

**Internal distribution code:**

- (A) [ ] Publication in OJ  
(B) [ ] To Chairmen and Members  
(C) [X] To Chairmen  
(D) [ ] No distribution

**Datasheet for the decision  
of 13 September 2007**

**Case Number:** T 1599/06 - 3.3.04

**Application Number:** 95901912.6

**Publication Number:** 0771322

**IPC:** C07K 14/35

**Language of the proceedings:** EN

**Title of invention:**

Abundant extracellular products and methods for their  
production and use

**Applicant:**

The Regents of the University of California

**Opponent:**

-

**Headword:**

Mycobacterium vaccinating agent/UNIVERSITY OF CALIFORNIA

**Relevant legal provisions:**

EPC. Art. 54(4), 54(5)

**Relevant legal provisions (EPC 1973):**

EPC Art. 54(1)(2), 56, 83, 84, 123(2)

EPC R. 67(1), 68(2)

**Keyword:**

"Amended claims - added matter (no)"  
"Support and clarity of claims (yes)"  
"Sufficiency of disclosure (yes)"  
"Novelty and inventive step (yes)"  
"Reimbursement of appeal fee (no)"

**Decisions cited:**

T 0026/81, T 0409/91, T 0659/93, T 0332/94, T 0091/98,  
T 0219/01, T 0127/02, T 0609/02, T 0889/02, T 0542/03,  
T 1020/03, T 1241/03, T 0297/05

**Catchword:** see points 13.1 to 14; 20.2, 22 to 22.3



Case Number: T 1599/06 - 3.3.04

**DECISION**  
of the Technical Board of Appeal 3.3.04  
of 13 September 2007

**Appellant:** The Regents of the University of California  
300 Lakeside Drive  
22nd Floor  
Oakland  
California 94612-3550 (US)

**Representative:** Gowshall, Jonathan Vallance  
FORRESTER & BOEHMERT  
Pettenkoferstrasse 20-22  
D-80336 München (DE)

**Decision under appeal:** Decision of the Examining Division of the  
European Patent Office posted 24 May 2006  
refusing European application No. 95901912.6  
pursuant to Article 97(1) EPC.

**Composition of the Board:**

**Chairman:** R. Moufang  
**Members:** G. Alt  
R. Gramaglia

## Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division whereby European patent application No. 95 901 912.6 (filed as international application No. PCT/US 94/13145 and published as WO 95/14713) with the title "Abundant extracellular products and methods for their production and use" was refused pursuant to Article 97(1) EPC because it did not comply with the requirements of Articles 54, 56, 83 and 84 EPC.

II. Claim 1 of the set of claims refused by the examining division read:

"A vaccinating agent for use in promoting a protective immune response, in a mammalian host, against an infectious pathogen from the genus Mycobacterium, said vaccinating agent comprising

at least one purified majorly abundant extracellular protein of Mycobacterium tuberculosis, selected from the group consisting of 30 kDa protein, 32A kDa protein and 32B kDa protein, wherein said Mycobacterium 30 kDa protein has an N-terminal amino acid sequence comprising residues 1 to 40 of SEQ. ID No. 15, said Mycobacterium 32A kDa protein has an N-terminal amino acid sequence comprising the residues FSRPG LPVEY LQVPS PSMGR DIKVQ FQSGG ANSP- LYLLD and said Mycobacterium 32B kDa protein has an N-terminal amino acid sequence comprising the residues FSRPG LPVEY LQVPS A-MGR DI".

III. The examining division held that the claims lacked support and that the disclosure of the invention was

insufficient with regard to the 32A kDa and 32B kDa proteins. While the application showed that the 30kDa protein was able to induce a protective immune response, no such data were available in the application for the 32A kDa and 32B kDa proteins. In view of the disclosure in document D1 that the immunological properties of the 30 kDa protein and the 32A kDa protein differed, there was reason to doubt that the 32A kDa and 32B kDa proteins were able to promote a protective immune response. The additional experimental data submitted in respect of the 32A kDa protein were not convincing owing to their statistical irrelevance: in fact, only one out of six animals had acquired immunity.

Claims 8 to 10 and 13 to 16 were considered to lack clarity since the definition of the proteins only by their molecular weight did not allow them to be identified beyond doubt.

The examining division moreover found that the subject-matter of claims 1 to 6 and 8 to 15 lacked novelty in relation to the disclosure in document D5 of the use of a fraction of extracellular proteins of *Mycobacterium tuberculosis* for inducing protective immunity in guinea pigs, since the fraction inherently contained the 30 kDa, 32A kDa and 32B kDa proteins.

The subject-matter of claims 7 and 16 was not considered inventive since it merely corresponded to the transposition of the result obtained in guinea pigs to human beings.

In an obiter dictum, moreover, the decision explained why the "core" of the invention, as the examining division called it, did not involve an inventive step.

- IV. Oral proceedings before the board of appeal took place on 13 September 2007. The appellant requested that the decision under appeal be set aside, that a patent be granted on the basis of claims 1 to 6 as filed at the oral proceedings, and that the appeal fee be reimbursed.
- V. Claim 1 of the sole claim in the request read as follows:

"A vaccinating agent for use in promoting a protective immune response, in a mammalian host, against the infectious pathogen *Mycobacterium tuberculosis*, said vaccinating agent comprising

at least one purified and isolated majorly abundant extracellular protein of *Mycobacterium tuberculosis*, selected from the group consisting of 30 kDa protein and 32A kDa protein, wherein said *Mycobacterium* 30 kDa protein has an N-terminal amino acid sequence comprising residues 1 to 40 of SEQ. ID No. 15 and said *Mycobacterium* 32A kDa protein has an N-terminal amino acid sequence comprising the residues FSRPG LPVEY LQVPS PSMGR DIKVQ FQSGG ANSP- LYLLD."

Dependent claims 2 to 6 related to specific embodiments of the subject-matter of claim 1.

VI. The present decision refers to the following documents:

- D1: *Infection and Immunity*, vol. 59, no. 1, 1991,  
pages 372-382, Nagai, S. et al.
- D2: *Microbiological Reviews*, vol. 56, no. 4, 1992,  
pages 648-661, Wiker, H.G. and Harboe, M.
- D3: *Scand. J. Immunol.*, vol. 36, 1992, pages 823-831,  
Andersen, P. et al.
- D4: *Infection and Immunity*, vol. 59, no. 9, 1991,  
pages 3205-3212, Content, J. et al.
- D5: *Infection and Immunity*, vol. 60, no. 11, 1992,  
pages 4781k-4792, Pal, P.G. and Horwitz, M.A.
- D6: *Infection and Immunity*, vol. 57, no. 10, 1989,  
pages 3123-3130, Borremans et al.
- D7: *Nature Medicine*, vol. 2, no. 8, 1996, pages 893-  
898, Huygen, K. et al.
- D8: *Infection and Immunity*, vol. 68, no. 7, 2000,  
pages 3854-3860, Tanghe, A. et al.
- D9: *Bull. World Health Organisation*, vol. 12, pages  
47-62, 1955, Palmer, C. et al.
- D10: *Acquired immunity in tuberculosis*, Youmans, G.P.,  
1979, pages 225-235. In G.P. Youmans (ed.),  
*Tuberculosis*, The W.B. Saunders Co., Philadelphia

- D11: Am. Rev. Tuberc., vol. 71, 1955, pages 228-248,  
Bloch, H. and Segal, W.
- D12: J. Exp. Med., vol. 97, 1953, pages 207-220, Dubos,  
R.J. et al.
- D13: Tubercle, vol. 37, 1956, pages 11-22, Meyer, S.N.
- D14: J. Clin. Invest., vol. 87, 1991, pages 1054-1059,  
Blander, S.J. and Horwitz, M.A.
- D15: J. Exp. Med., vol. 170, 1989, pages 1271-1283,  
Morrison, R.P. et al.
- D16: J. Immunol., vol. 139, 1987, pages 3118-3125,  
Scott, P. et al.
- D17: J. Exp. Med., vol. 172, 1990, pages 645-648,  
Jardim, A. et al.

Declaration 1 by Dr Horwitz dated 02 March 2006

Declaration 2 by Dr Horwitz dated 09 March 2006

Declaration 3 by Dr Horwitz dated 29 September 2006

Declaration 4 by Dr Horwitz submitted with the letter  
dated 10 September 2007

Annex A to Declaration 4

VII. The appellant's arguments, in so far as they are  
relevant to the present decision, may be summarised as  
follows:

The claims fulfilled the requirements of Articles 123(2) and 84 EPC. In particular, amended claim 4 overcame the examining division's clarity objection since it included the N-terminal sequences of each of the proteins in addition to their molecular weight.

The data filed with regard to the 32A kDa protein were clear evidence of its effectiveness. Moreover, it was known among scientists that even non-statistically significant data could provide evidence of the likelihood of a hypothesis being correct. Finally, post-published scientific publications confirmed that the 32A kDa protein provided protective immunity.

Document D5 disclosed a fraction containing many different proteins which are not isolated or purified. It does not therefore anticipate the subject-matter of any of the claims.

The skilled person had no reasonable expectation of obtaining the claimed subject-matter:

First, document D5 cast doubt on the general suitability of individual extracellular proteins from the fraction as immunising agents.

Second, as could be seen from the evidence submitted, no predictions could be made as to the ability of *Mycobacterium tuberculosis* proteins to promote a protective immune response.

