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D E C I S I O N
of 24 April 2001

Case Number: T 0377/95 - 3.3.4

Application Number: 83901021.2

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Language of the proceedings: EN

Title of invention:
Materials and methods for herpes simplex virus vaccination

Patentee:
UNIVERSITY PATENTS, INC.

Opponent:
SmithKline Beecham Biologicals SA

Headword:
HSV vaccine/UNIVERSITY PATENTS

Relevant legal provisions:
EPC Art. 56

Keyword:
"Claim 1 of main and auxiliary requests - inventive step (no)"

Decisions cited:
G 0003/98, T 0333/97, T 0338/97

Catchword:
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Case Number: T 0377/95 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 24 April 2001

Appellant I: (Proprietor of the patent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 7 April 1995 concerning maintenance of European patent No. 0 101 506 in amended form.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: L. Galligani
C. Holtz

Summary of Facts and Submissions

I. Both the patentees (appellants I) and the opponents (appellants II) lodged an appeal against the interlocutory decision of the opposition division dated 7 April 1995 whereby the European patent EP-A-0 101 506 (claiming priority from two US applications dated 18 February 1982 and 4 February 1983, respectively) was maintained on the basis of claims 1 to 5 filed on 21 November 1994 (second auxiliary request).

Claim 1 thereof read:

"Use of an immunologically active preparation of Herpes simplex virus type 1 envelope glycoprotein gD-1, purified by selective reversible binding to a monoclonal, anti-gD antibody immunoadsorbent, for preparing a vaccine composition for generating an immunological response protective against Herpes simplex virus type 1 and Herpes simplex virus type 2 disease states, by parenteral administration."

Independent claim 2 concerned the use of purified gD-2 glycoprotein for the same purpose, while claims 3 to 5 were centred on a polypeptide comprising a given amino acid sequence for use as a vaccine against a Herpes simplex virus disease state.

II. These claims were considered to meet the novelty requirements vis-à-vis the oral disclosure held by Dr Pereira at the 17th International Congress on "Herpes Virus of Man and Animal: Standardization of Immunological Procedures" held in Lyon, France in December 1981 (hereinafter the "Lyon disclosure"). This oral disclosure, the contents of which were considered to be reflected by the later publication:

M) L. Pereira, 17th International Congress on "Herpes Virus of Man and Animal: Standardization of Immunological Procedures", Lyon, France, 1981, "Develop. biol. Standard.", 1982, (S. Karger, Basel) Vol. 52, pages 115 to 131,

was the ground for the rejection of the main and first auxiliary claim requests. In fact, having decided that the "abuse" defence under Article 55(1)(a) EPC could not be validly invoked by appellants I because the "Lyon disclosure" had occurred more than six months before the **filing date**, the opposition division found that this disclosure was citable prior art which destroyed the novelty of the main request and of the first auxiliary request.

The claims of the second auxiliary request were also considered to involve an inventive step, having regard to the "Lyon disclosure" and the following document:

C) Dix R. D. et al., Infection and Immunity, October 1981, pages 192 to 199.

III. In their statements of grounds of appeal, both appellants addressed inter alia the issue of whether or not the "Lyon disclosure" fell within the provisions of Article 55 EPC. Appellants II filed also as a new document the master thesis work of T. J. Madara.

IV. With an interlocutory decision dated 5 August 1998, the board referred to the Enlarged Board of Appeal (EBA) a question of law, namely whether the six-month period referred to in Article 55(1) EPC had to be calculated from the date of filing or from the date of priority, this being relevant in respect of the "Lyon disclosure" which had taken place within six months before the first priority date. The EBA issued decision G 3/98 (OJ

EPO 2001, 62) stating: "For the calculation of the six-month period referred to in Article 55(1) EPC, the relevant date is the date of the actual filing of the European patent application; the date of priority is not to be taken account of in calculating this period".

V. On 22 December 2000, the board issued a communication informing the appellants that in consequence of this decision, the "Lyon disclosure" constituted prior art to be considered under Article 54(2) EPC, the question of the alleged abuse being now immaterial.

VI. In reply thereto, on 26 March 2001, appellants I replaced all requests previously on file. Their new main request consisted of claims 1 to 5 on the basis of which the patent was maintained by the opposition division. The auxiliary request consisted of claims 1 and 2 thereof.

Appellants II filed a declaration by Ms Carol Cooper in relation to question of the public availability of the Madara thesis.

VII. On 18 April 2001, appellants I submitted a joint declaration of Drs Cohen and Eisenberg in relation to the Madara thesis.

VIII. Oral proceedings took place on 24 April 2001. No new claim requests were filed by appellants I.

In addition to the documents cited above, the following documents were in particular referred to (the numbering used by the opposition division is adhered to):

D) Hilleman M. R. et al., in "The Human Herpesviruses - An Interdisciplinary Perspective" (A. J. Nahmias et al eds.), Elsevier, New York, N.Y. (USA), 1981, pages 503 to 506;

J) Norrild B., Current Topics in Microbiol. and Immunol., Vol. 90, 1980, pages 67 to 106.

IX. Appellants I substantially argued as follows:

- The Madara thesis should not be admitted into the proceedings because: i) it was late-filed; ii) it was not relevant enough, and iii) the date of its availability to the public could not be established with certainty;

- Claims 1 and 2 of both requests were entitled to the first priority date, while claims 3 to 5 of the main request were entitled to the second priority date;

- There was no substance in the appellants' II objection that the gD-2 vaccine was not sufficiently disclosed. A description of the purification of the gD-2 protein was provided in the specification. The working example showed the protective effect achievable with purified gD-1 protein, and, based on this, the skilled person expected the same activity with gD-2.

- As for inventive step, the closest prior art was represented by document D) which reported a protective effect against HSV by a mixture of all HSV-2 glycoproteins.

  The disclosures of documents C) and M) did not add any relevant information which could render obvious the subject-matter of the claims.

  The passive immunisation experiments reported in document C) with monoclonal antibodies against HSV-1 and HSV-2 would not have given any indication about a protective effect of HSV

glycoproteins as active immunogens. This was because the mechanisms of active immunisation were completely different from those of passive immunisation, as they involved triggering the memory response in the body of the immunised animal. No prediction could be made in this respect on the basis of passive immunisation which consisted in transferring into an animal the antibodies.

The "Lyon disclosure" (cf document M)) was concerned only with the neutralising activity of antisera produced in the framework of studies on the structure and function of the HSV glycoproteins. The author of the latter disclosure, Dr Pereira, was not at all concerned with the production of a protective vaccine. Nor was the finding of neutralising antibodies in vitro indicative of a possible protective effect in vivo, as this was an uncertain area where predictions were not possible. This was illustrated by the following later document, as expert opinion:

(41) Collet M. S., in "Advances in Veterinary Science and Comparative Medicine", Vol. 33: "Vaccine Biotechnology", 1989, Academic Press Inc., pages 109 to 172,

which, in particular on page 151, pointed to prior art examples, wherein certain purified proteins, although eliciting significant neutralising activity, failed to confer protection against challenge.

It had also to be observed that the prior art pointed to a large number of HSV glycoproteins (cf document J), and thus there were many options open

for the skilled person. Glycoproteins gD-1 and gD-2 were just two possible options for which no prediction could be made. Consequently, the skilled person could not have had a reasonable expectation of success using these glycoproteins.

X. Appellants II essentially submitted that:

- The Madara thesis was highly relevant. Based on the two declarations by Ms L. Rosenstein on file, it could be said with certainty that it had been made available to the public on a date between the first and second priority dates. Thus, it was prior art for any subject-matter not entitled to the first priority date;

- Claims 3 to 5, but also claim 2 were not entitled to the first priority date. This was because the first priority document did not provide the teaching that gD-2 was protective;

- The description of the patent specification did not enable the breadth of claim 2 because it taught expressly only one way of purifying gD-2, namely purification by selective reversible binding to a specific monoclonal antibody, and did not indicate other chromatographic procedures that could be employed;

- As for inventive step, the skilled person, based on document D), which had shown that protection against HSV-2 was possible using HSV glycoproteins, would have investigated which glycoproteins were responsible therefor. The studies on passive immunisation of document C) had shown that it was possible to protect naive mice against lethal challenge with either HSV-1 or HSV-2 by using a gD-specific monoclonal antibody

(HD1), and that this was a better choice than the gC-specific monoclonal antibody. The "Lyon disclosure" - which could also be considered as novelty-destroying for claims 1 and 2 - had shown that gD-1 and gD-2 proteins, purified by immunoaffinity with the HD1 monoclonal antibody, were highly immunogenic as they produced high titre cross-neutralising antisera in mice. Based on this, the skilled person would have expected vaccination with a purified gD-1 or gD-2 to provide protection against the virus.

XI. Appellants I requested that the decision under appeal be set aside and that the patent be maintained on the basis of either the main request or the auxiliary request, both submitted on 26 March 2001.

Appellants II requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

Admissibility into the proceedings of the Madara thesis

1. As the Madara thesis reports data of protection experiments in gD-immunised mice, it is considered by the board to be prima facie technically highly relevant, and for this reason it is admitted into the proceedings. It is apparent from the two declarations by Ms L. Rosenstein of the Medical School Library of the University of Pennsylvania (one filed by appellants I and the other by appellants II) that the thesis was available to the public in the period between the first and second priority date, and was thus prior art for any subject-matter not entitled to

the first priority date. However, in view of the outcome of the appeal (cf points 3 to 11 infra), it is not necessary to rely on this document in discussing any subject-matter.

Priority

2. The entitlement of claim 1 of the two requests on file to the first priority date is not in dispute. In view of the outcome of the appeal (cf points 3 to 11 infra), it is not necessary for the board to deal with the issue of the entitlement of claim 2 to the first priority date, which was a controversial issue in the written procedure.

Inventive step of claim 1 of the main and auxiliary requests

3. Claim 1 is identical in both requests. It is directed to the use of purified HSV gD-1 protein for preparing a protective vaccine against HSV-1 and HSV-2 which is to be administered parenterally.

4. In the board's judgment, the closest prior art is represented by the "Lyon disclosure", the contents of which are admittedly reflected by the later document M). In view of decision G 3/98(supra), this disclosure constitutes prior art to be considered under Article 54(2) EPC (cf Sections III to V supra). In her presentation, Dr Pereira, the author of the disclosure, described the preparation by selective reversible binding to a monoclonal anti-gD antibody (HD1) of purified HSV-1 and HSV-2 glycoproteins gD-1 and gD-2, and their use in mice as immunogens together with an adjuvant for the generation of neutralising antibodies (Tables V and VI of document M), which correspond to Tables 4 and 3, respectively, of the patent in suit, were shown during the presentation in Lyon).

5. Dr Pereira thus disclosed the use of an immunologically active preparation of HSV gD-1 or gD-2 protein (the immunological activity thereof having been tested in competition experiments beforehand) in the preparation of a composition for immunising mice by parenteral administration for the purpose of **titering the neutralising activity of the antisera produced**. This differs from the use of claim 1 only in that the latter refers to the purpose of **generating an immunological response protective against HSV-1 and HSV-2**.

6. The question raised by appellants II in the written procedure whether such a difference in wording is sufficient to establish novelty of the claim over the "Lyon disclosure" can be left unanswered in view of the board's finding on inventive step (see points 7 to 10 infra).

7. In the light of the "Lyon disclosure", the problem to be solved was finding a further use for the purified HSV gD-1 and gD-2 proteins.

8. Claim 1 proposes the use of gD-1 for preparing a protective vaccine.

9. The relevant question is whether such a use would have readily occurred to the skilled person in a reasonable expectation of success.

10. This question is answered by the board in the affirmative essentially for the following reasons:

- The results reported by Dr Pereira, namely the fact that parenteral administration to mice of purified gD-1 or gD-2 induced production of high

titered cross-neutralising antisera (cf Table VI), would have readily suggested to the skilled person that the said proteins were suitable candidates for use as a vaccine.

- As the essence of any vaccine is not only its safety, but also its ability to elicit a protective response in the targeted host, the skilled person would have been faced with the question whether a protective efficacy could be expected for such a vaccine;

- Although knowing that one should be cautious with predictions in this area of technology as a protective effect could not simply be based on the presence of neutralising activity (cf document (41) as expert opinion), the skilled person would have perceived the background art as being quite encouraging in this respect. In fact, document D) had shown that a vaccine containing HSV glycoproteins afforded protection, and document C) had shown that a preparation containing the same monoclonal antibody as the one used by Dr Pereira (HD1) for purifying by immunoaffinity the HSV gD-1 and gD-2 proteins, protected mice from a lethal HSV challenge with HSV-1 and HSV-2.

- Under these circumstances, the skilled person would have had either some expectations of success, or, at worst, no particular expectations of any sort, but only a "try and see" attitude. As stated in decision T 333/97 of 5 October 2000, the latter situation, however, does not equate with an absence of a reasonable expectation of success. As stated in decision T 338/97 of 7 February 2000, a reasonable expectation of success does not require certainty.

- Appellants I have not provided any evidence of any real obstacles or difficulties which would have crashed the skilled person's expectation that, by following the obvious route of using the purified gD-1 protein described by Dr Pereira, an effective vaccine would be obtained. The arguments put forward by appellants I based on the differences between passive and active immunisation and on the wide range of candidate glycoproteins which the skilled person could have selected, are not convincing in this respect. This is because the skilled person, while being aware of the different implications of passive vs active immunisation, would have derived from document C) mainly the encouraging information that passive transfer of the same monoclonal antibody as used by Dr Pereira to purify gD-1 provided protection, and that gD-1 was a suitable type-common subunit vaccine. In the light of this and of the "Lyon disclosure", the skilled person's options were in fact already reduced to gD-1 or gD-2.

11. As claim 1 is found to lack an inventive step, the main request and also the first auxiliary request, of which claim 1 is part, are not allowable under Article 56 EPC. Under these circumstances, it is not necessary to deal with any other issue in dispute between the parties.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The European patent is revoked.

The Registrar: The Chairperson:

U. Bultmann U. Kinkeldey