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Datasheet for the decision of 24 July 2008

Case Number: T 0372/06 - 3.3.08

Application Number: 98910557.2

Publication Number: 1002110

IPC: C12N 15/70

Language of the proceedings: EN

Title of invention:
Immune responses against HPV antigens elicited by compositions comprising an HPV antigen and a stress protein or an expression vector capable of expression of these proteins

Patentee:
Stressgen Biotechnologies Corporation

Opponent:
ANTIGENETICS Inc

Headword:
HPV-hsp fusion proteins/STRESSGEN

Relevant legal provisions:
EPC Art. 56, 83, 84, 123(2)

Relevant legal provisions (EPC 1973):
EPC R. 57a

Keyword:
"Main request - patent as maintained"
"Formal allowability of the amendments (yes)"
"Inventive step (yes)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0372/06 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 24 July 2008

Appellant: (Opponent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 1 December 2005 concerning maintenance of European patent No. 1002110 in amended form.

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
C. Heath

Summary of Facts and Submissions

I. European patent No. 1 002 110 with the title "Immune responses against HPV antigens elicited by compositions comprising an HPV antigen and a stress protein or an expression vector capable of expression of these proteins" was granted on European patent application No. 98 910 557.2 (published as WO 99/07860). The patent was granted with 25 claims.

II. A notice of opposition was filed on the grounds of Article 100(a) and (b) EPC 1973, in particular that the claimed subject-matter lacked an inventive step (Article 56 EPC 1973), and that the invention as claimed was not disclosed in the patent in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

III. In a interlocutory decision announced at the end of the oral proceedings on 19 October 2005 and posted on 1 December 2005, the opposition division established that, account being taken of the amendments introduced into the set of claims according to the main request (claims 1 to 23) and a description adapted thereto as filed at the oral proceedings, the patent and the invention to which it related met the requirements of the EPC, in particular those of Articles 123(2), 84, 56 and 83 EPC 1973. Consequently, the opposition division decided that the patent could be maintained in amended form on the basis of the main request.

IV. Amended claim 1 of the **main request** reads as follows:

"1. A fusion protein comprising an HPV protein antigen, or a portion thereof, and a heat shock protein, or a portion thereof, wherein the fusion protein induces an immune response against the HPV protein antigen, or the portion thereof, in a subject to whom it is administered, and the portion of the heat shock protein induces or enhances a cell-mediated, cytolytic immune response against the HPV protein antigen or the portion thereof."

The amended claim differs from claim 1 as granted in that the term "heat shock protein" has replaced the term "stress protein", and that the immune response induced or enhanced by the portion of the heat shock protein is qualified as a "cell-mediated, cytolytic immune response".

Dependent claims 2 to 11, which relate to different embodiments of the fusion protein of claim 1, differ from the corresponding granted claims in that in claims 2 to 6, 8 and 10 the term "stress protein" has been replaced by the term "heat shock protein", claim 6 has been restricted to fusion proteins comprising a heat shock protein or portion thereof selected from the Hsp100-200, Hsp100, Hsp40 or Hsp20-30 families, and claim 11 amended to refer to claim 1 (instead of claim 2).

Claims 12 to 15, which are identical to the corresponding claims as granted, are directed to a nucleic acid molecule encoding a fusion protein as claimed. Independent claim 16 and dependent claims 17

and 18, which correspond to, respectively, claims 16, 19 and 20 as granted, relate to a composition including the fusion protein. The use of the composition of claim 16 for inducing an immune response against an HPV protein antigen is claimed in claim 19 (claim 21 as granted).

Finally, claims 22 to 25 concern various embodiments of a composition comprising an expression vector which encodes the claimed fusion protein, and the use of this composition for inducing an immune response against an HPV protein antigen.

V. The opponent (appellant) lodged an appeal against the interlocutory decision of the opposition division. With the statement setting out the grounds of appeal, copies of a declaration by Dr Srivastava dated 9 September 2005 and the documents cited therein were re-filed. Oral proceedings under Article 116 EPC 1973 were requested in the event that the board considered any decision other than revoking the patent.

VI. The patent proprietor (respondent) filed observations to the grounds of appeal and requested oral proceedings in the event that the board was not inclined to dismiss the appeal.

VII. The parties were summoned to oral proceedings. In a communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) as in force from 13 December 2007, the board provided comments on some of issues discussed in the decision under appeal.

VIII. The respondent requested postponement of the oral proceedings on the grounds that its representative had already been summoned to attend oral proceedings in another case on the same date. Evidence for the alleged circumstances was provided.

IX. By letter dated 2 April 2008, the appellant withdrew its request for oral proceedings.

X. Since the board considered that the circumstances alleged by the respondent justified a postponement of the scheduled oral proceedings, new summons were sent to the parties.

XI. The respondent filed observations in response to the communication by the board, as well as four sets of amended claims as auxiliary requests I to IV.

XII. Oral proceedings were held on 24 July 2008. Although duly summoned, the appellant was not represented.

XIII. The following documents are referred to in this decision:

(1): R. W. Tindle et al., 1994, Virology, Vol. 200, pages 547 to 557;

(2): K. Suzue and R. A. Young, 1996, The Journal of Immunology, Vol. 156, pages 873 to 879;

(3): T.-C. Wu et al., December 1995, Proc. Natl. Acad. Sci. USA, Vol. 92, pages 11671 to 11675;

(4): R. Suto and P. K. Srivastava, 15 September 1995, Science, Vol. 269, pages 1585 to 1588;

(16): WO 97/10000, published on 20 March 1997;

(22): K. Suzue and R. A. Young, 1996, Stress-Inducible Cellular Responses, Birkhauser Verlag, Basel, Switzerland, ed. by U. Feige et al., pages 451 to 465;

(111): B. E. Clarke et al., 26 November 1987, Nature, Vol. 330, pages 381 to 384;

(150): K. Suzue et al., November 1997, Proc. Natl. Acad. Sci. USA, Vol. 94, pages 13146 to 13151;

(151): L. E. Hood et al., 1978, Immunology, The Benjamin/Cummings Publishing Company, Inc. Menlo Park (CA), USA, Jim Hall ed., pages 1 to 3;

(157): S. N. Chatfield et al., August 1992, Bio/Technology, Vol. 10, pages 888 to 892;

(158): M. J. Roossinck et al., May 1986, Molecular and Cellular Biology, Vol. 6, No. 5, pages 1393 to 1400;

Declaration of Dr. Pramod K. Srivastava dated 9 September 2005.

XIV. The submissions made by the appellant in writing may be summarized as follows:

Main request - Formal issues

It was acknowledged that the language "heat shock protein" could be found at page 6, lines 48 and 54 of the specification, *provided* it was accepted, as was stated at those parts of the specification, that stress protein and heat shock protein meant the same thing, in which case there was no need for amendment. But if "stress protein" and "heat shock protein" meant different things, then that was information not provided in the specification of the application as filed (or the patent as granted), and the replacement of "stress protein" by "heat shock protein" therefore offended against Article 123(2) EPC as well as caused lack of clarity under Article 84 EPC.

Inventive step

Document (1) as the closest prior art combined with document (2)

Document (1) taught that HBcAg-HPV protein antigen fusion proteins could induce an immune response in a subject, but only in the presence of an adjuvant, and that, in order for an HPV protein-antigen-specific CTL response to be induced, the HBcAg-HPV protein antigen fusion protein might have to be expressed intracellularly (eg. in the cytosol), in order to be processed and presented to the immune system *via* the MHC Class I pathway. Accordingly, document (1) directed the skilled person toward the goal of developing vaccines that would enter the MHC I antigen processing pathway in order to induce the HPV protein antigen-specific-CTL responses (which were driven primarily by

Th-1 cells) that were required for therapy of HPV E7-expressing tumour cells.

Starting from document (1) and attempting to develop a vaccine that induced an HPV-specific CTL response, a person skilled in the art would be expected to refer to art within the same general field of technology (antiviral vaccine development), particularly art addressing common problems. Thus, a skilled person would be aware of the art related to the development of antiviral vaccines that are capable of inducing humoral and cellular immune responses, including CTL responses, against virally-infected cells.