The requirement under Article 84 EPC that the claims must be supported by the description was a purely



formal requirement. This position was supported by the Travaux préparatoires for the EPC and confirmed by the preparatory documents for EPC 2000. Both groups of documents must be taken as indicating the intention of the lawmaker more cogently than the non-binding Guidelines for Examination. The examining division therefore committed a procedural violation in the decision under appeal when it cited the Guidelines in dismissing an argument supported by a reference to these documents.

## **Reasons for the Decision**

### *Article 123(2) EPC*

1. The subject-matter of claim 1 goes back to claim 8 as originally filed relating to a vaccinating agent comprising the 32A kDa protein of *Mycobacterium tuberculosis* and claim 9 relating to a vaccinating agent comprising the 30 kDa protein of *Mycobacterium tuberculosis*. The amendment restricting the use of the vaccinating agent for promoting a protective immune response to *Mycobacterium tuberculosis* is supported by the examples in the application as originally filed, which deal exclusively with *Mycobacterium tuberculosis* as the infectious pathogen. The feature whereby the constituents of the vaccinating agent according to claim 1 are "isolated and purified" is supported by pages 32, 33 and 35 of the application document as originally filed, which disclose the isolation and purification of the 32A kDa and 30 kDa proteins respectively. The mixtures according to claim 4 are based on (in the order given in the claim) page 73,

combination IV; page 73, combination IX; page 73, combination VI; claim 44 as originally filed; claim 46 as originally filed; claim 28 as originally filed; claim 29 as originally filed; page 73, combination V; and page 73, combination VII.

The requirements of Article 123(2) EPC are fulfilled.

*Article 84 EPC*

*Clarity*

2. The examining division reasoned in the decision under appeal that some of the claims lacked clarity because the proteins to which they referred were defined solely by their molecular weight. All the proteins referred to in the present set of claims, particularly in claim 4, are defined not only by their molecular weight, but also by their N-terminal protein sequences and their source, i.e. *Mycobacterium tuberculosis*. In the board's view, the combination of these characteristics allows the proteins concerned to be identified beyond any doubt. Therefore, there is no lack of clarity in the definition of the proteins.
  
3. In assessing the clarity of the claims, moreover, the board has considered whether or not the skilled person would have had doubts as to the meaning of the apparently somewhat contradictory terms in claim 1: "comprising" and "**at least one purified and isolated** majorly abundant extracellular protein of *Mycobacterium tuberculosis* selected from the group consisting of 30 kDa protein and 32A kD protein". In the decision under appeal the examining division interpreted the

term "comprising" broadly and held that the claimed subject-matter lacked novelty in relation to a protein fraction which, in their view, contained inter alia the 30 kDa and 32A kDa proteins.

- 3.1 The meaning of terms in a patent claim and the resulting meaning of the whole claim have to be determined from the point of view of the skilled person, who reads the claim in the context of the application and against the background of his/her common general knowledge.
  
- 3.2 In the general part of the application it is first set out that the only widely available vaccine against *Mycobacterium tuberculosis* is a life-attenuated vaccine. This is followed by a description of the drawbacks involved with the use of such life-attenuated vaccines (pages 8 to 12). The examples in the application disclose the isolation and purification of fourteen different extracellular proteins of *Mycobacterium tuberculosis* (Example 2, A to N) and also a number of assays relating to the determination of the immunological capacity of the 30 kDa and 71 kDa proteins alone or of different mixtures of some of the purified and isolated proteins. Dependent claim 4 relates to vaccinating agents which are mixtures of the 30 kDa protein with other purified and isolated proteins. According to dependent claim 5 the vaccinating agent may contain an adjuvant. In the board's view, the skilled person would derive from the application as a whole the information that the specific characteristic of the vaccinating agents according to the invention is their generation from isolated and purified *Mycobacterium tuberculosis*

proteins. Therefore, he/she would have considered that the definition in claim 1 covers vaccinating agents that, firstly, are constituted from isolated and purified proteins as mentioned in the claims and, secondly, contain those proteins as their main constituents. This view is supported by the description, page 18, lines 16 to 21: "Individual proteins or groups of proteins are then utilized in animal-based challenge experiments to identify those which induce protective immunity making them suitable for use as vaccines in accordance with the teachings of the present invention." Thus, the skilled person would for example not consider an agent used for the purpose indicated in claim 1, but containing only a minor amount of the 30 kDa or 32A kDa protein, as falling under the terms of claim 1. It follows that the skilled person would not have any doubts about the meaning of claim 1. Consequently, there is no lack of clarity.

