediators, leading to a good anti-Th2 profile.

30. Combining the teaching of document D1 with that of one or more of these documents, in the board's opinion, would not lead the skilled person to an obvious solution of the above-defined problem, either. This is because, as already emphasized under point 27 supra, the therapeutic effects and the underlying experiments, if any, disclosed in the above documents are predictive neither of the up-regulation of the immuno-suppressive condition in the skin caused by UV irradiation of the skin, nor of the down-regulation of the UV-irradiated skin's tendency to develop hyper-reactions. In fact, the knowledge that lactic acid bacteria stimulate the immune response against candidiasis (document D2), or that they are able to increase PKC (document D3) or IgA's (document A3) in vitro would not lead the skilled person to the unavoidable conclusion that up-regulation of the immuno-suppressive condition in the skin caused by UV irradiation will turn up. Nor would the knowledge by the skilled person that lactic acid bacteria are able to alleviate a series of type I allergic pathologies including atopic dermatitis (document D4) or that they have an impact in vitro on the synthesis of different immunological mediators, leading to a good anti-Th2 profile (document A8) allow any reasonable prediction to be formulated as regards the down-regulation of the UV-irradiated skin's tendency to develop hyper-reactions.

31. In view of the foregoing, the board concludes that the subject-matter of claim 1 and dependent claims 2 to 6 satisfies the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside
2. The case is remitted to the first instance with the order to grant a patent on the basis of the claims of the main request submitted by facsimile on 26 March 2009 and a description to be adapted.

The Registrar:

Chair:

P. Cremona

U. M. Kinkeldey