Document (2) disclosed that a fusion protein including a stress protein (hsp 70) and a HIV protein, when administered to a subject, without an adjuvant, induced humoral and cellular immune responses directed toward the HIV protein. Although HIV and HPV viruses were different, the induction of an HPV protein antigen-specific CTL response did not involve fundamentally different immunological processes than the CTL response to an HIV antigen. Moreover, it had been explicitly stated in document (7) that, for guidance with respect to the development of HPV vaccines, progress in the development of vaccines for other viruses, particularly HIV, should be considered.

Although there was no indication that the authors of document (2) tested for induction of a CTL response, induction of a cellular immune response specific to the target antigen was reported. The skilled person would understand that those cellular immune responses could include CTL responses. Support for this position was

found in document (2) and two later publications by the same authors (documents (22) and (150))

Starting from document (1) and taking document (2) into account, it was obvious to the skilled person to substitute the HBcAg carrier used in document (1) for a stress protein, in order to solve the objective technical problem. The suggestion in document (1) that CTL responses could be developed by *in vivo* expression using viral vectors or live *Salmonella* vaccines strains would not have been blindly followed by the skilled person in view of the perceived drawbacks of these approaches.

Moreover, the skilled person had a reasonable expectation of success. At the priority date claimed in the patent, it had been clearly and repeatedly described in the scientific literature that stress proteins were particularly effective carriers that could induce humoral and cellular immune responses, including CTL responses, against a plurality of attached peptide antigens, in the absence of adjuvant. In view of the weight of the state of the art in general, and the teaching of document (2) in particular, it would have been unreasonable for the skilled person not to expect that hsp-HPV fusions, when administered, without an adjuvant, to a subject would successfully induce HPV-specific humoral and cellular immune responses, including CTL responses.

Document (16) as the closest prior art combined with document (2)

The skilled person, faced with the task of developing an HPV vaccine, would start from document (16) as the closest prior art. This document described noncovalent hsp-protein antigen complexes that, when formulated without an adjuvant and administered to a subject, induced a CTL response directed against cells expressing the target protein antigen. It was disclosed on page 12, lines 15-32 that the protein antigen could be a papilloma viral protein antigen.

The skilled person, aware of the art directed toward the use of fusion proteins for antigen presentation and of a number of perceived advantages of fusion proteins over the non-covalent complexes, was motivated to review the art for an approach that could be combined with the approach described in document (16). That search would certainly lead directly to document (2) which disclosed a recombinant fusion protein including an hsp carrier and an HIV protein antigen, that induced both humoral and cellular immune responses directed toward the HIV protein. Since the method described in (2) captured the advantages of fusion proteins, the person skilled in the art would combine the teaching of document (16) with that of document (2) and arrive at the claimed fusion protein.

Document (3) as the closest prior art combined with either document (4) or (16)

The opposition division read document (3) too narrowly and limited the teaching of this document to the

illustrative example provided therein rather than considering its entire content. Document (3) taught the skilled person that the choice of carrier protein could determine the MHC presentation pathway through which a fusion protein antigen would be processed and, ultimately, presented to the immune system. Starting from document (3), the problem to be solved was the development of an improved, more potent HPV vaccine that induced an HPV-specific cellular immune response, particularly a CTL immune response. Having regard to document (4) and/or document (16), it was obvious and technically straightforward for the skilled person to modify the fusion protein described in document (3) by replacing the LAMP-1 carrier with a heat shock protein in order to provide an HPV vaccine that would be taken up by an antigen-presenting cell and directed toward the MHC I antigen processing system to stimulate an HPV antigen-specific $CD8^+$ T cell mediated CTL immune response. The skilled person had a reasonable expectation that this approach would be successful in view of the generality of the teaching of document (4) as well as in the light of the prior art taken as a whole, which had established the inherent ability of heat shock proteins to stimulate humoral and cellular, including CTL, responses against antigens attached to the hsp carrier, without the use of an adjuvant.

XV. The submissions made by the respondent in writing and during oral proceedings may be summarized as follows:

Main request - Formal issues

The amendment introduced into the claims to replace the term "stress protein" by the term "heat shock protein"

was made in response to the opponent's criticism that a fusion protein as defined in claim 1 as granted, which comprised a stress protein, did not necessarily induce a cell-mediated, cytolytic immune response. Literal basis for the term "heat shock protein" was found on page 12, lines 6 and 7 and lines 14 to 17 of the application as filed. The term "heat shock protein" conveyed a clear meaning to the person skilled in the art. This meaning was apparent from the patent specification (cf. page 6, line 53 to page 7, line 1).

Article 56 EPC - Inventive step

Document (1) as the closest prior art combined with document (2)

Document (1) described the development of improved vaccines for the treatment and prevention of HPV infection. When a fusion protein consisting of the hepatitis B virus core antigen (HBcAg) fused to a portion of the HPV E7 protein was administered to mice in combination with an adjuvant, a humoral immune response directed against the HPV E7 protein and a T cell proliferative response against E7 epitopes and HBcAg T cell epitopes were observed. No immune response, let alone a cell-mediated, cytolytic response was achieved without co-administration of adjuvant. Document (1) taught that CTL responses could be more efficacious than antibody responses for the control of HPV (see page 556, left column, second from paragraph). In order to attain the desired CTL response, the use of an *in vivo* intracellular expression system was suggested (see page 556, left column, second full paragraph).

Starting from document (1), the technical problem underlying the patent was the provision of a composition capable of eliciting a protective and/or therapeutic, cell-mediated, cytolytic immune response against an HPV protein antigen. The solution provided in the patent was the combination of an HPV protein antigen, or a portion thereof with a heat shock protein, or portion thereof, in the form of a fusion protein.

This solution was not obvious to a person skilled in the art. In contrast, document (1) suggested intracellularly expressing the HBV core antigen-HPV fusion protein by a viral expression system so as to direct antigen presentation to the MHC class I pathway, thus, leading to a cellular immune response.

XVI. The appellant (opponent) requested in writing that the decision under appeal be set aside and that the patent be revoked.

XVII. The respondent (patentee) requested that the appeal be dismissed (main request) or that the patent be maintained on the basis of one of the auxiliary requests I to IV filed on 24 June 2008.

Reasons for the Decision

Main request (claims 1 to 23 filed on 19 October 2005)

Formal issues - Articles 123 and 84 and Rule 57a EPC 1973

1. The finding of the opposition division that the amendment to claim 1 introducing the feature "cell-mediated, cytolytic" in order to define more precisely the type of immune response to be achieved conforms Articles 123(2) and 84 EPC, has not been contested on appeal.

2. However, the appellant objected to the substitution of the term "stress protein" by the term "heat shock protein" in, *inter alia*, amended claim 1, even though it conceded that the latter term has a basis in the specification. A formal basis for the amendment is, in fact, found in the passage on page 12, lines 6 to 27 of the application as filed, rather than in the corresponding passage of the patent indicated by the appellant and the opposition division (page 6, lines 48ff of the patent). The relevant passages (see page 12, lines 6, 7 and 14 to 17 of the application as filed) read:

"*Any suitable stress protein (heat shock protein (hsp)) can be used in the compositions of the present invention. [...] As used herein, a "stress protein", also known as a "heat shock protein" or "Hsp", is a protein that is encoded by a stress gene, and is therefore typically produced in significantly greater amounts upon the contact or exposure of the stressor to*

the organism. A "stress gene" also known as "heat shock gene"..."

3. These passages leave no doubt that there is no difference in meaning between the terms "stress protein" and "heat shock protein" as used in the application as filed. Both the scientific and the patent literature use the terms "stress protein" and "heat shock protein" interchangeably to designate a group of proteins synthesized by a cell under stress conditions, in particular in response to heat shock. This arises from the fact that many of the proteins which were first identified as being induced in response to heat shock, were subsequently found to be induced also under other stress conditions, such as nutrient deprivation. This is confirmed by document (16), to which the opposition division referred in its decision (see document (16), paragraph bridging pages 8 and 9, and first full paragraph on page 9). This evidence has not been contested by the appellant.

4. Nor has the appellant put forward any reasons against the finding of the opposition division that the requirements of Article 84 EPC are met. The sole issue that the appellant appears to question is the need for the amendment in question. In this respect, the board observed in its communication under Article 15(1) RPBA that, even though Rule 57a EPC 1973 was not explicitly mentioned in the decision under appeal, the opposition division had accepted the proprietor's argument that the replacement of the term "stress protein" by "heat shock protein" aimed at overcoming the objection raised in point 5.7.1 of the opponent's letter dated 9 September 2005. Since the opponent's objection was

made in connection with the issue of inventive step, it appears that the opposition division considered that the amendment in question was occasioned by grounds for opposition specified in Article 100 EPC, and, consequently, fulfilled the requirement of Rule 57a EPC 1973. No arguments have been put forward by the appellant in this respect, either in its statement of grounds of appeal or in response to the board's communication.

5. Consequently, the board sees no reason to disagree with the finding of the opposition division that the main request is formally allowable.

Article 56 EPC - Inventive step

6. In its statement of grounds of appeal, the appellant developed three lines of argument against the opposition division's finding that the claimed subject-matter meets the requirements of Article 56 EPC. These lines of argument relied on any of documents (1), (16) and (3) as the closest prior art.

Document (1) as the closest prior art combined with document (2)

7. Among the documents identified by the appellant as the closest prior art, the board considers document (1) as the most promising starting point towards the invention, because the fusion proteins described therein are conceived for the same purpose as the claimed invention, namely to induce or enhance an immune response against an HPV antigen, and also share with the claimed subject-matter the most relevant technical features, ie.

an HPV antigen linked to a carrier protein to form a fusion protein.

8. The experiments described in document (1) were designed with the aim of maximising the antibody responses to HPV E7 subunit vaccine peptides (see page 547, right column, first full paragraph). To this purpose, the possibility of enhancing the immunogenicity of HPV E7 peptides by presenting fusion proteins consisting of HBcAg and synthetic peptides containing HPV E7 epitopes was investigated. Hepatitis B core antigen (HBcAg) was known to form particles which were powerful immunogens.

9. Fusion proteins were produced by expressing a chimeric gene obtained by linking the entire HBcAg gene to synthetic oligonucleotides containing one, two or three HPV B-epitopes. Two of the fusion proteins contained also an HPV T-epitope (see Figure 1B). When mice were immunised intramuscularly with purified recombinant HBcAg particles in incomplete Freunds adjuvant, strong epitope-specific antibody responses were obtained for the particles containing one or two of the three HPV E7 B-epitopes considered. Moreover, T-proliferative responses were elicited to the HPV E7 T-epitope as well as to HBcAg T-epitope(s) (see chapter under the heading "T-proliferation and cytokine production" on page 552, and Figure 7A and B). It was observed that lymph node cells from immunized mice produced IL-2 and IL-4 when specifically recalled *in vitro* (see Figure 7C and E), indicating that both Th1 and Th2 helper cell compartments were stimulated (see Abstract, lines 8 and 9).

10. In the last two paragraphs of the chapter "Discussion" (see page 556, left column), the authors of document (1) drew some conclusions from their experimental results and made suggestions for further vaccine development. In particular, it was suggested that, in order to achieve cytotoxic T-lymphocyte (CTL) responses which may be more efficacious than antibody in controlling E7-expressing tumour cells, it may be necessary to express E7 sequences **from HBcAg constructs** intracellularly so as to target the MHC class 1 antigenic presentation pathway. Intracellular expression of HBcAg particles in mammalian cells and expression via vaccinia virus had been described in the literature. As an alternative route, introduction of recombinant HBcAg constructs in *Salmonella typhimurium*, a bacteria that colonizes the gut where it becomes intracellular, was suggested. As a further suggestion for improving the immunogenicity of the HPV E7-HBcAg fusion proteins, the use of specific adjuvants (Algammulin and Alhydrogel) was proposed, and it was stated that this approach may have implications for vaccine design for HPV 16 associated cervical cancer (see page 556, left column, last paragraph).

11. In the decision under appeal, the opposition division established that the fusion proteins defined in claim 1 differed from those described in document (1) both structurally and functionally. The structural difference arises from the presence in the claimed fusion proteins of a heat shock protein or a portion thereof as carrier for the HPV antigen, while in the fusion proteins described in the prior art document the HPV antigen is linked to hepatitis B core antigen. The capability of the claimed fusion proteins to elicit a

protective and/or therapeutic cell-mediated cytolytic (CTL) immune response against the HPV antigen, was regarded as the functional feature distinguishing the claimed subject-matter from the prior art.

12. In the view of the opposition division, the technical problem to be solved had to be defined as the provision of a composition that was capable of eliciting a protective and/or therapeutic cell-mediated cytolytic immune response against an HPV antigen, because it was expressly indicated in document (1) that this functional feature was desirable for controlling E7-expressing tumour cells. This has not been disputed on appeal.

13. The appellant has not disputed that this technical problem has been solved by the fusion proteins defined in claim 1 either. Having regard to the examples in the patent, the board has no reason to doubt that the invention as claimed indeed solves the stated problem.

14. The issue in dispute is however whether or not, starting from document (1) and seeking to obtain a composition that induces an HPV-specific CTL response, it was obvious to try to modify the fusion proteins described in document (1) by replacing HBcAg by a heat shock protein or a portion thereof.

15. The appellant contended that document (1) specifically directed the skilled person toward the goal of developing vaccines that enter the MHC I antigen processing pathway in order to induce HPV antigen-specific CTL responses. While this is true, it is also true that document (1) proposes a specific strategy to

achieve this goal, namely the intracellular expression of the HPV E7-HBcAg fusion protein, and further suggests two different methods to put it into practice. Thus, document (1) not only indicates the problem to be solved, but also provides the skilled person with a possible solution to the problem and, by reference to several scientific publications, the required technical information to put into practice the proposed solution.

16. In contrast, there is no indication whatsoever in document (1) that might prompt the skilled person to try to induce a CTL response to an HPV antigen by using a fusion protein comprising the HPV antigen and a carrier protein other than HBcAg. In view of these facts, the finding of the opposition division that a person skilled in the art seeking to induce a CTL response against an HPV antigen had no reason to deviate from the teaching of document (1) is held to be correct.

17. The board is not convinced by the appellant's argument that, in view of the drawbacks of the approaches proposed in document (1), the suggestion in this document that CTL responses could be developed by intracellular expression would have been met with scepticism by the skilled person. First, document (1) itself does not indicate any drawbacks associated with the suggested approaches for eliciting a CTL response. And second, while the appellant cited documents (111), (157) and (158), which are referred to in the relevant passage of document (1), as evidence for the alleged drawbacks, the appellant failed to identify specific drawbacks that might deter the skilled person from following the suggestions made in document (1). The

appellant's sweeping reference to possible infection and pathological consequences is not sufficient to substantiate its allegation.

18. Even if, for the sake of argument, it were considered that the skilled person, being an independent mind, would not have adopted the solution to the problem of inducing a CTL response proposed in document (1), but would have looked for alternative carrier proteins capable of inducing such a response, the board believes that he/she would not have been able to recognize from the disclosure of document (2) that the hsp70 protein used as a carrier in the fusion protein described therein might lead to the stimulation of a cell-mediated **cytolytic** response directed against the attached antigen.

19. The purpose of the experiments described in document (2) was to investigate whether *M. tuberculosis* heat shock protein 70 (hsp70) can be used as an adjuvant-free carrier to stimulate the humoral and **cellular** (ie. cell-mediated) immune response to an accompanying protein (see page 874, right column, first sentence of the second full paragraph). It was shown that, when administered in saline in the absence of adjuvant, a recombinant HIV p24-hsp70 fusion protein elicited both humoral and cellular immune response against p24 in mice (see Figure 3 on page 876). However, there is no clear and unambiguous indication in document (2) that a **cytolytic** immune response was induced by the fusion protein. Moreover, even though it is shown in document (2) that p24 antigen-specific cell proliferation was induced *in vitro* using splenocytes from mice immunized with the p24-hsp70 fusion protein,

there is no experimental support for the assumption that the cellular immune response induced by the hsp70-p24 was a **cytolytic** one.

20. Thus, whereas the statement of Dr Srivastava's declaration that a scientist would have recognized that hsp70 was a "carrier" protein that led to the stimulation of both humoral and **cellular** immune responses is correct, the board holds that it was not immediately apparent to a skilled person seeking to induce a cell-mediated **cytolytic** response to an HPV antigen that a fusion protein in which this antigen was linked to hsp70 would have solved his/her problem. Consequently, there was no reason for the person skilled in the art at the priority date to consider the approach disclosed in document (2). The fact that this document shows that hsp70 fusion proteins do not require an adjuvant for eliciting an immune response is of no bearing, because this additional advantage does not represent a solution to the technical problem addressed by the skilled person starting from document (1).

21. Thus, the arguments put forward by the appellant with respect to documents (1) and (2) fail to convince the board that the subject-matter of claim 1 does not involve an inventive step.

Document (16) as the closest prior art combined with document (2)

22. In the decision under appeal (see point 2.2.2), an objection of lack of inventive step raised by the opponent (the present appellant) relying on documents

(16) and (3) was overruled by the opposition division. In its statement of grounds of appeal, the objection based on document (16) as the closest prior art was further pursued, but the appellant relied on a combination with document (2) instead of document (3).

23. The appellant stated that document (16) represented the closest prior art because it described a vaccine that induced an HPV-specific CTL response when administered to a subject without the use of an adjuvant. This statement is, in the board's view, a misrepresentation of the teachings of document (16).

24. The invention disclosed in document (16) relates to compositions for the prevention and treatment of primary and metastatic cancers and/or infectious diseases (see page 1, lines 9 to 11). It is stated on page 2, lines 13 *et seq.* that a CTL response is crucial for protection against cancers, infectious viruses and bacteria and that, therefore, there is a need for methods which can lead to CD8+ CTL response by vaccination with non-live materials such as proteins in a specific manner. The solution proposed in document (16) is the provision of immunogenic complexes of heat shock proteins non-covalently bound to exogenous antigenic molecules. In Example 8, a non-covalent Hsp70-ovoalbumin complex is shown to induce a cytolytic response *in vitro*. It is noted that, even though papilloma virus antigens are mentioned among numerous tumour-specific translatable antigens or viral antigens suggested in document (16) as possible exogenous antigenic molecules in the immunogenic complexes (see page 12, lines 20 to 32 of document (16)), a complex containing a heat shock

protein and a protein antigen of the **human** papilloma virus is not specifically disclosed in this document.

25. The subject-matter of claim 1 at issue differs from the complexes described in document (16) in that the protein antigen and the heat shock protein are linked covalently to form a **fusion protein**, whereas the linkage between the two elements in the prior art document is a **non-covalent** linkage.

26. In its statement of grounds of appeal, the appellant argued that, in view of the advantages of fusion proteins compared to non-covalent complexes, the skilled person seeking to improve the compositions of document (16) was motivated to review the state of the art at the priority date for an approach that could be combined with that of document (16). That search would have allegedly led directly to document (2). While acknowledging that there was no indication that the authors of document (2) tested for induction of a CTL response, the appellant alleged that a skilled person would understand that the cellular immune response described in document (2) **could** include a CTL response. As a support for this argument, the appellant referred to documents (151), (22) and (150).

27. The board cannot accept this argument. Document (151) is a copy of an immunology text book published in 1978. Due to the considerable progress in the field of immunology in the nineteen years between the publication of this document and the priority date of the patent, the knowledge which can be gained from this text book can hardly reflect the common general knowledge of a person skilled in the art at the

priority date and the basis on which his/her understanding of the significance of the results provided in document (2) relied. As an example, document (151) does not provide any information on the sequence and mechanism of activation of the different types and subtypes of T cells required for the cellular immune response before the final lysis of a virus or cell occurs.

28. Moreover, the information content of the passage of document (22) cited by the appellant (paragraph bridging pages 456 and 457) does not go beyond the content of document (2). Neither document discloses a link between the observed production of interferon-gamma and cytolytic activity. This link may have been provided in document (150) (see page 13150, right column, second full paragraph, lines 1 to 7), but this document was published after the priority date of the patent and, therefore, its content was not available to the notional skilled person.

