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D E C I S I O N
of 19 January 1998

Case Number: T 1046/96 - 3.3.4

Application Number: 87311279.1

Publication Number: 0275689

IPC: C12N 15/31

Language of the proceedings: EN

Title of invention:
Modified pertussis exotoxin

Patentee:
The Board of Trustees of the Leland Stanford Junior University

Opponent:
SmithKline Beecham plc, Corporate Intellectual Property, SB House
Connaught Laboratories Limited
Chiron Corporation

Headword:
Pertussis/LELAND STANFORD

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
"All requests - amendments - added subject-matter (yes)"

Decisions cited:
T 0383/88, T 0187/91, G 0001/93

Catchword:
-

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Case Number: T 1046/96 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 19 January 1998

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 23 October 1996 revoking European patent No. 0 257 689 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: L. Galligani
W. Moser
F. Davison-Brunel
S. C. Perryman

Summary of Facts and Submissions

I. The appeal lies from the decision of the opposition division issued on 23 October 1996 whereby the European patent Nr. 0 275 689, against which opposition had been filed by three parties on the grounds of Article 100(a) to (c) EPC, was revoked pursuant to Article 102(1) EPC on the grounds that the main request as well as the first and second auxiliary requests then on file offended against the requirements of Article 123(2) and (3) EPC and that the third and fourth auxiliary requests did not meet the requirements of Article 123(2) EPC. The opposition division decided inter alia that there was no basis in the application as filed for a claim directed to a holotoxin comprising a mutated S1 subunit and thus Article 123(2) EPC was violated.

Independent claims 1 and 7 of the granted patent were as follows:

"1. A nucleotide sequence comprising genetic information coding for the S1 subunit of pertussis toxin protein isolated from Bordetella pertussis, wherein the sequence has been modified to code for a mutated S1 subunit of pertussis toxin, where said mutated S1 subunit is capable of interaction with pertussis toxin B subunit to form a holotoxin, which holotoxin lacks the toxicity of wild-type pertussis toxin but has protective immunogenicity.

7. A pertussis holotoxin comprising a B subunit of pertussis toxin and a mutated S1 subunit, which holotoxin lacks the toxicity of wild-type pertussis toxin but has protective immunogenicity."

II. With the statement of grounds of appeal filed on 18 February 1997, the appellant (patentee) requested accelerated handling of the appeal and filed its claim requests. These were as considered by the opposition division save for the second auxiliary request which was dropped with corresponding renumbering of the previous third and fourth auxiliary requests (now second and third). The appellants offered also to replace, if necessary, the phrase "pertussis toxin protein of *Bordetella pertussis*", where it occurred, with the phrase "pertussis toxin protein isolated from *Bordetella pertussis*".

Claims 1 and 2 of the **main request** read as follows:

"1. A pertussis holotoxin comprising a B subunit of pertussis toxin and a mutated S1 subunit, which holotoxin lacks the toxicity of wild-type pertussis toxin but has protective immunogenicity.

2. A *Bordetella pertussis* mutant whose pertussis holotoxin lacks the toxicity of wild-type pertussis toxin but has protective immunogenicity, the chromosome of the mutant comprising nucleic acid with a sequence comprising genetic information coding for the S1 subunit of pertussis toxin protein of *Bordetella pertussis*, wherein the sequence has been modified to code for a mutated S1 subunit of pertussis toxin, where said mutated S1 subunit is capable of interaction with pertussis toxin B subunit to form the holotoxin."

Claim 1 of the **auxiliary request 1** was identical to claim 2 of the main request. Claim 2 of the auxiliary request 1 read as follows:

"A pertussis holotoxin as obtainable from a *Bordetella pertussis* mutant according to claim 1."

Claim 1 of the **auxiliary request 2** read as claim 1 of the main request. Claim 2 of the auxiliary request 2 read as follows:

"A pertussis holotoxin comprising a B subunit of pertussis toxin and a mutated S1 subunit, which holotoxin lacks the toxicity of wild-type pertussis toxin but has protective immunogenicity, obtainable from a *Bordetella pertussis* mutant made by a method comprising

in vitro mutagenesis of nucleic acid having a sequence comprising genetic information coding for the S1 subunit of pertussis toxin protein of *Bordetella pertussis*, whereby the sequence is modified to code for a mutated S1 subunit of pertussis toxin, where said mutated S1 subunit is capable of interaction with pertussis toxin B subunit to form the holotoxin, and

allelic exchange to introduce the modified nucleic acid into the chromosome of *Bordetella pertussis* thereby producing said mutant."

The only claim of the **auxiliary request 3** was identical to claim 2 of auxiliary request 2 save for the substitution of "obtainable" by "obtaining".

III. Respondents II and III (opponents 02 and 03) submitted their comments on the statement of grounds of appeal. With letter dated 12 December 1997, respondents II requested the referral of an appropriate question to the Enlarged Board of Appeal in relation to the Article 123(3) EPC issue in the event the board had in mind upholding the appeal in favour of the appellant.

IV. Oral proceedings took place on 19 January 1998. Respondents I (opponent 01) did not attend oral proceedings.

V. The appellant referred to the slight difference in wording between Article 100(c) EPC, which was directly under consideration in opposition, and Article 123(2) EPC. The content of the application as filed had to be taken into account objectively as a person skilled in the art would have understood it. The invention at issue in the present case was of considerable scientific and commercial importance and thus the possible maintenance of the patent in amended form should not be prejudiced merely on the basis of a formalistic approach. In this context, amendments introduced in order to meet a substantive objection should be looked at not word-for-word, but in the light of the true technical information conveyed to the expert by the application as filed. In the present case, expert evidence, including evidence from the opponents (cf the affidavit of Prof. Murphy from respondents III and the declaration of Dr Richard from respondents II, this latter being in agreement with the former), supported the view that the embodiment of the preparation of a pertussis holotoxin comprising a B subunit of pertussis toxin and a mutated S1 subunit, which holotoxin lacked the toxicity of wild-type pertussis toxin but had protective immunogenicity, was indeed disclosed in the application as filed (see in particular the declarations of Drs Schmidt, Cowell and Kaslow). Criticism that the experts were either overqualified or too old to be acquainted with the new techniques was not justified as they unanimously agreed on this point.

Based on the balance of probability, the appellants had amply discharged their onus of proof. In the light of prominent expert evidence, it was not justified from the side of the opposition division to decide against

it by unduly relying on its technical knowledge which was less than that of the experts. Also the argument of the opposition division of an impermissible generalisation was misplaced.

As a matter of fact, as explicitly indicated in the "Summary of the invention", the application as filed described two different embodiments, one of them being the now claimed altered holotoxin with a mutated S1 subunit of which ptx3201 was just a specific example (cf page 3, lines 11 to 14 as well as page 4, lines 48 to 50 of the published application). Considered against the background of the common general knowledge about the oligomeric structure of pertussis toxin and the lack of toxicity of the individual subunits, the original disclosure would have been understood by the skilled person as having the toxic product, ie the holotoxin, as its starting point. The skilled person would have thus understood that what was meant in the disclosure of the said embodiment was the alteration by way of mutation in the S1 subunit of the holotoxin with the purpose of preparing a vaccine capable of inducing immunity against pertussis but lacking the toxic effects of holotoxin (ibidem, page 2, lines 43 to 44), the other subunits being inherently there. In fact, no reference whatsoever was made in the application as filed to the mutation of a subunit in concomitance with the deletion of another subunit. Therefore, although the wording of the claims as such was not explicitly found in the application as filed, the content of the disclosure, as confirmed by the experts, was directed inter alia exactly to the embodiment now claimed. In examining this issue, it was important to objectively assess the content of the original disclosure leaving aside issues related to the sufficiency of the disclosure and/or support by the description (Articles 83 and 84 EPC).

VI. As regards the Article 123(2) EPC issue, respondents II, with reference in particular to decision T 383/88 of 1 December 1992 (cf point 2.2.2 of the reasons), argued that the rigorous standard of "beyond reasonable doubt" had to be applied in examining amendments. If there was no explicit basis for a given amendment, then one should investigate, based on the knowledge and abilities of the skilled person, whether there was possibly an implicit disclosure thereof or whether a specific example justified it. In doing this, one could not rely too much on evidence from over-qualified persons because the common knowledge and skills relevant for interpreting a disclosure was that of the average skilled person, not that of leaders in a given scientific field (ibidem). In the case at issue, this standard was not met because, apart from the lack of an explicit basis, the skilled person could not derive in an implicit manner from the description the technical information in relation to the assembly of a complete holotoxin. The application contemplated all sorts of modifications and a mere reference to "an altered holotoxin" on page 4, line 49 of the published application as filed did not constitute a proper formal basis for a fully-assembled holotoxin, bearing specifically a mutation in the S1 subunit and having protective immunogenicity. Not even in respect of the specific example of the product of the TOX3201 mutant could the skilled person derive from the application as filed the said technical information. Thus, there was no basis under Article 123(2) EPC for a complete holotoxin as claimed.

Respondents III did not support the view of respondents II on the Article 123(2) EPC issue.

VII. The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of **a)** claims 1 to 4 filed on 18 February 1997 as main request or **b)** claims 1 to 4 filed on 18 February 1997 as auxiliary request 1 or **c)** claims 1 and 2 filed on 18 February 1997 as auxiliary request 2 or **d)** claim 1 filed on 18 February 1997 as auxiliary request 3.

The respondents requested that the appeal be dismissed. Respondents II further requested referral of questions to the Enlarged Board of Appeal in the event that the board had in mind upholding the appeal in favour of the appellant.

Reasons for the Decision

1. In all claim requests on file reference is made to a pertussis holotoxin, wherein a mutated S1 subunit interacts with the B subunit of pertussis toxin, which holotoxin lacks the toxicity of wild-type pertussis toxin but has protective immunogenicity. Amendments in this sense had been introduced during the proceedings before grant. At issue is whether a pertussis holotoxin with the stated features was disclosed in the application as filed.

2. The relevant EPC provisions in respect of this issue are those of Article 123(2) EPC, which is concerned with amendments in general, and those of Article 100(c) EPC, which is concerned with amendments as a ground for opposition.

Article 123(2) EPC states: "A European patent application or a European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed".

Article 100(c) EPC states that an opposition may be filed inter alia on the grounds that "the subject-matter of the European patent extends beyond the content of the application as filed,...".

3. There is no substantial difference between the wording of the two EPC articles. Both refer to the content of the application as filed as being decisive for the assessment of the admissibility of an amendment. According to the established case law of the boards of appeal, in order to determine whether an amendment does or does not extend beyond the content of the application as filed, it is necessary to examine whether the amendment results in the introduction in the specification of information which the skilled person cannot derive directly and unambiguously from that originally presented, when account is taken of matter which is implicit to a person skilled in the art in what has been expressly mentioned (cf eg T 383/88 supra, in particular point 2.2.2 of the reasons as well as T 187/91, OJ EPO 1994, 572, in particular point 4, last paragraph of the reasons). As stated in decision G 1/93 (OJ EPO 1994, 541), the idea underlying this EPC provision is that "an applicant shall not be allowed to improve his position by adding subject-matter not disclosed in the application as filed, which would give him an unwarranted advantage and could be damaging to the legal security of third parties relying on the content of the original application" (ibidem, point 9 of the reasons).

4. As observed in decision T 383/88 (supra, loc.cit.), the extent of what can be directly and unambiguously derived by the skilled person from an application as filed by reading it in the light of common general knowledge is often controversial. The parties, in order to make their point, often rely on expert evidence from qualified scientists. This approach should be viewed with some caution because quite frequently said expert evidence is given with the view of demonstrating that for a skilled person the invention is sufficiently disclosed or that a certain extent of generalisation of a specific teaching is permissible. In respect of the latter issues, a less rigorous standard is normally applied to the benefit of the patentee in the sense that objection is raised mainly when there are serious insufficiencies or doubts, substantiated by verifiable facts. However, when dealing with formal matters such as the admissibility of an amendment, although the assessment is made from the point of view of the same skilled person, by necessity a more rigorous standard must be applied, such as eg that of "beyond reasonable doubt" (cf T 383/88 supra), in view of the purpose of the relevant provision of the EPC (see point 3 above). This more rigorous standard must not necessarily be based on a literal reading of the application as filed. However, the information therein should be taken at its face value, leaving aside any possible subjective interpretation and any further element based on later findings. The assessment of the admissibility of an amendment is a matter which must be decided in each particular case on its own merits.

5. In the present case, the content of the application as filed, ie the description, figures and claims may essentially be summarised as follows (reference is made here to the published specification which is identical with the application as filed):

(a) The introductory part reviews the state of the art in the technical area of Bordetella pertussis (hereinafter: B. pertussis) vaccines and points to the need for a new pertussis vaccine capable of inducing immunity against pertussis but lacking the adverse effects of known vaccines (cf in particular page 2, lines 43 to 44).

(b) In the "Summary of the Invention", first paragraph, it is stated: "Mutations have been introduced into the Bordetella pertussis chromosome in the toxin gene which alter the toxicity of the toxin molecules produced by the organism while retaining immunogenicity. Two unmarked mutations, ptx3201 (with an insertion in the S1 subunit) and ptx058 (with the entire S1 subunit being deleted), are particularly important for vaccine purposes.".

(c) In the "Description of Specific Embodiments", it is indicated that, based on the identification and cloning of the genetic locus encoding pertussis toxin, expression of at least one subunit in E.coli can be sought or by in vitro mutagenesis and allelic exchange B. pertussis strains can be created which are deficient in production of toxin while still being capable of stimulating an immunogenic response (cf. page 3, lines 44 to 48). In connection with the latter aspect, reference is made to the operable insertion of an appropriate promoter upstream from a gene encoding a pertussis toxin subunit, or a number of genes encoding the various subunits of a complete pertussis toxin. Mention is made of the specific combination of an insertion of a tac promoter into a gene construction with a chromosomal deletion of a S1 pertussis toxin subunit gene which will result in a strain expressing only the B oligomer subunits

to be used as an active vaccine to generate antibodies or to generate antibodies in vitro for use in a passive vaccine (cf. page 4, lines 10 to 13).

Reference is made to different types of mutations which can be introduced by in vitro mutagenesis into a cloned pertussis toxin operon and which lead to altered toxin biosynthesis phenotypes (page 4, lines 26 to 34). On the same page, lines 46 to 50 it is stated: "The present invention has demonstrated the feasibility of selectively deleting genes from the B. pertussis chromosome and thus selectively deleting phenotypes from B. pertussis. The invention has demonstrated the pertussis toxin genes are not critical to in vitro B. pertussis viability and that strains deficient in the production of pertussis toxin can be routinely grown. Accordingly, mutants which produce only a limited number of the pertussis toxin subunits or an altered holotoxin may be used themselves as vaccines without the adverse affects associated with wild-type pertussis toxin."

The description refers in particular to "artificial" nucleotide sequences that code for a complete mature subunit of pertussis toxin, including any of the S1 - S5 subunits, to sequences including within them several sequences that code for individual subunits, such as eg the sequence encoding an entire B subunit of pertussis toxin, and to sequences that code for at least one but no more than three of the four subunits that make up a wild-type B subunit of pertussis toxin (cf passage bridging pages 4 and 5).

In the context of the preparation of a subunit vaccine, ie a vaccine containing some but not all of the S1-S5 subunits, the specification further examines then the relationship and the physical association of the different subunits (page 5, lines 16 to 47).

A plasmid designated pRTP1 (Return to Pertussis) specifically designed to facilitate the return of cloned and/or altered sequences to replace the corresponding sequence in the B. pertussis chromosome is also described (page 5, line 47 to page 6, line 11).

(d) The examples, with reference to the figures, report the results in respect of various deletion mutations (cf page 8, line 55 to page 9 line 12, figure 1) as well as in respect of the specific mutation ptx3201 resulting in a four amino acid insertion, val-asp-gly-ser, into the S1 sequence (cf page 9, lines 13 to 20, figures 4 and 5). The results in respect of this latter embodiment are reported in particular on page 10, lines 49 to 56 where it is indicated that the B. pertussis ptx mutant TOX3201 produced appropriate sized antigenic material corresponding to subunits S1, S2, and S3. Comparison of the S1 from TOX3201 and S1 from wild type strain BP370 indicates that the S1 from TOX3201 was, as expected, about 400 daltons larger in apparent molecular weight than the S1 from BP370. The process of replacement of ptx3021 on pTOX13-ptx3021 for ptx5171 in the chromosome of BP370 is described on page 15, line 43 to page 16, line 14.

(e) As for the "claims" as filed: independent claim 1 is directed to an artificial nucleotide sequence comprising genetic information isolated from B.

pertussis, said sequence encoding at least a portion but less than all of the pertussis toxin protein; independent claim 9 is directed to an artificial polypeptide consisting essentially of a sequence of amino acids identical to the amino acid sequence of a subunit of pertussis toxin. Independent claim 10 concerns a vaccine containing said polypeptide, while independent claim 11 is directed to a method of making a pertussis toxin subunit. Claims 13 to 17 are in relation to a Return to Pertussis plasmid.

6. The term "holotoxin" occurs four times in the application as filed (cf page 2, line 18; page 4, line 49; page 5, line 33 and page 10, line 37 of the published application). The reference on page 4, line 49 is the only one to imply that holotoxin may be altered, but then not in connection with the specific embodiment of a mutated S1 subunit capable of interacting with the B subunit of pertussis toxin.

The qualification "protective" in respect of immunogenicity is not found in the application as filed which refers either to immunogenicity (cf eg page 3, line 12) or to induction of immunity (cf eg page 2, line 43) or generally to vaccine (cf eg page 3, line 14). However, "protective immunogenicity" is a quite specific concept which implies protection against in vivo challenge by the pathogen, not merely the ability to generate a response in the immune apparatus, eg by production of antibodies which could be protective or not protective. Nowhere in the application as filed explicit reference is made to the specific protection against in vivo challenge by the pathogen.

The feature "capable of interaction with pertussis toxin B subunit to form holoxin" is not found in the application as filed in connection with a mutated S1 subunit.

There is thus **no explicit basis** in the application as filed for a holotoxin such as defined in the claims of the requests on file.

7. It must thus be decided whether for a person skilled in the art a holotoxin with the stated features, ie a fully assembled protective analog of pertussis holotoxin, is **implicitly** described in the original application in the light of what is explicitly mentioned therein.

8. The application as filed deals to a large extent with the making of a subunit vaccine against pertussis, ie a vaccine containing **some but not all** of the subunits of the natural pertussis holotoxin. This is reflected by the description in general (cf point 5, item c above) and confirmed by the initial version of the claims (cf "at least a portion but less than all...", cf. point 5, item e above).

9. However, as pointed out by the appellant, the description refers also to "mutations... which alter the toxicity of the toxin molecules" (cf page 3, lines 11 and 12) as well as to "an altered holotoxin" (cf page 4, line 49) and to the specific embodiment ptx3201 for the creation of the mutated B. pertussis TOX3201 in view of an allelic exchange with BP370-ptx5171. In the appellant's view, this constitutes a sufficient formal support for the purposes of Article 123(2) EPC for the second embodiment which is now claimed (cf Section V, second paragraph).

10. The board is unable to share the appellant's view for the following reasons:

(a) There is no direct and unambiguous relationship between the reference to the alteration of toxicity of the toxin molecules and/or to an "altered" holotoxin and the general proposition of a mutation specifically in the S1 subunit, said mutation being such as to leave intact its capability to interact with the B subunit. In fact, the passages in which the term "alter" or "altered" is used (see point 5, items (b) and (c), second paragraph supra) contain no indication that the mutation should specifically be at the level of the S1 subunit (this being only one of several options) and, in addition, be such as not to impair its ability to interact with the B subunit.

(b) The fact that in the "Summary of the Invention" the sentence in which reference is made to "mutations...which alter the toxicity of the toxin molecules" (cf page 3, lines 11 and 12; see point 5, item (b) above) is immediately followed by a sentence in which mention is made of the specific embodiment of ptx3201, which is an insertion in the S1 subunit (cf page 3, lines 12 to 14), is also not helpful. This is because from this latter sentence the skilled person cannot directly and unambiguously derive the information that the said mutation ptx3201 results in the production of a fully-assembled holotoxin as claimed. Nor can this information be gained from the description. In fact, although Figures 4 and 5 show that this embodiment is carried out by way of an allelic exchange between TOX3201, which contains a cloned DNA fragment with the structural genes for pertussis toxin with an insertion of twelve base pairs in the S1 gene, and BP370-

ptx5171, this being a B. pertussis strain with an insertion of a kanamycin resistance in the toxin operon, **nothing is said** about the technical features of the final product, save for the report that TOX3201 produced appropriate sized antigenic material corresponding to subunits S1, S2 and S3 and that the S1 from TOX3201 was about 400 daltons larger in apparent molecular weight than the S1 from BP370 (see point 5, item (d) supra). Thus, the skilled person cannot derive from the application as filed at its face value the information that the final product comprised the individually expressed subunits correctly assembled in a 1:1:1:2:1 stoichiometry typical of the pertussis holotoxin, said product having protective immunogenicity. The skilled person can at most derive from the application as filed the information that the material resulting from the various operations contains the mutated subunit S1 together with the subunits S2 and S3. However, he or she is unable to draw unambiguous conclusions about the presence of the remaining subunits, about the ability of the mutated S1 subunit to interact with a B subunit, about the way the subunits are assembled in the said material, and about their property to confer **protective** immunogenicity, ie protection against in vivo challenge by the pathogen. The skilled person might **suspect or hope** that the material is a fully-assembled holotoxin usable as a vaccine, but considerable doubts and uncertainties remain in this respect.

The structural features of the specific product not being available explicitly or by way of implication, are also unavailable in respect of the generally claimed holotoxin analogs.

(c) The fact that later evidence confirmed that the specific expressed product of TOX3201 was indeed a protective holotoxin analog as now claimed also does not assist the appellant in respect of the issue of the admissibility of the amendments because only the contents of the application as filed have to be taken into account therefor.

(d) As for the expert evidence, the board notes that some expert declarations (cf the declarations of Drs Schmidt, Cowell and Kaslow) were submitted indeed in the context of the Article 123(2) EPC issue. However, quite understandably, they do not apply the rigorous standard necessary when dealing with the admissibility of amendments (see point 4 supra). For example, Dr. Schmidt expresses in his declaration **the belief** that B. pertussis mutant ptx3201 of the patent specification produces a holotoxin containing all five subunits on the basis of what he considers a reasonable interpretation of the disclosure also in the light of the prior art (cf points 3 to 7) and in the light of the ability of the skilled person to test the protective effect of holotoxins (cf point 11). He also concludes that the methodology disclosed in respect of the specific example enables anyone skilled in the art to create additional and/or different mutations in the S1 subunit gene with a high likelihood of success (cf points 8 to 10). Such a declaration reflects the subjective assessment of a technical situation by a qualified scientist. However, in the board's judgement, while it can possibly be of some relevance in the framework of a discussion on the sufficiency of

disclosure or of the extent of generalisation, it does not meet the stringent conditions to be applied in the analysis of the compliance with the formal requirements of Article 123(2) EPC (see point 4 supra).

11. Thus, for the reasons given above (cf point 10 supra), the board concludes that from the description in the application as filed (cf point 5 supra) a person skilled in the art would not have unambiguously derived **by way of implication** a pertussis holotoxin with the features recited in the claims of all the pending requests.

12. Consequently, the claimed subject-matter of all requests on file extends beyond the content of the application as filed. Thus, the claims of these requests offend against Article 123(2) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairperson:

D. Spigarelli U. M. Kinkeldey