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D E C I S I O N
of 15 November 1999

Case Number: T 0791/96 - 3.3.4

Application Number: 86307705.3

Publication Number: 0223382

IPC: C12N 15/38

Language of the proceedings: EN

Title of invention:
Pseudorabies virus protein

Patentee:
The Upjohn Company

Opponent:
Akzo Nobel Pharma B.V.

Headword:
Pseudorabies/UPJOHN

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (yes)"

Decisions cited:
T 0455/91, T 0886/91, T 0223/92, T 0207/94, T 0386/94

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0791/96 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 15 November 1999

Appellant: (Opponent)
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Representative:
-

Respondent: (Proprietor of the patent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 3 July 1996 concerning maintenance of European patent No. 0 223 382 in amended form.

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: L. Galligani
S. C. Perryman

Summary of Facts and Submissions

I. An appeal was lodged both by the opponents and the proprietors of the patent against the interlocutory decision of the opposition division issued on 3 July 1996 by which the European patent No. 0 223 382 was maintained in amended form on the basis of claims 1 to 11 for all designated states except Austria and Spain (non-AT, non-ES states), claims 1 to 8 for AT and ES, and an adapted description. The patent had been opposed under Article 100(a) EPC to the extent of claims 1 to 7 (non-AT, non-ES states) as granted (corresponding to claims 1 to 5 for AT and ES).

Claim 1 as granted for the non-AT, non-ES states read as follows:

"A recombinant DNA molecule comprising a DNA sequence operatively linked to an expression control sequence, wherein the DNA sequence codes for a polypeptide displaying pseudorabies virus glycoprotein gp50, gp63 or gI immunogenicity, the glycoprotein having the amino-acid sequence shown in Chart A, B or C, respectively."

Dependent claims 2 to 3 concerned particular embodiments of the recombinant DNA according to claim 1, claims 4 to 6 were directed to a host cell transformed with the said recombinant DNA and claim 7 concerned a method for producing a polypeptide as defined in claim 1.

Claims 1 to 5 for AT and ES were correspondingly formulated as method claims.

Claim 1 as maintained by the opposition division both for the non-AT, non-ES states and for AT and ES differed from the claim 1 as granted by the presence of the feature "wherein the expression control sequence is not naturally operatively linked to the DNA sequence encoding a polypeptide displaying pseudorabies virus glycoprotein gp50, gp63 or gI immunogenicity".

All the remaining claims were as granted.

II. The opposition division considered that the subject-matter of the amended claims, the novelty of which was not contested by the opponents, involved an inventive step. In the decision, reference was made in particular to the following documents:

(1) Rea T.J. et al., J. Virol., 1985, Vol. 54, pages 21 to 29;

(2) Wathern M.W. et al., J. Virol., 1984, Vol. 51, pages 57 to 62;

(3) Watson R.J. et al., Science, 1982, Vol. 218, pages 381 to 384;

(4) Watson R.J., Gene, 1983, Vol. 26, 307 to 312;

(5) EP-A-0 101 655;

(6) McGeoch D.J. et al., J. Mol. Biol., 1985, Vol. 181, pages 1 to 13;

(7) Davison A.J. et al., J. Gen. Virol., 1983,

Vol. 64, pages 1927 to 1942;

(14) Petrovskis E.A. et al., J. Virol., 1986, Vol. 59, pages 216 to 223.

III. In their notice of appeal, the patentees requested that the decision of the opposition division be set aside, "insofar as it is decided that any amendment submitted by the Proprietor is unclear, and/or insofar as it allows any amendments made in contravention of Article 123 EPC." They further requested that the patent be maintained as granted, "subject to any amendment that is made that is clear and does not involve added subject matter.".

IV. With the statement of grounds of appeal, they submitted a new main request and auxiliary requests 1 to 5 in the two versions for the non-AT, non-ES states and for AT and ES. Auxiliary request 2 was the same as accepted by the opposition division.

V. The opponents-appellants disputed in their statement of grounds of appeal the patentability of claims 1 to 7 of the request maintained by the opposition division which in their view lacked an inventive step. They submitted further documents in support of their arguments, including the declaration of Dr Andrew J. Davison and abstracts of papers presented at the 10th International Herpes Virus Workshop in Ann Arbor (USA) on 11 to 16 August 1985 (hereinafter documents (18A to 18D)).

VI. On 28 November 1996, the board issued a communication pursuant to Article 12 of the rules of procedure of the boards of appeal with a provisional view on the

admissibility of the appeals. In particular the appeal filed by the patentees was provisionally held to be inadmissible.

VII. On 24 March 1997, the patentees (respondents) withdrew their appeal. On 26 May 1997, they replied to the statement of grounds of appeal of the opponents (appellants).

VIII. On 16 July 1999 the board issued a communication pursuant to Article 11(2) of the rules of procedure of the boards of appeal with a provisional, non-binding opinion on the matters in dispute.

IX. Oral proceedings took place on 15 November 1999.

X. The appellants maintained that the identification, cloning and expression of the gene encoding gp50 was feasible for the skilled person without real difficulties, reference being made to the findings in the decisions T 386/94 of 11 January 1996 and T 207/94 (OJ EPO 1999, 273). They argued essentially as follows:

- Document (2), which mapped the gp50 gene in the SalI subfragment B of the BamHI 7 fragment of the pseudorabies virus (PRV) genome in the Us (unique short) region, represented the **closest prior art**. This document indicated that the gp50 protein was a surface protein, that it reacted with antibodies in an immunoprecipitation assay and that it was a major protective immunogen;

- Faced with the technical problem of cloning and expressing the gp50 gene, the skilled person, when

evaluating the chance of success, would have taken into account the following technical facts:

(a) The genome of PRV was essentially collinear with the genome of other herpes viruses of which the HSV-1 (herpes simplex virus 1) was the prototype (cf documents (6) and (7)). This suggested similarities in the genomic organisation, ie head-to-tail arrangement of the genes, no overlapping, no splicing.

(b) Mapping, identification and sequencing of the complete Us region of HSV-1 and HSV-2 had been performed and the open reading frames (ORF) of all its genes, including that of the gD gene (corresponding to the gp50 gene of PRV), had been described (cf documents (3) to (5));

(c) Document (1) had successfully mapped, sequenced and expressed the gX protein gene of PRV which was located in the same genomic fragment wherein document (2) had mapped the gp50 gene. The document gave two options for the location of the gX and gp50 genes in this region of the PRV genome: either the gp50 mapped close to the gX or the two glycoproteins were somehow related (cf statement on page 27, at the end of the discussion). However, the skilled person would have considered that only the first of the two options had a practical value. This was because, apart from the obvious deductions which could be made based on the

similarity with the genome organisation of other herpes viruses (cf item (a)), the technical facts pointed away from the possibility of the two proteins or their respective genes being related: (i) the two proteins had different molecular weights; (ii) the gX protein was excreted, while gp50 was a structural protein (cf documents (1) and (2)); (iii) the gX protein was not involved in protection and did not induce virus neutralising antibodies, while gp50 was a major protective immunogen (cf document 18D); (iv) the anti gX-antiserum did not immunoprecipitate the gp50 protein (cf document (1)). The later publication by the present inventors, ie document (14), used as an expert opinion, indicated by way of its references to the prior art, that they also were convinced, already at the priority date, that the two genes encoded different products and were thus unrelated.

(d) Based on these technical facts, the skilled person would have reasonably expected to find the ORF for the gp50 protein downstream of the gX gene in the BamHI 7 fragment disclosed in documents (1) and (2), and would thus have expected to identify, clone and express the gene, the product of which he or she would have been confident of detecting by way of immunoprecipitation with an antiserum (cf Figure 1 in document (2)). This involved only the application of

routine techniques, greatly facilitated by the use of computer programs for aligning DNA sequences, and a modest amount of work.

(e) There were no real difficulties which would have deterred the skilled person from trying or which would have diminished his or her expectation of success: (i) **not** the absence of a signal sequence in Figure 6 of document (1), because the said figure only reported part of the sequence which the skilled person would have obviously analysed, and there were no reasons why a signal sequence had to be identifiable in the short nucleotide sequence shown in Figure 6 downstream from the gX coding sequence; (ii) **not** the apparent lack of homology between PRV and HSV in the Us region because this did not necessarily imply lack of homology between the encoded proteins; (iii) **not** the absence of N-glycosylation sites, because this would have been discovered only **after** sequencing, and, in any case, O-glycosylation was not uncommon for HSV (cf document (1), references to prior art in the introductory part on page 216).

- The declaration of Dr A. J. Davison confirmed that the data and the techniques available in 1985 would have led the skilled person to the conclusion that the gp50 gene was located close downstream from the gX gene and to the expectation that the identification of the said gene, and its cloning and expression would be achieved in a

straightforward manner by means of routine techniques.

XI. The respondents argued essentially that the arguments put forward by the appellants were based on hindsight. In retrospect, it was clear that HSV was a prototype of PRV, and that the gene gp50 was a homologue of the gD gene which was located downstream from the gX gene. However, at the time of the invention elements of confusion prevailed (lack of homology in the Us region between HSV-1 and PRV; the presence in the PRV genome of the gX which had apparently no counterpart in the HSV; unclear relationship between the gX and gp50 genes etc.) that justified the acknowledgement of an inventive step because the patent in suit had finally brought about the clarification of the matter. Later document (14) outlined the inventors' view at a later date, ie after the invention was made, and could not be used to represent the skilled person's view at the priority date. Dr Davison was not a person of ordinary skill and his views could not be used to establish what was obvious to the skilled person.

XII. The appellants requested that the decision under appeal be set aside and that the patent be revoked.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

The formal requirements: Articles 84 and 123 EPC.

1. The feature "wherein the expression control

sequence..." introduced in claim 1 has a restrictive effect on the extent of protection conferred by the claim. The said feature finds a basis in the application as filed on page 8 where reference is made to the embodiment of the use of "heterologous" expression control sequences. No objections have been raised by the appellants against this amendment under the terms of Articles 123 and 84 EPC. Nor does the board have any objections thereto.

Inventive step (Article 56 EPC)

2. The only point at issue in this appeal is the inventive step of the embodiment of the DNA molecule encoding the gp50 glycoprotein, the remaining embodiments of the DNA molecules encoding the gp63 and gI proteins, included in claim 1, being undisputed.

3. The most appropriate starting point for an inventive step analysis is represented by the knowledge about the position of the gp50 gene in the PRV genome. This knowledge derives from the combined reading of documents (1) and (2):

(a) **Document (2)**, published in July 1984, describes marker rescue experiments to map the gp50 gene. A mutation in the gp50 gene, causing an alteration in the protein which prevents its immunoprecipitation by a specific monoclonal antibody, is mapped within the gp50 gene to the Us region of the PRV genome in the SalI subfragment (ca 2.1 kilobase pairs) of the BamHI-H segment (ca 6.8 kilobase pairs). It is pointed out that the mRNA coding for gp50 may extend beyond the limits

demarcating the location of the mutation (cf page 61, left-hand column, last sentence of the second paragraph). The document discusses the similarities between the PRV gp50 protein and the HSV-1 gD protein, both of which map in the Us region of the respective genomes, have a molecular weight of ca 50 kd, and raise monoclonal antibodies capable of neutralising the respective viruses (cf page 61, paragraph bridging the left and right-hand columns). However, the document points to the lack of DNA homology between HSV and PRV in the regions coding for these proteins and indicates the necessity of further studies to determine whether the two proteins are functionally related (loc. cit., last sentence).

(b) **Document (1)**, published in April 1985, describes the mapping within the Us region of the PRV genome of an open reading frame (ORF) which is presumed to encode a glycoprotein which is excreted in the medium of virus infected cells. The glycoprotein is referred to as gX, because - as stated in the document (cf page 25, top of the right-hand column) - "there is as yet no systematic nomenclature for the PRV glycoproteins and the relationship between the glycoprotein in the medium of infected cells and the viral membrane glycoprotein is not well established". The said ORF, the sequence of which is reported in Figure 6, is located within the BamHI-PvuII subfragment of the BamHI 7 segment. It is stated that the protein sequence predicted from the ORF "has features of a membrane protein" (cf page 26, right-hand column, second paragraph). Whether this

protein is a proteolysis product of a membrane bound protein is not definitely established. The predicted molecular weight of the coded amino acid is 53,700; translation in the presence of microsomes of a large fragment of the genome, including segment BamHI 7, produced a protein of 95 kd; translation in the absence of microsomes produced a protein of 70 kd.

With reference to document (2), document (1) states in the last paragraph of the discussion that the BamHI-SalI subfragment, wherein the gp50 gene at least partially maps, contains only an additional 400 bases beyond the BamHI-PvuII fragment sequenced in Figure 6. Document (1) concludes that "The location of the genes for these two glycoprotein genes within the same small region raises the interesting possibilities that two glycoprotein genes map very close to each other, or that the glycoproteins are somehow related".

4. In summary, the starting point for an inventive step analysis is the knowledge that the gp50 gene mapped at least partially within a PRV genome fragment within the Us region which also contained the ORF for the gX protein.

5. In the light of the said knowledge, the underlying technical problem is defined as being the identification and cloning of the gp50 gene in view of its expression in a recombinant DNA system.

6. The solution is given in claim 1 which concerns inter alia a recombinant DNA molecule comprising the DNA sequence which codes for a polypeptide displaying PRV

glycoprotein gp50 immunogenicity, operatively linked to an expression control sequence, the glycoprotein having the amino-acid sequence shown in Chart A.

7. The relevant question in relation to inventive step is whether, starting from the prior art information referred to in point 4 above, and based on other relevant prior art knowledge, the skilled person would have arrived in an obvious manner at the said recombinant DNA molecule, and would have reasonably expected so to arrive.

8. In seeking an answer to the above question, the technical circumstances of the case should be investigated from the point of view of the skilled person, avoiding any ex-post facto analysis. In the board's judgement, the skilled person would not have been in the position to carry out the analysis of the situation that Dr Davison made in his declaration. This is, because differently from Dr Davison, who was undisputedly a highly skilled virologist, the skilled person for the purpose of Article 56 EPC, when dealing - like in the present case - with a relatively unexplored technical area, adopts a cautious attitude and is unable to arrive at what later turns out to be the correct conclusion unless there is solid evidence pointing to this conclusion and only filling minor gaps in existing knowledge is needed (cf eg decisions T 223/92, T 886/91, T 455/91). The latter was the case, for example, in the technical circumstances of decision T 386/94 (supra), where the skilled person's only task was to complete, by applying known techniques, the work of cloning and expressing a DNA encoding chymosin, whose characterisation had already reached an advanced

stage in the prior art.

9. That in document (2) a PRV glycoprotein was designated gp50, and that the claim now refers to this name, must not be allowed to obscure the fact that what is meant by gp50 in the patent is clearly identified by reference to an amino acid sequence and the DNA sequence encoding it (cf. Chart A), whereas in document (2) this was only the estimated molecular weight of an immunologically tested glycoprotein. As a matter of fact, the molecular weight can be smaller (ca. 45 kd) for the non-glycosylated protein and higher (ca 60 kd) for the fully processed protein (cf document (14), page 220). Thus, the estimated molecular weight alone gave the skilled person no very clear guidance as to what to look for, and he or she could not have been sure that anything found was the same as that identified in document (2), as the immunological tests as applied in document (2) have not been shown to be publicly available.

10. Further, the skilled person, faced with the technical problem as depicted above, was confronted with some puzzling information which, in the board's judgement, rendered difficult the prediction of the outcome of the endeavour of cloning and expressing the gp50 gene. This is because if, on the one hand, document (2), by locating the gp50 gene mutation in the SalI subfragment of the BamHI-H segment within the Us region of the PRV genome, indicated the region of the PRV genome where the skilled person could possibly find at least part of the gp50 gene, the subsequent document (1) pointed to the presence in the very same region of the gX gene **presumably** encoding a protein which, differently from the gp50 protein, was

excreted. Contrary to the appellants' view, the board is of the opinion that the skilled person would not have immediately understood that the gp50 and gX genes were aligned one after the other on the genome, and that they encoded unrelated glycoproteins. This is because, in spite of some differences between the two glycoproteins (cf Section X, item (c), subitems (i) to (iv) supra), the close location within the same genomic fragment of the gp50 gene mutation and of the gX gene and the fact that deduced protein sequence from the ORF of Figure 6 had features of a membrane protein rendered unclear the relationship between the two genes and between the two proteins. One could not exclude, for example, that the gX gene produced gp50 as an alternative product (cf declaration by Dr L. Post dated 24 March 1995, page 1, last paragraph). Document (2) itself emphasised the fact that the relationship between the excreted glycoprotein and the viral membrane glycoproteins was not well established. Moreover, no amino acid sequence information whatsoever was available in respect of the gp50 protein which could in any way assist the skilled person in any comparison.

11. The appellants argued that the similarities between PRV and other herpes viruses, in particular the fact that HVS-1 was regarded as a prototype of PRV, would have guided the skilled person. However, such proximity was far from certain at the priority date. In spite of some reported similarities in the genomic organisation between PRV and HSV (cf document (7)), the lack of DNA homology precisely in the Us region (cf loc. cit., Figure 2 and Table 5) and the finding therein of a gene which had no apparent counterpart in the HSV (document (1)) caused uncertainties in this respect. This

would not have encouraged the skilled person to rely on alleged similarities to anticipate gene locations. Moreover, a correspondence between the HSV-1 gD protein and the PRV gp50 protein was not yet established as demonstrated by the indication in document (2) that further studies were necessary therefor.

12. As for the appellants' argument based on the later publication by the present inventors (cf Section X, item (c), last sentence supra), in the board's opinion nothing can be inferred from document (14), as expert opinion, concerning the skilled person's perception of the relationship between the gp50 and gX genes at the priority date. The document reports the authors' views on the matter in the light of the identification of the DNA sequence encoding the gp50 and its expression in a host which they had achieved, and does not refer to any particular information on the subject which was publicly available already in 1985.

13. Given the rather confused technical circumstances, in the board's judgement, the skilled person would have had no reasonable expectation of successfully finding of the gp50 gene identified in document (2) within the known segment of the PRV genome, nor of successfully cloning and expressing it. Also the disclosure in document (18D) that a recombinant HSV containing, inserted into a thymidine kinase gene, another fragment from within BamHI 7 fragment on the Us region of the PRV genome expressed two PRV-specific glycoproteins, and was capable of raising PRV neutralising antibodies in infected mice would not have facilitated the task of the skilled person. In fact, the said document did

not provide any information about the nature of the glycoproteins, about the location of the DNA sequences encoding them, and whether the measured activity was attributable to one of them or both or something else.

14. As the elements of confusion alone justify the acknowledgement of an inventive step to the subject-matter of claim 1, it is not necessary to examine whether other factors (cf Section X, item (e), subitems (i) and (iii) supra) would have rendered difficult the identification of the gp50 gene.

15. The subject-matter of claims 2 to 7 derives its inventive step from the non-obviousness of the subject-matter of claim 1 upon which they depend.

16. For the above reasons, the board decides that the requirements of Article 56 are fulfilled.

17. This finding is not in contradiction with that of the previous decisions T 207/94 and T 386/94 (supra), which were referred to by the appellants. In the latter cases there was no puzzling information in the state of the art, and the technical circumstances were such that the skilled person would have reasonably expected to solve the respective underlying technical problem by applying routine techniques without any difficulties.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

U. Bultmann U. M. Kinkeldey