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D E C I S I O N
of 4 June 2003

Case Number: T 0493/01 - 3.3.8

Application Number: 92901932.1

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Title of invention:
Acellular Vaccine

Patentee:
Celltech Pharmaceuticals Limited

Opponent:
Aventis Pasteur Limited/Aventis Pateur Limitée

Headword:
Acellular vaccine/CELLTECH

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - no"

Decisions cited:
T 0110/92, T 0455/91

Catchword:
-



Case Number: T 0493/01 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 4 June 2003

Appellant: Celltech Pharmaceuticals Limited
(Proprietor of the patent) 208 Bath Road
Slough
Berkshire SL1 3WE (GB)

Representative: Campbell, Patrick
J.A. KEMP & CO.
Gray's Inn
14 South Square
London WC1R 5JJ (GB)

Other party: Aventis Pasteur Limited/Aventis Pasteur Limitée
(Opponent) 1755 Steeles Avenue
Toronto
Ontario M2R 3T4 (CA)

Representative: Bizley, Richard Edward
Hepworth, Lawrence, Bryer & Bizley
Merlin House
Falconry Court
Baker's Lane
Epping
Essex CM16 5DQ (GB)

Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 28 February 2001
revoking European patent No. 0 573 435 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
S. C. Perryman

Summary of Facts and Submissions

- I. European patent No. 0 573 435 with the title "Acellular vaccine" was granted with 16 claims on the basis of the European patent application No. 92 901 932.1.

Claims 1 and 16 read as follows:

"1. A protein which is uncontaminated by components from B.parapertussis, which is capable of binding to antibody which also binds the native P.70 antigen of B.parapertussis and which has (a) the amino acid sequence shown in Figure 1 from amino acid residue Asp 35 to Asn 643, or (b) an amino acid sequence which has a homology of more than 98% with the said amino acid sequence (a)."

"16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a protein as defined in claim 1 or 5."

Claim 5 related to a protein with the amino acid sequence shown in Figure 1 or an amino acid sequence which is more than 98% homologous to said sequence. Dependent claims 2 to 4, 6 to 9 related to DNA sequences encoding the proteins of claims 1 or 5. Claims 10 to 15 respectively related to vectors, transformed host cells and processes for the expression or the production of said proteins.

- II. One opposition was filed. The Opposition Division revoked the patent pursuant to Article 102(1) EPC for lack of inventive step.

- III. The Appellants (Patentees) filed an appeal, paid the appeal fee and submitted a statement of grounds of appeal.
- IV. The Opponents withdrew their opposition thereby remaining party to the proceedings only for formal matters.
- V. The Board sent a communication pursuant to Article 11(2) of the Rules of procedure of the Boards of Appeal, stating its preliminary, non-binding opinion.
- VI. The Appellants sent a further submission in answer to the Board's communication.
- VII. The documents mentioned in the present decision are the following:
- (4): Makoff, A.J. et al., *Biotechnology*, Vol. 8, pages 1030 to 1033, November 1990;
 - (9): Linnemann, C.C. et al., *Am.J.Dis.Child*, Vol. 131, pages 560 to 563, May 1977;
 - (14): Lautrop, H., *The Lancet*, pages 1195 to 1197, 12 June 1971;
 - (16): Munoz, J.J. et al., *Microbiol.Immunol.*, Vol. 33(4), pages 341 to 355, 1989;
 - (18): Declaration of Dr E.L. Hewlett dated 29 November 2000.

VIII. The Appellants' arguments in writing and during oral proceedings may be summarized as follows:

- In accordance with the case law relating to biotechnology, a decision on inventive step was generally made by assessing whether or not a claimed subject-matter was obvious to try with a reasonable expectation of success. In most of the previous cases, it was accepted that it was obvious to try cloning the relevant gene and the key question was whether there was a reasonable expectation of success. The present case was quite different in that the cloning of the B.parapertussis gene encoding P70 was not an obvious target: at the priority date, B.parapertussis was known to be the agent responsible for whooping cough in no more than 3 to 4% of all cases and to cause only mild symptoms (document (14)). In document (18), Dr Hewlett, an expert in the field of acellular pertussis vaccines, explained that there was a lack of general interest in the organism because it appeared not to be a universally widespread infectious agent but an agent prevalent in some specific areas of the world. The situation was, thus, that B.parapertussis was not considered worthy of clinical investigation.

- It also could not be ignored that there were many organisms causative of much more severe diseases than B.parapertussis which obviously had priority when developing research programs for producing vaccines. Thus, besides being medically relatively insignificant, B.parapertussis was also of commercially dubious worth.

- At the priority date, a lot of efforts were directed to producing a safe, acellular vaccine against B.pertussis which caused a severe illness. The skilled person who, in accordance with the case law, was at the same time cautious and conservative would have, thus, refrained from working with any other species. Accordingly, he/she would have failed to attribute any relevance to document (4) when trying to solve the problem of providing an antigen useful in a vaccine against whooping cough.

- Even if the skilled person considered B.parapertussis as worthy of having a vaccine made against it, he/she would not have had any particular reasons to direct his/her attention to P70 as the relevant antigen. Indeed, in document (16) discussing potential protective antigens of B.pertussis (page 352, 2nd full par.), many proteins were cited but the B.pertussis antigen P 69 corresponding to P70 was not mentioned.

In summary, when turning their interest to B.parapertussis, the Appellants had gone against the general trend at the priority date, which concentrated on vaccination against B.pertussis. The skilled person would have ignored information concerning B.parapertussis and if not, he/she would not necessarily have chosen P70 as a protective antigen. For these reasons, inventive step had to be acknowledged.

- IX. The Appellants requested that the decision under appeal be set aside and that the patent be maintained as granted, or auxiliarily, that the patent be maintained

based on claim 16 only.

Reasons for the Decision

1. The patent was opposed under Article 100(a) to (c) EPC for lack of novelty and inventive step, lack of sufficient disclosure and added subject-matter. The Opposition Division found in favour of the Appellants insofar as novelty and sufficiency of disclosure were concerned. They also decided that the content of the granted patent did not extend beyond the content of the application as filed. The Board agrees with these findings. The issue which remains to be decided is that of inventive step in relation to the subject-matter of claims 1 and 16.

2. The closest prior art is document (4). In this document, B.pertussis and B.parapertussis are identified as the causative agents of whooping cough in children; B.bronchiseptica is said to be the corresponding pathogen in piglets. Each of the three bacterial species is described as producing a protein contributing to virulence: P69, P70 and P68 respectively. It is stated that B.pertussis P69 and B.bronchiseptica P68 are both protective antigens. B.parapertussis P70 is described as immunologically related to P69 and P68. On page 1030, right-hand column, the following opinion is expressed: "Clearly, this family of antigens is important in protection against diseases caused by *Bordetella* species." The document describes, in particular, the expression of B.pertussis P69 in *E.coli*. On page 1033, left-hand column, it is mentioned that this antigen "represents an attractive means of producing large amounts of a

potentially important component of a subunit vaccine against this common disease".

3. Starting from the closest prior art, the objective technical problem to be solved may be defined as providing a further protective antigen potentially useful in a vaccine against whooping cough.
4. The solution given is the B.parapertussis P70 antigen, in particular, recombinantly expressed, and a pharmaceutical preparation thereof.
5. In the Board's judgement, the teachings of document (4), in particular that P70 is of the same family as P69 and P68 which are known protective antigens and that P69 would be a worthy component of a vaccine against whooping cough, made it obvious to the skilled person wanting to solve the above mentioned problem to try and determine whether P70 would be equally useful in this respect.
6. The Appellants, while agreeing to the content of document (4), argued that the information it provided on B.parapertussis would be ignored by the skilled person for two reasons: firstly, his/her attitude would prevent him/her from focusing on B.parapertussis because it was B.pertussis which up till then had been most intensively studied, and because its effects were geographically limited; secondly, the general opinion at the time was that B.parapertussis was medically relatively insignificant which implied that developing a vaccine against it was a commercially dubious endeavour.
7. As pointed out by the Appellants, decision T 455/91 (OJ

EPO 1995, 684) defines the skilled person as being cautious and conservative. This, however, does not mean that he/she will refrain from considering information because it does not concern the **main stream** of research in his field of specialisation or because it "only" applies to some parts of the world. The skill and knowledge of the skilled person are not geographically limited; he/she will rather have a global point of view. Thus, if as in the present case, a pathogen constitutes a known threat in some restricted parts of the world, the skilled person will not refrain from taking into consideration prior knowledge about said pathogen nor from using it as a basis for his/her activities. Accordingly, it is concluded that the skilled person at the priority date would have regarded B.parapertussis as a causative agent of whooping cough worthy of interest and would have been aware of the technical information concerning it, including that which is contained in document (4).

8. The Appellants emphasized that B.parapertussis was of little interest from the clinical point of view, citing document (14) as evidence that, in 1971 (some 19 years before the priority date), it was thought responsible for at most 3 to 4% of the clinical cases of whooping cough. The Board notices that, in 1977, document (9) described B.parapertussis as the causative agent of pertussis syndrome in 20% to 30% of the cases in Europe and reflected that its occurrence in the United States was probably more common than generally recognized. On page 560, middle-column, it is stated: "Although the reported cases of B.parapertussis have been mild, two cases of fatal pneumonia have been reported, which raises the question of whether the organism may cause severe disease". Document (16) published within the

year preceding the priority date mentions whole-cell vaccines against B.parapertussis in a study of the effect of pertussigen on the protective effect of said vaccines in mice. This, in the Board's judgment, implies that the medical community did not disregard B.parapertussis as an organism worthy of having a vaccine made against it. In view of these teachings, and although it is admitted that B.parapertussis was considered a less dangerous infective agent than B.pertussis, it cannot be concluded that B.parapertussis was thought by the skilled person to be medically insignificant.

9. The Appellants also argued that at the relevant date B.parapertussis could not be given priority in programmes for developing vaccines. They pointed out that "in real life", the commercial benefits to be expected from selling a pharmaceutical product had to counterbalance the costs of developing this product. The Board would agree that the development of a parapertussis acellular vaccine may have been considered as a commercially dubious venture. Yet, in accordance with the case law, commercial success, even if due to the claimed features of an invention cannot impart inventive step to this invention if it is found not to be inventive on technical grounds (T 110/92 of 12 October 1994). In the same manner, a lack of expectation of commercial success for a given project is immaterial if from a technical point of view, said project is obvious to try and can be completed without any difficulties on the basis of the technical information existing in the prior art.

10. The further argument was presented that even if it was obvious to try and obtain a protective antigen and the

corresponding vaccine against B.parapertussis, there were no reasons to choose P70 as it was only one amongst many known proteins of B.parapertussis. This argument is not found convincing since P70 is identified in document (4) as being part of a family of three antigens, of which the two others (P69 and P68) are protective, which, in fact, means that the skilled person did not have to make any particular selection. In view of this very clear statement in document (4) which was published after document (16) and, thus, represents the latest technical advance in the prior art, the Appellants' reference to document (16) as identifying other antigens than P69 as protective antigens against B.pertussis and the implication they drew therefrom as regards B.parapertussis are not considered relevant.

11. For the reasons given in points 5 and 10, the Board concludes that it was obvious to try and isolate P70 in order to solve the problem defined in point 3.
12. It was never argued that the skilled person would not have had a reasonable expectation of success when cloning and expressing the P70 gene or when formulating the P70 protein as a pharmaceutical composition. The Board understands from reading the patent specification that the task was achieved as a matter of routine work on the basis of common general knowledge, the homologous P69 DNA being already cloned.
13. It is, thus, concluded that the subject-matter of claims 1 and 16 lacks inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

P. Cremona

L. Galligani