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**D E C I S I O N**  
**of 27 February 2004**

**Case Number:** T 0999/03 - 3.3.8

**Application Number:** 94930490.1

**Publication Number:** 0737085

**IPC:** A61M 36/14

**Language of the proceedings:** EN

**Title of invention:**

Vaccine for *Branhamella catarrhalis*

**Applicant:**

The Research Foundation of State University of New York at  
Buffalo

**Opponent:**

-

**Headword:**

CD protein/State University of New York

**Relevant legal provisions:**

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

**Keyword:**

"New request: clarity (yes)"

"Inventive step (yes)"

**Decisions cited:**

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**Catchword:**

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Case Number: T 0999/03 - 3.3.8

**D E C I S I O N**  
**of the Technical Board of Appeal 3.3.8**  
**of 27 February 2004**

**Appellant:** The Research Foundation of State University of  
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Amherst, NY 14228 - 2561 (US)

**Representative:** Ritter, Stephen David  
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**Decision under appeal:** Decision of the Examining Division of the  
European Patent Office posted 27 February 2003  
refusing European application No. 94930490.1  
pursuant to Article 97(1) EPC.

**Composition of the Board:**

**Chairman:** L. Galligani  
**Members:** M. R. Vega Laso  
C. Rennie-Smith

## Summary of Facts and Submissions

- I. The applicant lodged an appeal against the decision of the examining division dated 27 February 2003 whereby the European patent application No. 94 930 490, published as WO 95/09025 with the title "Vaccine for *Branhamella catarrhalis*", was refused pursuant to Article 97(1) EPC.
- II. The claims 1 to 33 which constituted the basis for the decision of the examining division were directed to an isolated pure antigenic peptide, oligopeptide or protein having one or more epitopes of the CD outer membrane protein of *Branhamella catarrhalis*, as well as to methods and means for their production by recombinant DNA techniques and a vaccine formulation comprising the antigenic CD peptide, oligopeptide or protein. In the view of the examining division, the subject-matter of the claims as then on file did not fulfil the requirements of Articles 84 and 56 EPC. With respect to Article 56 EPC, the examining division held that, having regard to the following document:

- (1) J. Sarwar et al., Infection and Immunity, March 1992, Vol. 60(3), pages 804 to 809,

in combination with common general knowledge related to gene cloning, it was obvious to the skilled person seeking to clone the CD gene from *Branhamella catarrhalis* to use one of several routine methods available in the art at the priority date of the application, for instance the use of the specific anti-CD antibodies described in document (1). The examining division acknowledged that document (1) did

not provide conclusive evidence as to whether the so-called "CD protein" corresponded to one or more protein species; nevertheless, it considered that the finding, that "CD protein" was indeed only one protein, did not go against a technical prejudice and was the result of routine investigation based on the teachings of document (1). In the view of the examining division such experimentation would be a "one way street" situation.

III. The appellant filed a statement of grounds of appeal in which the following new document:

(3) P. S. Hoffman et al., Journal of Bacteriology, February 1992, Vol. 174(3), pages 914 to 920

was introduced into the proceedings. Oral proceedings were requested in the event that the board should consider a dismissal of the appeal.

IV. With the summons to oral proceedings the board issued a communication with its provisional, non-binding opinion on some issues to be discussed, raising in particular objections under Article 84 EPC against some of the claims at issue.

V. In reply thereto, the appellant submitted an amended set of claims as well as a declaration by Dr. Timothy F. Murphy (the sole inventor) dealing with issues raised by the board in connection with inventive step.

VI. Oral proceedings took place on 27 February 2004. In place of the main request then on file, the applicant

filed amended claims 1 to 32 as a new main request.

Claim 1 of the new request read as follows:

"1. A method of producing an isolated antigenic peptide, oligopeptide, or protein having one or more epitopes of CD, wherein CD is an outer membrane protein of *Branhamella catarrhalis* of an apparent molecular mass of from about 55,000 to about 60,000 daltons by SDS PAGE and having an amino acid sequence as depicted in SEQ ID NO. 14, which comprises (1) forming said antigenic peptide, oligopeptide or protein recombinantly or (2) forming said antigenic peptide or oligopeptide by a method of peptide synthesis."

Dependent claims 2 to 6 concerned particular embodiments of the method of claim 1. Independent claim 7 was directed to a method of producing a vaccine formulation, this method comprising the production of an isolated CD peptide, oligopeptide or protein by a method according to any of the preceding claims. Dependent claims 8 to 10 concerned embodiments of the method of claim 7. Claims 11 to 14 were directed to recombinant vectors, claim 15 concerned a composition useful to passively immunize individuals suffering from an infection caused by *B. catarrhalis* and claim 16 an isolated gene or fragments thereof encoding epitopes of the CD outer membrane protein. Independent claim 17 was directed to a vaccine formulation comprising a nucleic acid molecule which encodes either the CD protein or one or more CD peptides or CD oligopeptides. Dependent claims 18 to 20 concerned embodiments of the vaccine of claim 17. Independent claim 21 was directed to an infectious, recombinant microorganism capable of expressing CD protein, CD peptides or CD oligopeptides,

and claims 21 and 22 depending thereon concerned specific microorganisms. Claims 24 and 25 were directed to a method for the detection of *B. catarrhalis*-specific antisera, and claims 26 and 27 concerned oligonucleotides useful in the detection of *B. catarrhalis*. Finally, independent claims 28 and 31 were directed to methods for the detection of *B. catarrhalis* in a clinical specimen, and the respective dependent claims 29 to 30 and 32 concerned specific embodiments thereof.