*Support of the claims by the description*

4. In the decision under appeal the examining division raised a combined objection of lack of sufficiency of disclosure and lack of support. Hence, the reasons for refusal under Article 83 EPC were the same as under Article 84 EPC, namely that, on the available evidence, it was not plausible to claim that the 32A kDa protein was able to promote protective immunity. The appellant considers that it is inappropriate to request substantive evidence under Article 84 EPC because the support requirement is to be regarded as a formal requirement.

4.1 The boards of appeal have taken different views on this issue. Some have held that the support requirement is fulfilled if the claims cover only subject-matter which is formally derivable from the information content of the document (see for example T 26/81, OJ EPO 1982, 211; T 409/91, OJ EPO 1994, 653; T 1020/03, OJ EPO 2007, 204); others require that the claims reflect the actual contribution of an application by enabling the skilled person to carry out their teaching throughout the field to which they apply (T 659/93 of 7 September 1994; T 332/94 of 18 February 1998; T 127/02 of 16 September 2002). Sometimes, the boards consider both aspects (T 297/05 of 2 February 2005, points 8 and 10).

4.2 In the present case the description discloses that all the isolated proteins, including the 30 kDa and 32A kDa proteins, are to be used as vaccinating agents for promoting a protective immune response. Moreover, the application reveals as technical information that, in technical terms, the compounds qualify as vaccinating agents (see points 6 to 9 below). Hence, the claims are supported by the description, both formally and substantively.

5. The board sees no reason for other objections under Article 84 EPC. The requirements of Article 84 EPC are fulfilled.

*Article 83 EPC*

6. The requirement of sufficiency of disclosure in Article 83 EPC has been interpreted by the boards of appeal as meaning that the description of the invention

must enable the skilled person to carry out the invention over the whole claimed scope.

Moreover, if a therapeutic application is to be accepted as sufficiently disclosed, the application or the patent, respectively, and/or the common general knowledge has to provide some information rendering it technically plausible for the skilled person that the claimed compounds can be applied for the claimed therapeutic use (T 219/01 of 15 December 2004; T 609/02 of 27 October 2004).

7. The application discloses that guinea pigs immunised with the 30 kDa protein are protected against challenge with *Mycobacterium tuberculosis*. No such data are reported for the 32A kDa protein.

7.1 In the decision under appeal the examining division considered that no conclusion could be drawn from data in the application demonstrating an immunoprotective effect for the 30 kDa protein or the 32A kDa protein. It supported its view by referring to evidence in document D1 describing differing immunological properties of the 30 kDa and the 32A kDa proteins in a skin test for assaying the induction of delayed-type hypersensitivity.

For the skin test, guinea pigs were sensitised by intramuscular injection of dried cells of *Mycobacterium tuberculosis*. The induction of delayed-type hypersensitivity was assayed by skin-testing the sensitised guinea pigs, inter alia with isolated MPT59 and MPT44. (MPT59 and MPT44 are alternative designations for the 30 kDa and the 32A kDa proteins.)

- The results in Table 3 of document D1 indicate that the 30 kDa protein provokes a strong reaction, while the 32A kDa protein does not induce any skin reaction.
- 7.2 However, the authors of document D1 see a possible reason for this difference in the fact that the 32A kDa protein is "more efficiently released from the bacilli, and the dose of this antigen may therefore be markedly reduced by use of killed cells for sensitization"(page 381, left-hand column). Thus, the failure to induce a reaction is not necessarily ascribable to the immunological capabilities of the protein, but to the low quantities present in the killed bacteria used for sensitisation. Hence, in the board's view, the results in document D1 pointed to by the examining division are not conclusive evidence of a difference in the immunological reactivities of the two proteins. Therefore, the extrapolability of data in the application concerning the immunoprotective effect of the 30 kDa protein to the 32A kDa protein cannot be called into doubt by the disclosure in document D1.
8. The board sees no other evidence on file which would justify calling the immunoprotective properties of the 32A kDa protein into question. In fact, the available evidence points to the contrary.
- 8.1 It is known that, on the amino acid level and with regard to the mature protein, the sequence homology between the 30 kDa and the 32 kDa protein is as high as approximately 80% (document D4, page 3209, right-hand column column, first paragraph). In the board's view, the extensive sequence homology between the 30 kDa and the 32A kDa protein suggests to the skilled person that

epitopes relevant to the induction of T-cell immunity may be shared by the two proteins. Seeing the data for the 30 kDa protein in the application, the skilled person would therefore consider it technically plausible to use the 32A kDa protein, too, to promote protective immunity. Hence, the data in the application, in combination with the common general knowledge, provide an indication of the immunoprotective properties of the 32A kDa protein. In addition, there is technical evidence on file corroborating the board's conclusion. Documents D7 and D8, both filed during the appeal proceedings, confirm that the 32A kDa protein induces a protective immune response in animal models of Mycobacterium infection.

8.2 In view of the above conclusion it is not necessary for the board to consider in detail the examining division's dismissal of the data submitted with Declaration 2, on the grounds of statistical irrelevance.

9. The requirements of Article 83 EPC are fulfilled.

*Article 54 EPC*

Document D5

10. In the decision under appeal it was held that claim 1 of the request before the examining division lacked novelty in relation to the disclosure in document D5 of a partially purified fraction of extracellular proteins of Mycobacterium tuberculosis and its use for promoting protective immunity in guinea pigs. The examining



division held that the said fraction inherently comprised the 30 kDa and the 32A kDa proteins.

11. The board has considered whether there is indeed sufficient evidence to justify that conclusion.
- 11.1 In document D5 the 30 kDa and 32A kDa proteins (or synonyms thereof) are not mentioned, let alone their N-terminal sequences.
- 11.2 Figure 2 in document D5 shows an SDS-PAGE, i.e. an analysis of the proteins present in the fraction of extracellular proteins of *Mycobacterium tuberculosis* obtained by the method set out on page 4782, right-hand column, of that document. The figure has two parts. Figure 2A is a photograph of the Coomassie brilliant blue-stained gel, while Figure 2B is the silver-stained version of the same gel. Molecular mass markers of 66, 45, 36 and 29 kilodaltons are shown on both parts of the figure. Only a single band appears in Figure 2A at a molecular mass of approximately 66 kDa. This protein is identified by the authors of document D5 as a polypeptide with "an apparent molecular mass of approximately 68 kDa" (see page 4784, right-hand column, last full paragraph) and will be referred to by that molecular weight hereinafter. Several bands appear after silver staining, which is a highly sensitive visualisation method (Figure 2B). In accordance with the result in Figure 2A, the most prominent band is situated at approximately 68 kDa. Further bands appear between the 66 kDa and 36 kDa markers, in addition to a doublet of bands at a molecular mass of and shortly below 29 kDa.

The board thus concludes that neither the 30 kDa nor the 32A kDa protein is derivable from Figure 2, which is the most relevant one in the present context.

11.3 The board moreover notes that according to document D5 the last step in the purification process of the fraction is a filtration step with a filter having a molecular weight cut off at 30 kDa, the retentate being used for the subsequent experiments. It is not impossible that, under the influence of the purification conditions, proteins acquire a three-dimensional structure permitting them to pass through the pores of the filter, although they should theoretically be retained. The more the cut-off weight and the molecular weight of a protein resemble each other, as in the present case, the more probable it becomes that this will occur. Moreover, it is unlikely that all the pores will have exactly the same size. In the board's view, therefore, the skilled person recognising these potential irregularities could not be sure whether or not relatively small proteins such as the 30 kDa or the 32A kDa protein had been discarded with the filtrate. And even if proteins of low molecular weight were retained, they would probably be present in trace amounts only. In fact, this expectation appears to be confirmed by the appearance of bands with a molecular weight below 30 kDa in Figure 2B only, which shows the SDS gel stained by the highly sensitive silver-staining method.

11.4 All in all, the board considers that on the basis of the available evidence it cannot be said with certainty whether any of the 30 kDa or 32 kDa protein is present in the fraction of the extracellular proteins of

Mycobacterium tuberculosis disclosed in document D5. However, the subject-matter of a claim is considered as lacking novelty in relation to a prior art disclosure only if that subject-matter is clearly and unambiguously derivable from that document, i.e. with certainty. Therefore, under the present circumstances, the subject-matter of claim 1 cannot, in the board's judgment, be regarded as anticipated by the teaching in document D5.

- 11.5 However, even assuming that the 30 kDa and/or the 32 kDa protein was/were present in the fraction, its/their quantity would have been low, as evidenced by their invisibility in each of the two stained protein gels. However, in view of the interpretation of claim 1 adopted by the board (see point 3.2 above), the relevant proteins in the vaccinating agent have to be present as the principal constituents, i.e. not just in trace amounts. For that reason also, therefore, the fraction disclosed in document D5 would not be regarded as novelty-destroying for the subject-matter of claim 1.

Documents D1 to D4 and D6

12. The board has additionally considered whether the disclosures in documents D1 to D4 and D6 anticipate the subject-matter of the claims. Documents D1 and D2 disclose strong reactivity on the part of the 30 kDa protein in a delayed-type hypersensitivity reaction. Document D3 discloses that MPT59 (corresponding to the 30 kDa protein) initiates gamma interferon production. Document D4 suggests that the 32A kDa protein is useful in serodiagnosis (see the paragraph bridging pages 3211 and 3212). Document D6 discloses that the isolated

32 kDa protein induces immunoproliferation and gamma interferon production in peripheral blood leukocytes (page 3123, right-hand column).

13. Claim 1 has the following structure: "A vaccinating agent for use in promoting a protective immune response, in a mammalian host, against the infectious pathogen *Mycobacterium*, ..."

13.1 Under the currently valid version of the EPC (EPC 1973) this claim is regarded as a product claim to a first medical use under Article 54(5) EPC, although the therapeutic use is indicated in a specific manner.

A revised version of the EPC will enter into force on 13 December 2007 (EPC 2000). In EPC 2000 the former Article 54(5) has been renumbered to become Article 54(4) and a new Article 54(5) has been introduced to provide protection for second medical uses. Articles 54(4) and (5) read: "Paragraphs 2 and 3 shall not exclude the patentability of any substance or composition, comprised in the state of the art, for use in a method referred to in Article 53(c), provided that its use for any such method is not comprised in the state of the art" and "Paragraphs 2 and 3 shall also not exclude the patentability of any substance or composition referred to in paragraph 4 for any specific use in a method referred to in Article 53(c), provided that such use is not comprised in the state of the art". Hence, claims to a second medical use can be drafted as product claims relating to a specific second or further medical use.

Hence, under the legal situation as from 13 December 2007 claim 1 will be regarded as a claim relating to a second medical use under Article 54(5) EPC 2000 since it defines the use in a specific manner.

13.2 Under the transitional provisions for EPC 2000, Article 54(5) EPC will apply to pending applications in so far as a decision on grant has not been taken. Although pursuant to Article 111(1) EPC the boards of appeal may exercise any power within the competence of the department responsible for the decision under appeal, the boards in practice do not take decisions to grant patents themselves, but remit the case for that purpose to the department of first instance. This is because several further requirements of a formal nature, such as the provision of a translation of the claims, still have to be fulfilled. Since the present board follows this practice, it will de facto not be possible for the patent on the present application to be granted before 13 December 2007. The board has therefore considered it necessary to take the new situation under EPC 2000 into account already when examining the claims at issue. Claim 1 is thus interpreted as a product claim for a second medical use in accordance with Article 54(5) EPC 2000.

14. Consequently, the question in relation to documents D1 to D4 and D6 is whether the properties described therein for the 30 kDa and the 32A kDa proteins, such as their reactivity in a delayed-type hypersensitivity reaction, usefulness in serodiagnosis, induction of immunoproliferation and gamma-interferon production in peripheral blood leukocytes, represent the disclosure

of the medical use in claim 1, namely "promoting a protective immune response".

14.1 There is no doubt that the use of the 32A kDa protein in serodiagnosis is different from its use for immunisation.

14.2 Dr Horwitz, the inventor, has repeatedly stated in his declarations that a cell-mediated immune response is a necessary prerequisite for a substance to be able to promote protective immunity, but does not equate to the said immunity. He points to several examples where hosts responded with a strong cell-mediated immune response to certain protein antigens, but where these antigens were nevertheless not immunoprotective (Declaration 2, paragraph 5.) Thus, in the absence of evidence to the contrary, the board concludes that none of documents D1 to D4 or D6 provides a clear and unambiguous disclosure of the feature "promoting a protective immune response".

15. Hence the subject-matter of claim 1 and its dependent claims is novel in relation to the disclosure in document D5 and in documents D1 to D4 and D6, as assessed in accordance with EPC 2000.

*Article 56 EPC*

16. The present application relates to vaccines against *Mycobacterium tuberculosis*. According to the established case law of the boards of appeal the main criterion for a piece of prior art to qualify as the closest prior art is that it should serve the same purpose as the invention. Therefore, in agreement with

the appellant and the examining division, the board considers document D5 as the closest prior art. It discloses the immunisation of guinea pigs with a fraction containing extracellular proteins of *Mycobacterium tuberculosis* and the subsequent challenge of these animals with aerosolised virulent *Mycobacterium tuberculosis*. It was found that immunised guinea pigs are protected from severe clinical illness, or in other words that immunisation with the fraction induced protective immunity.

17. The board considers that, provided the immunoprotective function is retained, a more purified vaccine is preferable to a less purified one, primarily because unwanted immune reactions may be avoided. Therefore, the problem to be solved may be formulated as the provision of an improved vaccine against *Mycobacterium tuberculosis*.

17.1 The solution to this problem according to the invention covered by claim 1 consists in vaccinating agents comprising "at least one purified and isolated majorly abundant extracellular protein of *Mycobacterium tuberculosis*, selected from the group consisting of 30 kDa protein and 32A kDa protein".

17.2 In view of points 6 to 9 above the board is convinced that the claimed agents solve this problem.

18. The appellant submitted that the claimed subject-matter was not obvious because the skilled person would not even have tried to prepare a subunit vaccine from extracellular proteins of *Mycobacterium tuberculosis* in view of doubts expressed in document D5 on the

suitability of such vaccines. The appellant pointed to the following passage on page 4790 of document D5: "In our study, we deliberately isolated M. tuberculosis proteins from the logarithmic phase of growth to minimize contamination with lytic cell products. Thus, the immunoprotective molecules in our EP vaccine **may be secretory proteins, although it is possible that structural or cytoplasmic proteins released by multiplying bacteria are playing a role in immunoprotection**". (emphasis added by the board).

- 18.1 However, in the board's view, this statement should rather be understood to mean that **in addition to** extracellular proteins other proteins may also induce protective immunity and therefore would not dissuade the skilled person from trying individual extracellular proteins as vaccinating agents. This view is moreover supported by the statement at the end of the abstract: "This study demonstrates that actively growing M. tuberculosis cells release immunoprotective molecules extracellularly, that a subunit vaccine against tuberculosis is feasible, and that extracellular molecules of M. tuberculosis are potential candidates for a subunit vaccine". Hence, the board considers that the skilled person would not have ruled out that individual Mycobacterium tuberculosis proteins in general may be potential vaccinating agents.
19. The next question is whether there is information in the prior art indicating to the skilled person that the 30 kDa and 32A kDa proteins referred to in claim 1 induce immunoprotection.



- 19.1 As already stated above, document D5 does not disclose anything relating specifically to the 30 kDa and the 32A kDa proteins. In the board's view, the use of a filter with a cut-off at a molecular weight of 30 kDa in the purification process according to document D5 would motivate the skilled person to concentrate on proteins of higher molecular weight. Moreover, if the skilled person concentrated on a specific protein, he/she would, in view of document D5, focus his/her attention on a protein with a molecular mass of 68 kDa because this is quantitatively the major species among the proteins in the fraction (page 4784, second column, last full paragraph). Hence, document D5 alone would not lead the skilled person to the claimed invention.
20. The next question is whether the claimed subject-matter would be suggested to the skilled person by a combination of the teachings in document D5 and other prior documents, in particular D1 and D3.
- 20.1 The examining division argued that by applying the "sib-selection-approach" known from document D1 or D3 ("fractionate the initial mixture of proteins in mixtures of lower complexity, selecting within said mixtures of lower complexity the mixture(s) having the ability to promote protective immunity, and repeating this process until individual proteins having the ability to promote protective immunity are obtained", point 7.5.c of the decision under appeal) to the protein fraction in document D5, the skilled person would inevitably identify **all** the major extracellular proteins promoting a protective immune response, and thus automatically also the 30 kDa and 32A kDa proteins. As the board understands it, this means that the

skilled person would try and see which proteins of the fraction have an immunoprotective function.

20.2 There have been cases where inventive step was denied by the boards of appeal because the skilled person was in a "try and see" situation. Such a situation was considered to have occurred if the skilled person, in view of the teaching in the prior art, had already clearly envisaged a group of compounds or a compound and then determined by routine tests whether such compound/s had the desired effect (T 91/98 of 29 May 2001, points 7 and 8 of the reasons; T 889/02 of 22 March 2005, point 7 of the reasons; T 542/03 of 14 July 2005, point 14 of the reasons; T 1241/03 of 1 September 2005, point 31 of the reasons). However, in the case in hand the skilled person is, in the board's view, not in a "try and see" situation because nothing in document D5 or the other prior art documents (see points 21 to 21.7 below) points to the 30 kDa or 32A kDa protein as a possible agent for inducing a protective immune response.

21. The examining division further reasoned that the use of the 30 kDa and 32A kDa proteins was obvious in view of their known immunological properties. Document D1 discloses inter alia that the 30 kDa protein has a marked ability to induce delayed-type hypersensitivity (page 376, right-hand column). Document D6 reports that the 32 kDa protein induces specific lymphoproliferation and gamma interferon production in peripheral blood leukocytes from patients with active tuberculosis.

21.1 The appellant argues that, on the basis of the disclosed immunological properties, the skilled person

could not predict whether a protein would be useful as a vaccinating agent and therefore had no reasonable expectation of success when attempting to solve the problem - formulated above - of providing an improved vaccine against *Mycobacterium tuberculosis*.

21.2 In support of his argument the appellant refers to Declaration 1, where the inventor states: "That a cell-mediated immune response does not equate to protective immunity is a well-established undisputed tenet of immunology". Evidence for this statement was filed in the form of documents, further statements in Declarations 1, 3 and 4 and experimental results (see Declaration 4). In the assessment of inventive step, however, when it is necessary to determine the skilled person's knowledge and, therefore, what would have influenced his/her course of action, only evidence published before the priority date can be taken into account. So in the present case, only documents D9 to D16 are relevant.

21.3 As stated by the appellant, it is reported in documents D9 to D13 that animals infected with *Mycobacterium tuberculosis* respond to dead bacilli with a strong cell-mediated immune response. However, immunisation with killed tubercle bacilli fails to induce protective immunity (see also Declaration 1, point 5; Declaration 4, point 9).

21.4 Further examples of specific antigens of intracellular pathogens which stimulate cell-mediated immune responses but do not provide protective immunity are found in, for example, document D15 (immunisation with the 57 kDa protein from *Chlamydia psittaci* exacerbated

the infection), document D16 (both fraction 1 and fraction 9 of Leishmania major stimulated cell-mediated immune responses, but only fraction 9 induces protective immunity) and document D17 (both synthetic T cell epitopes PT6 and PT3 of Leishmania major gp63 protein stimulated cell-mediated immune responses (Figure 1, upper right), but only PT3 induces protective immunity (Figure 3)) (see Declaration 4, point 12, and Annex A).

21.5 Thus, according to the appellant, a person skilled in the art had **no guarantee** of knowing whether any of the extracellular proteins could provide protective immunity. However, it has been established by the case law that subject-matter is obvious not only when results are clearly predictable, i.e. when it is certain that a result will be achieved, but also when there is a reasonable expectation of success (for example T 1241/03 of 1 September 2005). Therefore, this argument cannot succeed.

21.6 Evaluating the "reasonable expectation of success" involves analysing the prior art to determine the degree of confidence it gives the skilled person that an envisaged result will be obtained. If that degree of confidence is too low, the reasonable expectation turns into a mere hope to succeed. A skilled person working on that basis follows a non-obvious course of action.

21.7 For the board the evidence cited above indicates that at the priority date the skilled person could in general not make any reliable rational predictions about the likelihood of obtaining protective immunity with an antigen even if it elicited a cell-mediated

immune response. There is no evidence before the board on which it could be established that *Mycobacterium tuberculosis* was an exception from that general rule. Consequently, the skilled person's level of confidence in finding any individual *Mycobacterium tuberculosis* antigen with the ability to elicit a protective immune response was, perhaps with the exception of the 68 kDa protein, too low for him/her to perceive a reasonable expectation of success. Hence, the board concludes that if the skilled person, in the light of the prior art, had embarked on the project of providing a subunit vaccine against *Mycobacterium tuberculosis*, this would have been done in the hope of succeeding and not because there was any reason to expect a favourable outcome.

21.8 In summary, the skilled person would not have used the subject-matter of claim 1 with a reasonable expectation of success. Therefore, it is not obvious. The same applies to the subject-matter of dependent claims 2 to 6. Consequently, the requirement of Article 56 EPC is fulfilled.

*Rule 67 EPC*

22. The appellant argues that a procedural violation justifying the reimbursement of the appeal fee has occurred since the examining division interpreted the support requirement in Article 84 EPC in accordance with the Guidelines for Examination, and not in line with the interpretation emerging from the *Travaux préparatoires* and confirmed by the preparatory documents for EPC 2000, both of which must be

considered as indicating the intention of the legislator more cogently than the Guidelines.

- 22.1 As stated above, there are conflicting views in the case law on the criteria for assessing support under Article 84 EPC. Following one of these views - which has even entered the Guidelines - cannot be considered as a procedural violation.
- 22.2 However, it might be questioned whether, in order to comply with the requirement laid down in Rule 68(2) EPC that decisions must be reasoned, the examining division should have provided the appellant with more than a mere reference to the Guidelines. After all, he had put forward detailed reasons substantiated by a reference to a decision of the boards of appeal, which in turn refers to the Travaux préparatoires and the preparatory documents for EPC 2000.
- 22.3 There is no need to decide on this point, however, because even if the examining division had committed a procedural violation by giving inadequate grounds for refusal under Article 84 EPC, the board would not have considered a reimbursement of the appeal fee as justified. Rule 67(1) EPC states that the reimbursement of the appeal fee must be equitable. When applied to the present case this means that the fee would only be reimbursed if the procedural violation, i.e. the insufficient grounds, were the principal factor which had triggered the filing of the appeal and payment of the appeal fee. However, it is apparent from the decision under appeal that the refusal was due mainly to objections under Articles 83 and 54 EPC. Therefore, since the appellant would have had to file the appeal

even if the examining division had set out its reasons for the objections under Article 84 EPC in more detail, the board does not consider a reimbursement of the appeal fee equitable.

## **Order**

### **For these reasons it is decided that:**

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance with the order to grant a patent on the basis of claims 1 to 6 filed at the oral proceedings and a description yet to be adapted.
3. The request for reimbursement of the appeal fee is refused.

The Registrar:

The Chairman: