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D E C I S I O N
of 26 May 2004

Case Number: T 0893/02 - 3.3.8

Application Number: 91908003.6

Publication Number: 0522078

IPC: C12N 15/11

Language of the proceedings: EN

Title of invention:
GP75 as a tumor vaccine for melanoma

Patentee:
Sloan-Kettering Institute For Cancer Research

Opponent:
Aventis Pasteur Limited

Headword:
GP75/SLOAN-KETTERING

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - no"

Decisions cited:
T 0301/87, T 0950/99, T 1080/01, T 0939/92

Catchword:
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Case Number: T 0893/02 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 26 May 2004

Appellant: (Proprietor of the patent)	Sloan-Kettering Institute For Cancer Research 1275 York Avenue New York 10021 (US)
Representative:	Barth, Renate Dr. Vossius & Partner Postfach 86 07 67 D-81634 München (DE)
Respondent: (Opponent)	Aventis Pasteur Limited 1755 Steeles Avenue Toronto Ontario M2R 3T4 (CN)
Representative:	Lawrence, Malcolm Graham Hepworth, Lawrence, Bryer & Bizley Merlin House Falconry Court Baker's Court Epping Essex CM16 5DQ (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 12 June 2002 revoking European patent No. 0522078 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent No. 0 552 078 with the title "gp75 as a tumor vaccine for melanoma" was granted with 16 claims on the basis of the international application No. PCT/US91/01942.

Granted claims 1, 2, 5, 8 and 9 read as follows:

"1. An isolated nucleic acid molecule which encodes the amino acid sequence of a gp75 comprising the amino acid sequence asn-thr-val-glu-gly-tyr-ser-asp-pro-thr-gly-lys-tyr-asp-pro-ala-val, and met-phe-val-thr-ala-pro-asp-asn-leu-gly-tyr-thr-tyr-glu."

"2. An isolated cDNA molecule of the nucleic acid molecule of claim 1."

"4. A polypeptide having the amino acid sequence encoded by the isolated cDNA molecule of claim 3."

"5. An expression vector comprising a DNA sequence essential for replication and the cDNA molecule of claim 2 or 3."

"8. A vaccine comprising the expression vector of claim 5, an effective amount of an adjuvant and a pharmaceutically acceptable carrier."

"9. A vaccine comprising a polypeptide having the amino acid sequence of claim 4, an effective amount of an adjuvant and a pharmaceutically acceptable carrier."

Claim 3 related to the isolated cDNA molecule of claim 2 defined by part of its sequence. Claims 6 and 7 related to further embodiments of the expression vector of claim 5. Claims 10 and 11 related to further embodiments of the vaccines of claims 8 and 9. Claim 12 related to the use of the expression vector or the polypeptide of the preceding claims for the preparation of a pharmaceutical composition; and claims 13 to 16 related to further embodiments of that use.

II. An opposition was filed relying on the grounds in Article 100(a) to (c) EPC. The Opposition Division, which revoked the patent in its decision dated 12 June 2002, considered that the subject-matter of claim 4 of the main, second and third auxiliary requests then on file corresponding to claim 4 as granted, namely the gp75 protein, lacked novelty and that none of the claims of the first auxiliary request involved an inventive step. In particular, claims 7 to 15 corresponding to claims 8 to 16 as granted, were considered merely to express an obvious desideratum and to relate to matter which had not been shown to solve the underlying technical problem of "providing a vaccine effective against melanoma".

III. The Appellant (Patentee) filed a notice of appeal, paid the appeal fee and submitted a statement of grounds of appeal together with a main request containing eight claims.

Claims 1 and 3 thereof read as follows:

"1. A vaccine comprising an expression vector comprising a DNA sequence essential for replication and

an isolated cDNA molecule which encodes the amino acid sequence of a gp75 comprising the amino acid sequence asn-thr-val-glu-gly-tyr-ser-asp-pro-thr-gly-lys-tyr-asp-pro-ala-val, met-phe-val-thr-ala-pro-asp-asn-leu-gly-tyr-thr-tyr-glu, and asn-phe-asp-ser-thr-leu-ile-ser-pro-asn-ser-val-phe-ser, an effective amount of an adjuvant and a pharmaceutically acceptable carrier."

"3. A vaccine comprising a polypeptide having the amino acid sequence encoded by the cDNA molecule as defined in claim 2, an effective amount of an adjuvant and a pharmaceutically acceptable carrier."

Claim 2 related to the vaccine of claim 1 wherein the isolated cDNA molecule was defined by a large portion of its sequence. Claims 4 and 5 related to further embodiments of the vaccines of claims 1 to/or 3. Claim 6 related to the use of the expression vector or the polypeptide of the preceding claims for the preparation of a pharmaceutical composition. Claims 7 and 8 related to further embodiments of the use of claim 6.

IV. The Respondent (Opponent) filed written submissions in reply to the grounds of appeal.

V. The Board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal indicating its preliminary, non-binding opinion.

VI. The Appellant made written submissions in answer to this communication.

VII. On 21 and 24 May 2004 respectively, the Appellant and the Respondent informed the Board that they would not attend the oral proceedings appointed for 26 May 2004.

VIII. The following documents are referred to the present decision:

(16): Mattes, M.J. et al., Int.J.Cancer, 1983, Vol.32, pages 717 to 721,

(29): Hirschowitz, E.A. et al., Gene Therapy, 1998, Vol.5, pages 975 to 983,

(30): Weber, L.W. et al., J.Clin.Invest., 1998, Vol.102, No.6, pages 1258 to 1264,

(31): US 6 328 969.

IX. The Appellant's written submissions may be summarised as follows:

Documents filed on appeal; admissibility

Documents (29), (30) and (31) were filed in the appeal proceedings in response to the decision of the Opposition Division. The appeal had not been delayed. As the documents were prima facie highly relevant, they should be admitted in the proceedings.

Article 84 EPC; clarity and support

The claims for consideration by the Board were identical to the corresponding claims as granted and, therefore, they were not open to objection under Article 84 EPC.

Article 56 EPC; inventive step; claims 1 and 3
The closest prior art was document (16) which disclosed a protein similar or identical to the gp75 protein of the present invention.

The technical problem to be solved was the provision of means for treating tumors, in particular melanomas. The solution provided in claims 1 and 3 was vaccines based on gp75 encoding DNA /gp75 protein.

Document (16) taught away from using gp75 as a basis for vaccine development since it disclosed that gp75 was an intracellular antigen and that auto-antibodies to gp75 were extremely rare (abstract and page 719, right-hand column, third and fourth full paragraph). It was, thus, not obvious to try and develop a gp75 vaccine.

Furthermore, there was no reasonable expectation of success when purifying gp75 as the purification process was disclosed in document (16) as being "work in progress" and had not been further documented in the interval between the publication of document (16) and the priority date of the patent. In addition, even after the publication date of the patent, the purification of melanosomal proteins was considered particularly difficult.

The Opposition Division erred in law when it revoked the patent on the ground that it did not provide experimental evidence that gp75 could be used as an effective vaccine. Article 56 EPC did not require experimental proof of inventive step to be included in the specification. In addition, post-published document

(29) (page 975, end of right-hand column and page 979, left-hand column), document (30) (pages 1260, right-hand column and passage bridging pages 1263 and 1264) and document (31) (passage bridging columns 1 and 2) all reported immunisation based on gp75 vaccination. The general conclusions in document (31) (column 2, lines 50 to 57) about the necessity for the therapeutic differentiation antigen to be altered relative to the target were mere speculations. None of the documents provided any evidence that human gp75 could not be used for immunotherapy of human beings.

Inventive step of the claimed subject-matter could be acknowledged.

X. The Respondent's written submissions may be summarised as follows:

Documents filed on appeal; admissibility

The documents filed on appeal having been published and therefore known to the Appellant long before the date, they were filed, they should be ruled as inadmissible unless they were considered relevant to invalidity of the patent.

Article 84 EPC; clarity and support

The Board should exercise its jurisdiction to apply Article 84 EPC to the amended claims, although in large part identically worded to the granted claims, because in the context of a patent which was devoid of valid claims to gp75, its DNA and expression vectors containing such DNA, the facts were substantially different from those on which the Examining Division

had found the vaccine claims supported by the description.

Article 56 EPC; inventive step; claims 1 and 3
In its submissions dated 9 July 2003, the Respondent expressed the wish to rely on the arguments and submissions presented at the first instance. It was stated that: "in particular, the opponent reiterates its orally submitted arguments". In the Minutes of the oral proceedings before the Opposition Division, it is mentioned that at oral proceedings, the Respondents (then Opponents) referred to six different documents to argue their position on inventive step and that they concluded that "the skilled person was aware of the problem and was stimulated to employ the protein for pharmaceutical uses...". Furthermore, according to the Minutes, the Respondents had also "referred to the preliminary opinion of the Opposition Division as detailed in the summons for oral proceedings. The vaccine and use claims were a mere desideratum and only theoretically addressed in the patent publication as granted."

XI. The Appellant requested in writing that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed on 22 October 2002.

Reasons for the decision

Documents filed on appeal

1. In the Board's judgment, documents (29), (30) and (31) were filed with the statement of grounds of appeal in answer to the reasoning which led the Opposition Division to revoke the patent on the basis that the claimed effect (gp75 ability to induce protective immunity against melanoma) which might have justified acknowledging inventive step had not been proved. These documents are prima facie concerned with the potential of gp75 to induce protective immunity. Thus, in accordance with the case law (eg. decisions T 1080/01 of 24 October 2003 and T 950/99 of 11 November 2002), they are admitted into the proceedings.

Article 123(2)(3) EPC, Article 84 EPC; formal requirements

2. Claim 1 now on file corresponds to granted claim 8 (dependent on granted claim 5 itself dependent on granted claim 2), the cDNA being additionally characterised by the fact that it encodes the stretch of amino acids asn-phe-asp-ser-thr-leu-ile-ser-pro-asn-ser-val-phe-ser (see Sections I and III, supra). The latter feature is found in Figure 2 and claim 5 of the application as filed. The combination of the three sequence stretches to identify the cDNA results from the fact that they are three fragments of the same gp75 molecule. The scope of the claim is, thus, narrower than that of granted claim 8. A vaccine according to claim 1 is the subject-matter of originally filed claim 14.

3. Claim 2 corresponds to granted claim 8 (dependent on granted claim 5 itself dependent on granted claim 3) and claims 3 to 8 respectively correspond to granted claims 9 to 11 and 14 to 16 (Article 123(3) EPC). Although Article 100(c) EPC was cited as a ground of opposition, it was not against any of these claims. The Board is satisfied that they do not contain subject-matter which extends beyond the content of the application as filed.

4. The requirements of Article 123(2)(3) EPC are fulfilled.

5. As mentioned above and also acknowledged by the Respondents in its answer to the grounds of appeal, claims 2 to 8 "have in substance identical wording to the granted claims". In accordance with the case law, they are not open to an objection under Article 84 EPC (see eg. decision T 301/87, OJ EPO 1990, 335). The feature added in claim 1 to characterise the cDNA encompassed within the claimed vaccine does not render the claim unclear. Furthermore, the claim is supported by the description of the patent specification (page 4, lines 39 to 41 together with page 5, lines 21 to 34 and Figure 2). The requirements of Article 84 EPC are fulfilled by claim 1.

Article 56 EPC; inventive step; claims 1 and 3

6. The issue of inventive step arises, in particular, in relation to the subject-matter of claims 1 and 3 respectively directed to a vaccine comprising an expression vector carrying a gp75 cDNA and to a vaccine comprising a gp75 polypeptide.

7. The closest prior art is document (16). This document discloses an antigen with a molecular weight of 70.000 which is precipitated by auto-antibodies present in the serum of a patient suffering from melanoma (page 718, right-hand column, Results). This antigen, named PAA, is said to be specific to pigmented melanomas yet probably not located at the surface of melanoma cells. Furthermore, auto-antibodies to PAA were only found in one out of 96 sera of melanoma patients (abstract, page 719, right-hand column, third and fourth full paragraphs).

8. In the "Background of the invention " part of the patent in suit (page 2, lines 37 to 44), document (16) is cited as disclosing the immunoprecipitation of a gp75 antigen from autologous melanoma cells by serum antibodies of a patient with metastatic melanoma. As PAA is the only antigen which is isolated in this manner in document (16), it is taken that PAA and gp75 are, in fact, the same antigen. In this context, it is worth noticing that the Appellants did not challenge the Opposition Division's conclusion that the then claimed gp75 molecule was not novel over the disclosure of PAA in document (16).

9. Starting from the closest prior art, the problem to be solved can be defined as finding means to fight melanomas.

10. Although document (16) does not mention any form of therapy in relation to melanomas, formulating this problem starting from its teaching is not in itself inventive because at the priority date (1990), it was known as admitted by the patentee, that the course of

metastatic melanoma could be changed and that melanosomal antigens were recognized by the immune system (see "Background of the invention", patent in suit, page 2, lines 32 to 37).

11. The solutions provided in claims 1 and 3 are vaccines comprising either an expression vector carrying the gp75 cDNA or the gp75 molecule *per se*.

12. The Board agrees with the Appellants that the technical effect of inducing immunoprotection against melanoma would probably not be expected by the skilled person to result from human gp75 cDNA expression nor from the presence of the human gp75 protein in a subject-individual since document (16) teaches that gp75 is not a protein present at the surface of melanoma cells and that human anti-gp75 auto-antibodies are only very rarely found in the sera of melanoma patients. Thus, if the effect of inducing immunoprotection had been proven, it might have justified acknowledging inventive step to vaccines containing the human gp75 cDNA expression vector or the human gp75 protein as an active ingredient.

13. However, the patent in suit fails to provide any evidence to this effect. The gp75 protein is not tested in any in vitro or in vivo model system. As for the expression vector containing the gp75 cDNA, it is mentioned on page 3, lines 54 to 56 as being "vaccinia virus or preferably an Imclone vector". Yet, no data are presented relative to the cloning of that cDNA in such a vector, a fortiori, of course, it is not shown that the gp75 protein was ever expressed in recombinant

form nor was a recombinant vector carrying gp75 cDNA ever tested for its ability to induce immunoprotection.

14. Thus, the technical effect on the basis of which the Appellant argues that inventive step should be acknowledged has not been established in the patent in suit. To remedy this deficiency, post-published documents (29), (30) and (31) were filed which show that gp75 or gp75 cDNA expression induce immunoprotection at least when these molecules present specific structural characteristics and/or under special circumstances. This the Appellant took as being proof that gp75 or a vector for gp75 cDNA expression could be used as a vaccine.

15. It is stated in document (31) (column 2, lines 50 to 57) published 11 years after the priority date: "*It has been found experimentally, however, that administration of syngeneic differentiation antigens expressed in cells of the same species as the subject-individual are not effective for stimulating an immune response.*" In the same manner, document (29) (page 979, right-hand column) discloses that a modified form of murine gp75 protein or the human gp75 protein (which may be considered as an example of a modified murine gp75 as it is 80.2% homologous to said protein) will induce protective immunity in mice **but that non-modified wild-type murine gp75 will not**. This teaching can also be derived from document (30) (abstract). If any conclusion is to be drawn from the disclosures of these documents, it is that a composition comprising human gp75 (as the vaccine of claim 3) would not be expected to induce immunoprotection in humans, the gp75 protein being syngeneic to the human melanoma.

16. Document (29) is the only document concerned with an expression vector carrying gp75 cDNA. It describes an adenovirus mediated delivery of murine gp75 cDNA to mice and teaches that induction of protective immunity against syngeneic tumors ensues. Yet, it is mentioned twice in the article that the adenovirus was chosen on purpose: page 975, right-hand column: "*based on the knowledge that Ad-mediated in vivo transfer of transgenes often evokes both a cellular and a humoral immune response against the transgene..."* and page 979, left-hand column: "*The reasons the Ad vector gene-based gp75 vaccine is capable of inducing protective immunity to an autologous antigen remain to be evaluated but differences from peptide-vaccines may result from the protracted expression of antigen following gene delivery* ***in the setting of an inflammatory response known to result from Ad vector infection***" (emphasis added by the Board). Thus, the teachings of document (29) are that the immunoprotection resulting from the in vivo expression of the gp75 cDNA present in the adenovirus appears to be in part due to the metabolic changes caused by the presence of this specific vector in which the cDNA was cloned. Accordingly, it cannot be informative as to the ability of gp75 cDNA to trigger a protective immune response when expressed from any other expression vectors (such as those envisaged in the patent in suit).

17. Thus, it must be concluded that while the patent in suit provides no evidence of the technical effect relied on to show that the claimed subject-matter was unexpected, post-published documents show that this technical effect either does not exist or that it is

achievable only under very specific conditions which are not described in the patent in suit. In the Board's judgment, it is not possible to acknowledge inventive step for subject-matter which, in the absence of concrete technical elements disclosed in the patent specification, does not differ from an obvious goal to achieve. In accordance with the case law, if the inventive step of a claimed invention is based on a given technical effect, the latter should, in principle, be achievable over the whole area claimed (see eg. T 939/92, OJ EPO 1996, 309). As this is not the case here since the patent specification does not demonstrate the achievement of the desired technical effect in any area of the claims, inventive step must be denied.

18. In the grounds of appeal, it was also argued that purifying the gp75 antigen to the required degree of purity could not have been achieved with a reasonable expectation of success. No evidence was provided to show that any difficulties were encountered when purifying the protein nor is there any mention in the patent in suit of difficulties having to be overcome. The argument, thus, does not hold good. And besides, it is not a relevant argument in view of the fact that the problem to be solved has not in fact been solved by the claimed subject-matter (points 13 to 17 supra).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani