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D E C I S I O N
of 25 October 2004

Case Number: T 0843/03 - 3.3.4

Application Number: 94912186.7

Publication Number: 0688227

IPC: A61K 39/12

Language of the proceedings: EN

Title of invention:

Production of human papillomavirus capsid protein and virus-like particles

Applicant:

THE UNIVERSITY OF ROCHESTER

Opponent:

-

Headword:

Human papillomavirus/THE UNIVERSITY OF ROCHESTER

Relevant legal provisions:

EPC Art. 87, 111(1)

Keyword:

"Right to priority (yes)"
"Remittal to first instance (yes)"

Decisions cited:

G 0012/91, G 0002/98, T 0081/87, T 0019/90, T 0464/94,
T 0193/95

Catchword:

-



Case Number: T 0843/03 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 25 October 2004

Appellant: THE UNIVERSITY OF ROCHESTER
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 17 December 2002
refusing European application No. 94912186.7
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairwoman: U. Kinkeldey
Members: M. Wieser
R. Moufang

Summary of Facts and Submissions

I. The appeal was lodged by the Applicants (Appellants) against the decision of the Examining Division to refuse under Article 97(1) EPC the patent application EP 94 912 186.7, publication number EP-A-0 688 227 (international publication number WO-A-94/ 20 137). The patent application claims priority from US 08/028,517; 9 March 1993 and US 08/207,309; 7 March 1994, and has the title: "Production of human papillomavirus capsid protein and virus-like particles".

II. The Examining Division concluded that the claims of a main request and an auxiliary request before them were not entitled to the earliest priority date claimed. Document (10), The Journal of Virology, vol. 67, no. 12, pages 6929 to 6936, published in December 1993, was therefore considered to belong to the state of the art according to Article 54(2) EPC and to anticipate the novelty of the claims of both, the main and the auxiliary request (Article 54 EPC) and therefore decided to refuse the application.

Claim 1 of the main request read:

A purified recombinant human papilloma virus-like particle or capsomere which comprises genital type human papilloma virus L1 capsid protein expressed from an L1 protein coding sequence which produces a protein or protein complex which possesses immunological and morphological characteristics similar to those of native papillomavirus wherein said particle or

capsomere is able to recognise antibodies in human sera from persons known to be infected with homologous virus."

III. Claim 8 referred to a vaccine comprising the virus-like particle or capsomere, claim 9 to its use in the manufacture of a vaccine and claim 12 to a method for its production.

The claims of the auxiliary request were restricted to a virus like particle or capsomere comprising human papilloma virus-16 (HPV-16) L1 capsid protein.

IV. Besides document (10) (see section (II) above) the following documents are referred to in this decision:

(4) WO-A-93/02 184

(6) Virology, vol.185, 1991, pages 251 to 257

(20) Cancer cells, vol.5, 1987, pages 275 to 280

(21) Oncogene, vol.7, 1992, pages 459 to 465

(24) J.Gen.Virol., vol.70, 1989, pages 2555 to 2562

(26) Statement of Dr. Rose, 7 May 2003

V. The Examining Division concluded that the first priority document, US 08/028,517, was not enabling for the production of a purified recombinant human papilloma virus-like particle (VLP) or capsomere comprising HPV-16 L1 capsid protein.

They considered that a skilled person when trying to produce VLP's comprising HPV-16 L1 capsid protein, either would have isolated and purified genomic DNA from infected cells, or used already cloned and available DNA material. Since the first priority document referred on page 9 to document (20), co-authored by L.Gissmann, they concluded that "...it is more likely that the skilled person would have requested the HPV 16 genome, available on plasmid from Dr Gissmann directly". Moreover, the first priority document acknowledged document (6) on page 3, which used the pHPV16 plasmid, made by L.Gissmann, for isolating the HPV-16 L1 coding region. Document (6) also disclosed PCR primers suitable for isolating the L1 gene from said plasmid.

Since the first priority document did not disclose such primers, the Examining Division reasoned their decision such that a skilled person being provided by the prior art with both, PCR primers and a source for HPV-16 DNA, "...would not ... consider isolating a genomic source of HPV-16, purifying it and then designing de novo new primers when this information was already available in D6...Consequently a skilled person would probably not have taken the option of isolating and purifying genomic HPV 16 DNA when cloned material was already available from Dr Gissmann."

The decision under appeal mentions document (4) as further prior art document using the pHPV16 plasmid as source for the HPV-16 L1 coding sequence. However, this coding sequence, also designated as 'prototype sequence', "...contained, as shown later, an error at nt 6240 which resulted in a non conservative amino acid

change from histidine to aspartate at aa 202 (see D10, p.6933, col.1)". Documents (4) and (6) both showed poor results as to the production of VLP's with a vector expressing HPV-16 L1 alone, which according to document (10) resulted from the fact that this single amino acid change at position 202 prevented efficient assembly of the HPV-16 L1 capsid protein encoded by the prototype sequence.

The Examining Division drew the following conclusion: "Consequently the skilled person could just as easily have started with a source of HPV 16 L1 suggested in the first priority document as being available from, for example the Gissmann reference on page 9, which contained the erroneous sequence", and "..it appears more likely that if the skilled person were to have followed the suggestions in the priority document unambiguously he/she would have ended up in exactly the same position as the authors of D4 and had few and malformed particles thanks to the use of the erroneous genetically engineered sequence available from sources such as Gissmann."

Figure 7 of the first priority document, an electron micrograph (EM) of HPV-16 VLP's produced according to the claimed invention, was *inter alia* judged by the Examining Division in the following way: "The ED (Examining Division; added by the Board) therefore considers that from the very few particles shown in figure 7 of the priority document and the obvious effect EM of preparative techniques no absolute fact can be deduced from figure 7 as to whether it shows correctly formed HPV 16 particles or not."

The Examining Division concluded that "[c]onsequently the first priority document does not provide an enabling disclosure of the claims of the MR (main request; added by the Board) and thus the first claimed priority is invalid (Article 88(3) EPC)". The same reasoning was applied to the auxiliary request and consequently the same decision was reached.

VI. The Appellants requested that the decision under appeal be set aside and that the case be remitted to the first instance for further prosecution.

VII. The submissions by the Appellants, as far as they are relevant for the present decision, may be summarized as follows:

The first priority document was fully enabling for the production of a VLP comprising HPV-16 L1 protein. The citation of document (20) on page 9 of the first priority document could not be construed as indication that one of the authors of document (20) was contacted for his plasmid containing the HPV-16 genome. The document has been cited as a review article pointing out that HPV-16 has been found in a large number of cell lines and how readily available therefore sources of genomic HPV-16 were.

The first priority document contained a detailed protocol describing the production of a genital type HPV VLP with reference to HPV-11. Before the first priority date it was known from prior art to isolate sequence and amplify protein coding sequences from HPV-16 infected cells.

There was no need for designing de novo new primers, as held by the Examining Division.

The comments of the Examining Division regarding the electron micrograph in figure 7 of the first priority document were wrong and did not consider what Appellant's technical expert submitted at the oral proceedings before the Examining Division.

VIII. On 19 March 2004 the Board received observations by a third party according to Article 115 EPC. The submissions by the third party, as far as they are relevant for the present decision, may be summarized as follows:

The application was not entitled to the first priority date as the first priority document did not disclose that its technical teaching was concerned with "genital" HPV-types and because it was not enabling for the production of HPV-16 VLP's capable of vaccine use.

At the first priority date, the state of the art, represented by document (4), included a technical teaching against being able to make enough authentic HPV-16 VLP's suitable for vaccine use. This prejudice was overcome for the first time by document (10) showing that an amino acid substitution at position 202 in the Gissmann prototype clone for HPV-16 L1, which was used in documents (4) and (6), prevented authentic HPV-16 VLP's having a native configuration similar to intact virions from being made efficiently.

The first priority document, which acknowledged the state of the art for HPV-16 genomic sequence as represented by the Gissmann 'prototype' clone and how this did not enable the prior art to produce authentic HPV-16 VLP's, did not meet the requirements of Article 83 EPC as laid down in decision T 792/00 of 2 July 2002.

- IX. In the framework of considering whether they should rectify their decision, the Examining Division crossed both of the main alternative boxes (rectification and non-rectification) on the relevant form 2701, which was signed by all three members. The form 2701 remained in the non-public part of the file and was not despatched by the Examining Division to the parties. The competent formalities officer referred the appeal to the Boards of Appeal.

Reasons for the Decision

1. The competence of a Board of Appeal in ex parte cases depends on whether or not the first instance has rectified its decision pursuant to Article 109(1) EPC. Since, in the present case, on the form 2701 both of the main boxes, i.e. the box for rectification and the box for non-rectification were crossed, doubts as to the true intention of the Examining Division arise. However, even if the Examining Division had intended to rectify its decision, no interlocutory revision took place within the period foreseen in Article 109(2) EPC since a decision on rectification was never despatched by the Examining Division to the Appellants. Decisions taken following written proceedings only enter into

force when they are notified (G 12/91, OJ EPO 1994, 285, point (2) of the reasons for the decision). The Board is therefore competent to deal with the present appeal.

2. The appeal meets the requirements of Articles 106 to 108 EPC and Rule 64 EPC and is thus admissible.
3. According to decision G 2/98 (OJ EPO 2001, 413), the requirement for claiming priority of 'the same invention', referred to in Article 87(1) EPC, means that priority of a previous application in respect of a claim in a European patent application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole (cf decision G 2/98, point (9) of the reasons for the decision).

Further, the priority document has to provide an enabling disclosure (cf e.g. decisions T 81/87, OJ EPO 1990, 250, cf point (8) of the reasons for the decision; T 193/95 of 26 November 1998, cf point (3.1) of the reasons for the decision). This is well within the concept of 'the same invention' of Article 87(1) EPC as an incomplete technical disclosure cannot be seen as being 'the same' as a complete one.

It has been established in a number of decisions of the Boards of Appeal that sufficiency of disclosure presupposes that the skilled person is able to obtain substantially all embodiments falling within the ambit of the claims (see Case Law of the Boards of Appeal of the EPO, 4th edition 2001, English version, page 147),

and that he/she, in order to reach this goal, may not be confronted with undue burden (see Case Law of the Boards of Appeal of the EPO, 4th edition 2001, English version, pages 150 to 152).

4. VLPs comprising HPV-16 L1 capsid protein are an embodiment of claim 1 of the main request, which is explicitly claimed in dependent claim 4 and in claim 1 of the auxiliary request. Thus, a document from which priority is claimed for this subject-matter must contain an enabling disclosure as to the production of these VLPs.

5. As can be seen from the quotations of the reasons given by the Examining Division ("... , it is **more likely** that the skilled person would have requested the HPV 16 genome, available on plasmid, from Dr Gissmann directly...The skilled person would not in the opinion of the ED therefore consider isolating a genomic source of HPV-16, purifying it and then designing de novo new primers when this information was already available in D6... Consequently a skilled person would **probably** not have taken the option of isolating and purifying genomic HPV 16 DNA when cloned material was already available from Dr Gissmann", emphasis added by the Board), cf section (V) above, they based their decision to refuse the Applicant grant of a patent on probability assumptions as to what the skilled person would have done when considering the disclosure of the priority document. When a procedural instance such as the present one, in *ex parte* proceedings in which the EPO has to examine whether or not a claimed subject matter meets the requirements of the EPC, comes to the conclusion that one or more of these requirements are

not met, it has to be convinced and can only decide on the basis of verifiable facts (see e.g. decisions T 19/90 OJ EPO OJ EPO 1990, 476; T 464/94 of 21 May 1997). If the deciding body was not sure about something and expressed this in words such as those quoted above this inherently already implies that it may have erred. A rejection of an application, or revocation of a patent, based on an error cannot, however, be rectified (unless appealed).

6. In decision T 19/90 (see above; point (3.3) of the reasons for the decision) the Examining Division rejected the application *inter alia* because it could not be **assumed** that the sole example in the application - that of mice - could be extended to all other mammals and thus the requirement of Article 83 EPC was not fulfilled. The Board, however, decided that only if there are serious doubts, substantiated by verifiable facts, may an application be objected to for lack of sufficient disclosure. This also applies in the present case to the position of the Examining Division on the enablement of the first priority document.

7. Decision T 464/94 (see above; point (16) of the reasons for the decision) dealt with an "assumption"-approach of an Opposition Division considering a prior art document under Article 54 EPC (Novelty). The Opposition Division reasoned the revocation of the patent on the consideration that **probably** a certain technical effect was achieved in a piece of prior art. The Board decided that considerations about probability when judging on a novelty destroying disclosure are not justified. Rather, if a patent is revoked for lack of novelty the deciding body must be sure, after having considered all

arguments and facts on file that these justify the revocation. If doubt remains, further investigation is necessary - otherwise the patent should not be revoked. This equally applies in the present case.

8. In this same context the Examining Division's position as to the results shown in figure 7 of the first priority document, an electron micrograph (EM), has to be considered. When an Applicant provides a technical disclosure and *prima facie* evidence as to certain technical elements in an application, here the electron micrographs, it is not the legally appropriate approach to decide to the disadvantage of the applicant with the reason that "... no absolute fact can be deduced from figure 7 as to whether it shows correctly formed HPV 16 particles or not", because, as follows from the case law mentioned above, it is the EPO which has the burden of proof when judging that something is not shown. In the present case one of the inventors, heard as technical expert at the oral proceedings before the Examining Division, pointed to four particles in figure 7 representing icosahedral HPV virions. Appellant's expert has repeated his statement in document (26) and again drew attention to spherical particles in figure 7 of the size expected for human papillomavirus virions.

9. Whilst the Board agrees with the Examining Division that "no absolute fact can be deduced from figure 7" it does not see full proof of such facts as a requirement within the framework of the EPC and the case law

- evaluated above and cannot see any serious doubts of the Examining Division substantiated by verifiable facts.
10. Furthermore, the Examining Division did not examine in detail whether or not there is sufficient technical disclosure in the first priority document which would allow the skilled person to succeed in producing the claimed subject matter. Rather the Examining Division's main concern was that the skilled person would have failed when choosing the track to reproduce the virus particles by relying on already available starting sources. Ignoring the reasons for the failure, he "... would have an awful lot of work to do in order to find out exactly why the method did not work." The Board agrees that this may be so, but the approach taken by the Examining Division does not take into consideration the decisive question, namely whether or not there is further disclosure in the first priority document which would lead to success. The only remark on this further possibility seems to be the last sentence of the first paragraph on page 7 of their reasons: "Even if the skilled person did opt for the fresh isolation of the HPV genome from a clinical sample there is still a chance, albeit very small ... that a mutant might have been isolated." - this mutant again being one which would not form correctly and thus not provide the particles looked for and as claimed.
11. The Board, therefore, in the following examines whether or not the claimed subject matter of the first priority document is enabling as required by the case law (see point 3 above) taking into account the **whole technical**

disclosure as pointed out in Decision G 2/98 (see point (3), first paragraph above).

12. Example 1 of the first priority document gives a detailed protocol on how to obtain a genital type HPV VLP with reference to HPV-11, containing the following steps:

- preparation of PCR primers,
- purifying genomic DNA from HPV-11 infected tissue,
- amplifying the HPV-11 L1 coding region,
- cloning this coding region into an expression vector,
- transfecting cells with the expression vector,
- expressing recombinant VLPs,
- purifying the VLPs,
- determining their morphology, and
- determining that the VLPs recognise antibodies in human sera from persons known to be infected with homologous virus.

13. Document (6) is discussed on page 3, lines 16 to 24 of the first priority document. It is said that the authors of document (6) were not able to produce VLPs with a vector expressing L1 alone. The authors of document (6) used the pHPV16 plasmid, provided by Dr Lutz Gissmann (see page 256, right column of document (6)).

14. The following passages of the first priority document need attention:

Page 8, lines 3 to 4:

"Fig. 7 is an electron micrograph of HPV type 16 VLPs, produced by the construction and expression of an HPV-16 L1 recombinant baculovirus (Ac16L1)."

Page 8, lines 26 to 28:

"The L1 coding sequence used in the invention can be isolated and purified from papillomavirus genomic DNA or synthesized using standard genetic engineering techniques."

Page 9, lines 4 to 14:

"In a preferred embodiment of the invention, there is provided a method of expressing the coding sequence for the L1 capsid protein of human papillomavirus type-11 (HPV-11), human papillomavirus type-6 (HPV-6), or human papillomavirus type-16 (HPV-16) in Sf-9 insect cells using the baculovirus expression system. It is understood that the capsid protein coding sequences of these HPV types are used for purposes of illustration only, and that any L1 capsid protein coding sequence for any animal or human papillomavirus type can be used without deviating from the intended scope of the invention. Such HPV types include, without limitation, HPV types 16, 18, 31, 33, 35 (Gissmann et al., Cancer Cells, 1987, vol. 5, p. 275, which disclosure is hereby incorporated by reference); and those HPV types disclosed in PCT publication no. WO 92/16636 to Boursnell et al., which disclosure is hereby incorporated by reference."

15. Contrary to the view taken by the Examining Division, the Board does not see that the citation of document (20) on page 9 of the first priority document can be

- construed as indication that one of the authors of document (20) was contacted for his plasmid containing the HPV-16 genome by the present inventors. Thus, no recommendation can be inferred from the disclosure of the first priority to choose, what the Examining Division considered as being "the easier way".
16. Further, document (24) discloses the amplification of HPV-16 sequences, including segments from the E1 and L1 open reading frame of the HPV-16 genome, using PCR (see figure 1 and page 2556). Document (21) describes isolation and sequencing of protein coding sequences from HPV-16 infected cells (see abstract).
 17. From all this technical disclosure the board cannot conclude, as the Examining Division did, that there is a need to create new primers for carrying out the claimed invention. PCR-amplification of a genetic HPV-16 L1 coding sequence which is distinguished from the 'Gissmann prototype sequence' by one single C to G base change in position 6240 is possible with the primers already disclosed in documents (4) and (6).
 18. Thus, the board is convinced that the skilled person, if he had failed when firstly choosing the way to reproduce the invention as described in the first priority application according to a seemingly easier route, is provided by explicit instructions on how to perform the claimed invention and the board sees no substantiated and reliable facts on file why he would not have turned to them.
 19. Thus, the Board comes to the conclusion that a skilled person at the filing date of the first priority

document was not confronted with undue burden when putting into practice the claimed invention according to page 8, lines 26 to 28 of the first priority document, namely by isolating and purifying the HPV-16 L1 coding sequence from genomic DNA, and thereafter processing it according to the protocol given in example 1 with regard to HPV-11 L1 coding sequence.

The results of this procedure are shown in figure 7 of the first priority document, an electron micrograph (EM) which was stated by one of the inventors to be the particles as claimed and the board sees no substantiated evidence on file to put this into question as required by law and case law (see above points (5) to (7)).

20. With regard to the observations filed by a third party according to Article 115 EPC (see section (VIII) above for details), the Board is of the following opinion:

Claim 5 of the first priority document refers to a method of expressing the capsid protein coding sequences of "genital type human papilloma virus". The third parties argument, that the first priority document did not disclose that its technical teaching was concerned with "genital" HPV-types thus cannot be followed.

With regard to non-enablement of the production of HPV-16 VLPs the third party refers to decision T 792/00 of 2 July 2002. This decision is based on a situation where a patent, whose teaching goes against prevailing technical opinion, contains only one example which is marked as being a hypothetical experimental protocol.

The competent Board came to the decision that in such a situation, where the Patentee has failed to give even a single reproducible example, it would amount to undue burden for the cautious and conservative skilled person to have to carry out research of his own to establish whether the invention can be put into practice in some circumstances, not described in the patent, when prevailing technical opinion suggests the outcome will be failure. Sufficiency of disclosure was therefore denied.

The present Board does not consider this decision to be relevant for the present patent application, and, respectively for its first priority document. This priority document, firstly, as set out in detail above in point (12), contains a detailed protocol of one way to carry out the claimed invention, and secondly, with regard to one embodiment falling within the scope of the claims, is not going against prevailing technical opinion, but is faced with negative results of one working group only, published in documents (4) and (6). These negative results are discussed in the description of the first priority document and a different way of obtaining genetic starting material - which seems to be the reason for the failure of prior art experiments - is described.

21. In conclusion, the Board concludes that firstly the Examining Division did not apply the legally correct approach when judging the probability or non-probability of the way in which the skilled person would proceed when being confronted with failure when following one way to carry out the invention, and secondly that the first priority document discloses in

technical terms a reliable way to achieve the claimed subject matter sufficiently clear and complete so that a skilled person is able to obtain substantially all embodiments falling within the ambit of the claims without being confronted with undue burden.

The subject matter of the claims the main and the auxiliary request are thus entitled to the first priority date claimed, 9 March 1993; US 08/028,517, within the meaning of Article 87(1) EPC.

22. Consequently, the decision under appeal reasoning that the subject matter of claim 1 of the main and auxiliary request lacks novelty over the disclosure of document (10), published in December 1993, i.e. after the first priority date, has to be set aside.
23. As no examination of further substantive issues was carried out, the Board exercising its discretion under Article 111(1) EPC remits the case to the examining division for further prosecution.

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 for further prosecution.

The Registrar:

The Chairwoman:

P. Cremona

U. Kinkeldey