VII. In addition to the documents already referred to in the previous sections, the following further document is referred to in the present decision:

(2) M. E. Helminen et al., *Infection and Immunity*, May 1993, Vol. 61(5), pages 2003 to 2010.

VIII. The arguments in support of inventive step put forward by the appellant can be summarized as follows:

On the basis of the disclosure content of document (1), it was not known at the priority date of the application that there existed a single protein designated "CD". In view of the double band resolved on SDS PAGE several different possibilities might have been considered by the skilled person, for example, that the two bands represented two gene products originating from two different genes, or that the double band represented two different populations produced from a single gene due to different post-transcriptional processing.

The skilled person had no reasonable expectation that antibodies 7D6 or 5E8 as described in document (1) (or other antibodies produced using the techniques disclosed in the same publication) would be suitable for identifying putative clones that contained a gene encoding CD protein(s), because it was not known whether these antibodies would recognize linear or conformational epitopes, and whether the antibodies would work on an heterologously expressed protein.

The cloning of the CD gene was replete with unexpected difficulties; thus, the skilled person at the priority date could not have achieved the solution disclosed in the application only by means of routine experimentation. It was also uncertain whether the protein could be expressed in an heterologous system. The success in cloning and expressing a gene encoding a 82 kD outer membrane protein from *Branhamella catarrhalis* reported in document (2) could not be extrapolated to the CD protein, because the use of pBR322 as an expression vector for the CD protein would have led to toxicity problems.

Since the CD protein(s) run as a doublet, the skilled person would have thought that protein excised from the SDS PAGE gel would contain too much cross-contamination between the protein bands for N-terminal sequencing to be successful. Furthermore, the fact that blocked N-termini had been observed in many bacterial outer membrane proteins would have deterred the skilled person from attempting to sequence the N-terminus of the CD protein. Finally, the information eventually obtained from the actual N-terminal amino acid sequence of the CD protein would only have allowed the synthesis

of highly degenerated oligonucleotides, which would not have been considered to be suitable for use as probes.

- IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed during the oral proceedings (claims 1 to 32).

### **Reasons for the Decision**

1. The requirements of Article 123(2) EPC are satisfied by the appellant's request filed during the oral proceedings, support for the claim wording being found throughout the application as filed (see in particular pages 4 to 6 thereof). Furthermore, the deficiencies with respect to clarity pointed out by the examining division in its decision as well as those raised by the board in its communication have been remedied in the new claims 1 to 32. In the board's judgement the claims as now on file meet the requirements of Article 84 EPC because they are clearly worded and supported by the description.
  
2. The issue of novelty (Article 54 EPC) was not discussed by the examining division in its decision; therefore, it is assumed that none of the prior art on file was considered to anticipate the claimed subject-matter. The board sees no reason to question this finding with respect to the new request of the appellant, in view of any of the documents on file.



3. Accordingly, the sole issue that remains to be assessed is whether the subject-matter of claims 1 to 32 at issue involves an inventive step in the sense of Article 56 EPC, ie whether, having regard to the prior art on file, the claimed subject-matter was not obvious to a person skilled in the art.
  
4. The closest prior art is represented by document (1) which concerns the characterization of antigenic determinants of the CD protein of *B. catarrhalis* with the aim of understanding the role of this protein in pathogenesis and its potential role as a vaccine antigen. Two monoclonal antibodies that recognize epitopes of the CD protein as well as a method to obtain such antibodies are disclosed. Further, it is described how, when the outer membrane proteins of *B. catarrhalis* were solubilized at room temperature, the CD protein appeared on SDS PAGE gels as a broad band of approximately 55 kDa, whereas a band of approximately 60 kDa was observed when the proteins were solubilized at 100°C for 5 min. A shift to a doublet of approximately 60 kDa was observed when the samples were heated at 100°C for 60 min. However, both bands of the doublet contained epitopes recognized by the disclosed monoclonal antibodies. The authors concluded that this observation was consistent with two hypotheses. First, CD was a single protein with two different stable conformations or, second, CD actually represented two proteins encoded by different genes but sharing epitopes.
  
5. In the light of this document and with the aim of producing a vaccine, the technical problem to be solved can be defined as being the provision of a method for

producing an antigenic preparation based on the CD protein(s). Since the clinical relevance of *B. catarrhalis* and the potential role of the CD protein(s) of this organism as a vaccine antigen were already mentioned in document (1) (see page 808, right column, last paragraph of the discussion), the formulation of this technical problem did not require an inventive step.

6. As a solution to the problem stated above, claims 1 to 32 at issue propose methods and means for producing by recombinant DNA techniques or peptide synthesis an isolated antigenic peptide, oligopeptide or protein having one or more epitopes of a CD protein showing an amino acid sequence as depicted in SEQ ID NO: 14, and the use thereof for immunization or diagnosis.
  
7. In the board's judgement, at the priority date of the application it was generally obvious to attempt to produce a CD protein or peptide by recombinant DNA methods (see document (1), page 808, right column, last two sentences of the first paragraph). However, at the priority date of the application neither the amino acid sequence of a CD protein nor a gene encoding the same were available. Thus, the question that remains to be answered is whether, on the basis of the information provided in the prior art on file, the skilled person would have had a reasonable expectation of success when attempting to prepare the desired antigenic preparation, ie whether he/she would have been able to predict rationally, on the basis of the knowledge at the priority date, the successful cloning of a gene encoding a CD protein of *B. catarrhalis* and its expression to produce the antigenic preparation.

8. In this context it should be noted that, as the examining division acknowledged in its decision, at the priority date it was not even known whether the CD protein(s) described in document (1) was (or were) a single protein or two different proteins. Proteins designated C and D that differed slightly in apparent molecular weight had been identified by analysis of crude extracts of the outer membrane of *B. catarrhalis* by SDS PAGE (see prior art cited in the present application in the paragraph bridging pages 3 and 4). Document (1) describes that, in samples solubilized at room temperature in the absence of  $\beta$ -mercaptoethanol only one broad band is observed, whereas a double band appears in samples solubilized at 100°C in the presence of  $\beta$ -mercaptoethanol. This represented a first uncertainty encountered by the skilled person trying to clone a gene encoding a CD protein.
9. In the view of the examining division, document (1) would have enabled the person skilled in the art to isolate the CD protein(s) using the specific antibodies disclosed therein, thus allowing the demonstration that CD was indeed only one protein, without the use of any inventive skills. The board disagrees with this view. Document (1) discloses two monoclonal antibodies that recognize the CD protein(s). This document, however, neither suggests isolating the protein(s) using the described monoclonal antibodies nor provides a method to achieve this goal. The board notes that the two monoclonal antibodies disclosed in document (1) appeared to bind to both bands as separated by SDS PAGE. On this account, a separation of the two proteins using the disclosed antibodies - as suggested by the

examining division - does not seem to be feasible relying only on the information provided in document (1).

10. In the board's judgement, the relevant question in the present case is not whether a technical prejudice with respect to the CD protein(s) existed. The fact that the skilled person was confronted with the uncertainty as to whether the double band observed in SDS PAGE corresponded to one or two proteins, the antibodies available at the time not allowing to discriminate between them, constituted an obstacle to be surmounted and already indicates that the "one way street" situation alleged by the examining division was not present.
  
11. Furthermore, even if it were accepted that the skilled person could have experimentally proved that the two bands observed in SDS PAGE corresponded to a single CD protein, the cloning of the CD gene could not be considered to be straightforward, as cloning of genes encoding outer membrane proteins of non-enteric pathogens (as *B. catarrhalis*) had often proved unsuccessful, possibly because of overproduction lethality in *E. coli* (see for example document (3), abstract and page 914, right column, first full paragraph). Thus, on the basis of the evidence on file the board is convinced that the skilled person at the priority date would have not expected the cloning and, especially, the expression of the gene encoding the CD outer membrane protein of *B. catarrhalis* in *E. coli* and thus the elucidation of its structure to be a straightforward task.

12. Contrary to the opinion of the examining division, the board believes that, in order to clone and express the gene encoding the CD protein, the person skilled in the art at the priority date would have expected to be confronted with some difficulties and a substantial amount of experimentation, most probably being forced also to depart from routine cloning protocols. For instance, if the candidate DNA fragments were fused to another gene for expression in *E. coli*, it would have been difficult for the skilled person at the priority date to predict whether the CD fusion protein would be recognised by a certain monoclonal antibody.
  
13. For the above reasons the board comes to the conclusion that the skilled person at the priority date could not have rationally predicted the successful cloning and expression of the CD gene, and therefore he/she could not have had a reasonable expectation of success when attempting to devise a method of producing an antigenic preparation based on the CD protein by recombinant DNA techniques.
  
14. As for the production of an antigenic preparation by peptide synthesis, the prior art neither suggests such an approach nor discloses any sequence information for the CD protein that would allow the synthesis of antigenic peptides or oligopeptides derived from the CD protein. This information only became available after the gene encoding the CD protein had been cloned as described in the application.

15. Therefore, the Board concludes that the subject-matter of claim 1 involves an inventive step. The subject-matter of claims 2 to 32 relies on the successful cloning of the gene encoding the CD protein. Thus, this subject-matter also fulfils 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 filed during the oral proceedings, a description and drawings to be adapted thereto.

The Registrar:

The Chairman:

A. Wolinski

L. Galligani