29. Having considered the arguments put forward by the appellant on appeal, the board is not convinced that, starting from document (16) and in view of the results described in document (2) for a **HIV** antigen-hsp fusion protein, the skilled person would have been motivated to combine specifically an **HPV** antigen and a heat shock protein in a fusion protein, let alone that he/she could clearly predict or at least had a reasonable expectation that immunization with this fusion protein would induce a cytolytic immune response.

30. Thus, the objection of lack of inventive step relying on a combination of documents (16) and (2) must fail.

Document (3) as the closest prior art combined with either document (4) or (16)

31. In the decision under appeal, an objection of lack of inventive step based on documents (16) and (3) was discussed. The opposition division stated that it was not able to see how, starting from document (16) as the closest prior art, the skilled person could have been motivated by the teaching of document (3), which addresses the problem of targeting an HPV antigen into the endosomal and lysosomal compartments, to modify immunogenic complexes formed by non-covalently linking a heat shock protein and an immunogenic protein. Consequently, the opposition division concluded that, having regard to documents (16) and (3), the subject-matter of the claims was not obvious to a person skilled in the art.

32. On appeal, the appellant reversed its line of argument by starting from document (3) as the closest prior art, and combining the teaching of this document with that of document (16). Document (3) describes the fusion of the sorting signal of the lysosomal-associated membrane protein LAMP-1 to the HPV E7 protein to target this protein into the endosomal and lysosomal compartments, in order to enhance MHC class II presentation and vaccine potency. When antigen-presenting cells were transfected with a chimeric DNA construct encoding HPV E7 fused to the LAMP-1 signal peptide, an enhanced proliferative response was obtained (see Figure 4). *In vivo* immunisation experiments in mice demonstrated that a vaccinia virus containing the chimeric HPV-16 E7/LAMP-1 **gene** generated greater E7-specific

lymphoproliferative activity, antibody titers, and cytotoxic T lymphocyte activities than a vaccinia virus containing the wild-type HPV-16 E7 gene. The authors concluded that specific intracellular antigen-targeting strategies can be successfully utilised to enhance the presentation of antigenic epitopes, thereby increasing T-cell stimulation.

33. The appellant argued that the E7/LAMP-1 recombinant vaccine described in document (3) provided "a modest but real stimulation of an HPV E7-specific CTL response". It also contended that, in view of the results in document (3), the skilled person would review the art in search of other carrier proteins, and would find document (16) and/or (4) teaching immunogenic complexes of a heat shock protein non-covalently linked to an immunogenic protein. In view of either document (16) or document (4), it was obvious to a skilled person and also technically straightforward to modify the fusion protein disclosed in document (3) by replacing the LAMP-1 carrier with a heat shock protein in order to provide an HPV vaccine that would be taken up by an antigen-presenting cell and directed toward the MHC I antigen processing system.

34. This line of argument is not convincing. Document (3), on the one hand, and documents (16) and (4), on the other hand, represent different approaches in the development of therapeutic vaccines. Whereas the strategy used in document (3) is aimed at enhancing MHC II presentation to CD4+ T helper lymphocytes by specifically targeting the antigen to the endosomal and lysosomal compartments (see Abstract), in document (16) the stated goal is to induce a CD8+ cytotoxic (CTL)

response (see page 2, lines 23 to 25). The appellant has failed to explain why a person skilled in the art was motivated to combine teachings aimed at different purposes, and how he/she would have arrived at the claimed subject-matter by combining a recombinant vaccinia virus containing a **DNA construct** as described in document (3), which upon expression and subsequent processing in the cell results in the production of the HPV E7 protein as such, with immunogenic protein complexes as described in documents (16) and (4), in which a heat shock protein is non-covalently linked to an immunogenic protein.

35. In the absence of convincing arguments in this respect, the objection of lack of inventive relying on documents (3) and (16) or (4) must fail.

36. In sum, the arguments put forward by the appellant in support of its objection of lack of inventive step fail to convince the board that, having regard to the documents cited, the claimed subject-matter was obvious to a person skilled in the art.

Article 83 EPC - Sufficiency of disclosure

37. No arguments have been submitted by the appellant against the finding of the opposition division that the application as filed disclosed the invention as claimed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and the board sees no reason to question this finding of its own motion.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani