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**Datasheet for the decision  
of 15 February 2012**

**Case Number:** T 1496/08 - 3.3.04

**Application Number:** 99945967.0

**Publication Number:** 1117421

**IPC:** A61K 38/17, A61K 38/18,  
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C07K 14/71, C12N 15/63,  
C12N 5/16, C12N 15/12

**Language of the proceedings:** EN

**Title of invention:**  
Methods for therapeutic vaccination

**Patentee:**  
BN ImmunoTherapeutics, Inc.

**Opponent:**  
GlaxoSmithKline Biologicals s.a.

**Headword:**  
Therapeutic vaccination/BN IMMUNOTHERAPEUTICS, INC.

**Relevant legal provisions:**  
EPC Art. 83  
RPBA Art. 12(1), 12(4), 13(3)

**Keyword:**  
"Admissibility in appeal proceedings of submissions which  
could have been made at first instance (no)"  
"Main request - sufficiency of disclosure (no)"  
"Auxiliary request 1 - sufficiency of disclosure (yes)"

**Decisions cited:**  
T 0019/90, T 0792/00, T 0609/02, T 0390/07

**Catchword:**  
-



Case Number: T 1496/08 - 3.3.04

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.04  
of 15 February 2012

**Appellant:** GlaxoSmithKline Biologicals s.a.  
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**Decision under appeal:** Interlocutory decision of the Opposition  
Division of the European Patent Office posted  
28 May 2008 concerning maintenance of European  
patent No. 1117421 in amended form.

**Composition of the Board:**

**Chairman:** C. Rennie-Smith  
**Members:** R. Morawetz  
B. Claes

## Summary of Facts and Submissions

- I. This is an appeal by the opponent (hereinafter "appellant") against the interlocutory decision of the opposition division whereby European patent No. EP 1117421 has been maintained in amended form.
- II. The patent at issue has the title "Methods for therapeutic vaccination". It was granted on European application No. 99 945 967.0 which originated from international application PCT/DK1999/000525 published as WO 00/20027.
- III. The patent was granted with a set of 88 claims of which claims 1, 46, 49, 50, 62, 65, 68, 71, 72, 73, 78, 79, 80, and 81 were independent. Only claims 1, 46, 62, 65 and 68 are of relevance to this decision. These claims read:
- "1. Use of
- 3) at least one CTL epitope derived from a cell-associated polypeptide antigen that is weakly immunogenic or non-immunogenic in an animal, and
- 4) at least one first T-helper lymphocyte (T<sub>H</sub>) epitope which is foreign to the animal,
- or of
- 3) at least one nucleic acid fragment encoding a CTL epitope derived from a cell-associated polypeptide antigen that is weakly immunogenic or non-immunogenic in an animal, and
- 4) at least one first nucleic acid fragment encoding a T-helper lymphocyte (T<sub>H</sub>) epitope which is foreign to the

animal,

or of a non-pathogenic microorganism or virus which carries a nucleic acid fragment which encodes and expresses

- 3) at least one CTL epitope derived from a cell-associated polypeptide antigen that is weakly immunogenic or non-immunogenic in an animal, and
- 4) at least one first T-helper lymphocyte ( $T_H$ ) epitope which is foreign to the animal,

for the preparation of an immunogenic composition for treating a pathological process selected from a tumour, a viral infection and an infection caused by an intracellular parasite or bacterium, by effecting, in the animal, simultaneous presentation by a suitable antigen-presenting cell (APC) of the at least one CTL epitope and the at least one first  $T_H$  epitope and thereby inducing a specific cytotoxic T-lymphocyte (CTL) response in the animal against cells carrying the cell-associated polypeptide antigen on their surface or harbouring the cell-associated [sic] antigen in their intracellular compartment, wherein the cell-associated polypeptide antigen is selected from a tumour-associated polypeptide antigen, a self protein, a viral polypeptide antigen, and a polypeptide antigen derived from an intracellular parasite or bacterium.

46. A method for selection of an immunogenic analogue of a cell-associated polypeptide antigen which is weakly immunogenic or non-immunogenic in an animal, said immunogenic analogue being capable of inducing a CTL response in the animal against cells displaying an

MHC Class I molecule bound to an epitope derived from the cell-associated polypeptide antigen, the method comprising

- a) identifying at least one subsequence of the amino acid sequence of the cell-associated polypeptide antigen which does not contain known or predicted CTL epitopes,
- b) preparing at least one putatively immunogenic analogue of the cell-associated polypeptide antigen by introducing, in the amino acid sequence of the cell-associated polypeptide antigen, at least one T<sub>H</sub> epitope foreign to the animal in a position within the at least one subsequence identified in step a),
- and c) selecting the/those analogues prepared in step b) which are verifiably capable of inducing a CTL response in the animal,

wherein the cell-associated polypeptide antigen is selected from a tumour-associated polypeptide antigen, a self-protein, a viral polypeptide antigen, and a polypeptide antigen derived from an intracellular parasite or bacterium.

62. An analogue of human PSM which is immunogenic in humans, said analogue comprising a substantial part of all known and predicted CTL and B-cell epitopes of PSM and including at least one foreign T<sub>H</sub> epitope as defined in any of claims 16-19.

65. An analogue of human Her2 which is immunogenic in humans, said analogue comprising a substantial part of all known and predicted CTL and B-cell epitopes of Her2 and including at least one foreign T<sub>H</sub> epitope as defined in any of claims 16-19.

68. An analogue of human/murine FGF8b which is immunogenic in humans, said analogue comprising a substantial part of all known and predicted CTL and B-cell epitopes of FGF8b and including at least one foreign T<sub>H</sub> epitope as defined in any of claims 16-19."

IV. The patent was opposed under Article 100(a) EPC, on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), Article 100(b) EPC and Article 100(c) EPC. The opponent requested revocation of the patent in its entirety.

V. The opposition division decided that claim 1 of the main request before it failed the requirements of Article 123(2),(3) and Rule 80 EPC but that claims 1 to 81 of auxiliary request 1 filed at the oral proceedings met all requirements of the EPC.

Claim 1 of auxiliary request 1 before the opposition division (which corresponds to the main request before the board) reads:

"1. Use of

a) an adjuvant and a first analogue of a cell-associated polypeptide antigen, said first analogue comprising known and predicted CTL epitopes recognized by at least 50% of the MHC-I haplotypes recognizing all known and predicted CTL epitopes in the cell-associated polypeptide antigen that is weakly immunogenic or non-immunogenic in an animal, and said first analogue further comprising

at least one first T-helper lymphocyte (TH) epitope which is foreign to the animal, which is promiscuous and which is introduced in the amino acid sequence of

the cell-associated polypeptide antigen by means of substitution and/or deletion and/or insertion,

or of

b) at least one nucleic acid fragment encoding a CTL epitope derived from a cell-associated polypeptide antigen that is weakly immunogenic or non-immunogenic in an animal, and at least one first nucleic acid fragment encoding a T-helper lymphocyte (TH) epitope which is foreign to the animal, wherein, when said nucleic acid fragments encode said CTL and said TH epitopes so that they are part of the same polypeptide, said CTL epitopes are recognized by at least 50% of the MHC-I haplotypes recognizing all known and predicted CTL epitopes in the cell-associated polypeptide antigen

or of

c) a non-pathogenic microorganism or virus which carries a nucleic acid fragment which encodes and expresses

at least one CTL epitope derived from a cell-associated polypeptide antigen that is weakly immunogenic or non-immunogenic in an animal, and

at least one first T-helper lymphocyte (TH) epitope which is foreign to the animal, wherein, when said nucleic acid fragments encode said CTL and said TH epitopes so that they are part of the same polypeptide, said CTL epitopes are recognized by at least 50% of the MHC-I haplotypes recognizing all known and predicted CTL epitopes in the cell-associated polypeptide antigen,

for the preparation of an immunogenic composition for treating a tumour by effecting simultaneous presentation by a suitable antigen-presenting cell of the at least one CTL epitope and the at least one first TH epitope by administering to said animal said immunogenic composition and thereby inducing a specific cytotoxic T-lymphocyte (CTL) response in the animal against cells carrying the cell-associated polypeptide antigen on their surface or harbouring the cell-associated antigen in their intracellular compartment, wherein the cell-associated polypeptide antigen is a tumour-associated polypeptide antigen or a self protein."

Claims 39, 55, 58, and 61 of auxiliary request 1 were identical to claims 46, 62, 65 and 68, respectively, as granted.

VI. The minutes of the oral proceedings before the opposition division state (see page 2, lines 4-10), in the context of the discussion of a first auxiliary request 1, that:

*"The O [opponent] had no objections under Article 123(2) or (3) EPC.*

...

*Turning to Article 84 EPC the C [chairman] reminded the O [opponent] that the only amendment being open for objections under Article 84 EPC was the replacement of 90% by 50% of the MHC-I haplotypes and the introduction of a TH epitope into the amino acid sequence by means of substitution and/or deletion and/or insertion.*

*The O [opponent] indicated that they did not want to*

*raise an objection under Article 84 EPC.*" (Insertions in square brackets by the board).

After the opposition division had pointed out that the request comprised an unallowable disclaimer the proprietor submitted a new auxiliary request 1. The minutes of the oral proceedings before the opposition division (see page 4, line 5) report that:

*"The O [opponent] refrained from raising further objections under Article 84 or 123 EPC".*

The patent was maintained on the basis of this request.

VII. The appealed decision (see page 9, 5th paragraph) states:

*"The parties and the OD [opposition division] agreed in that the amendments carried out in the claims of the first Auxiliary Request [which corresponds to the main request before the board] fulfilled the requirements of Art. 123(2) EPC, Art. 123(3) EPC, Rule 80 EPC and Art. 84 EPC."*

VIII. In a communication which was annexed to the summons to oral proceedings the board informed the parties of its preliminary view on the admissibility of the appellant's submissions relating to the provisions of Articles 123(2) and 84 EPC, and of its preliminary view on the issues of sufficiency of disclosure, novelty and inventive step with regard to the claims of auxiliary request 1 then on file.

IX. In response the respondent filed auxiliary requests 1 to 4 with its letter dated 13 January 2012. Previous auxiliary request 1 which had been upheld by the opposition division became the main request.

X. The appellant confirmed in its letter of 16 January 2012 that it would attend the oral proceedings but did not file any further written submissions.

XI. At the oral proceedings held before the board on 15 February 2012 the respondent withdrew auxiliary requests 1 to 3 and filed a corrected version of previous auxiliary request 4 as auxiliary request 1.

Claim 1 of auxiliary request 1 was identical to claim 46 as granted and claims 7, 11, and 14 corresponded to claims 62, 65, and 68 as granted, respectively (see section III, above).

XII. The appellant (opponent) requested that the decision under appeal be set aside and the patent be revoked.

The respondent (patentee) requested that the appeal be dismissed or that the decision under appeal be set aside and that the patent be maintained on the basis of auxiliary request 1 filed during the oral proceedings.

XIII. The following documents are referred to in this decision:

(01) WO 95/05849

(22) Steinaa L. et al., The Journal of Immunology, 2005, 175: 329-334

XIV. The appellant's arguments insofar as they are relevant to the present decision, may be summarised as follows:

*Main request*

*Admissibility of the submissions under the provisions of Articles 123(2) and 84 EPC in the appeal proceedings.*

The terms "introduced in" and "known and predicted" led to a lack of clarity of claim 1 of the main request as did the removal of the term "and/or addition". Claim 1 of the main request contravened Article 123(2) EPC because the term "introduced in" found no basis in the application as originally filed and because claim 1(a) contained a selection of features from multiple lists. The opposition division had not allowed the opponent to present arguments at oral proceedings under Article 84 EPC with regard to the term "introduced in...". During the oral proceedings before the board the appellant merely referred to its written submissions.

*Sufficiency of disclosure*

Claim 1 was a second medical use claim. The mechanism underlying the therapeutic application in claim 1 was the breaking of tolerance. The patent in suit provided a prophetic statement but no evidence showing that the claimed constructs had any effect on tolerance or could be used to treat a tumour. In particular example 5 did not show the breaking of tolerance. Pursuant to decision T 609/02 (points 8, 9, 13 of the reasons) the respondent could not rely on post-published document (22) as evidence. It was necessary that the patent provide some information in the form of, for example,

experimental tests to the effect that the claimed compound had a direct effect on the metabolic mechanism specifically involved in the disease.

*Auxiliary request 1*

*Admissibility in the appeal proceedings*

The respondent should have set out its complete case when responding to the appeal. Auxiliary request 1 constituted a different case and the respondent had failed to justify the late submission of this request. Revocation of the patent had always been requested although the argumentation had focused on the second medical use claim. The request should not be admitted in the appeal proceedings.

*Amendment of the appellant's case*

New arguments should be allowed as the second medical use claim was no longer part of the request. Throughout the proceedings all claim requests had failed following an attack on the second medical use claim. The legal framework of the opposition extended to all claims of the main request. The appellant should not be criticised for not submitting arguments on claims other than the second medical use claim earlier.

*Sufficiency of disclosure*

Since the breaking of tolerance had not been shown in the patent in suit, the same arguments as for the main request applied to auxiliary request 1. The method according to claim 1 was based on the hypothesis that

insertion of a T<sub>H</sub> epitope into a T<sub>CTL</sub> epitope could increase immunogenicity. The patent specification provided neither guidance nor evidence that showed that this method worked. The skilled person had no reasonable expectation of success as he could run the screening forever and not find a single immunogenic analogue. In reply to the question by the board whether it was an undue burden to perform the method, i.e. to carry out the individual steps of the method or to achieve a result, the appellant stated that if the skilled person could never select a suitable analogue than it was not really a method for selection. It was submitted that this argumentation also applied to independent claims 7, 11 and 14.

- XV. The respondent's arguments insofar as they are relevant to the present decision, may be summarised as follows:

*Main request*

*Admissibility of the submissions under the provisions of Articles 123(2) and 84 EPC in the appeal proceedings.*

The objections raised in the grounds of appeal had not been raised against auxiliary request 1 before the opposition division, now the main request.

*Sufficiency of disclosure*

The requirements set forth in Article 83 EPC specified that the application must put the skilled person in a position that enabled him to carry out the claimed invention. The EPC did not require the presence of a working example and no experimental evidence was

required. Example 5 of the patent in suit explicitly reported that tolerance towards OVA was successfully broken in a mouse model using the claimed technology. The general concept of immunizing against cancer-specific antigens was already well-described in the art. It was accepted that if an effective immune response could be induced against such antigens, then cancer cells could be directly targeted by the immune system. It was also the prevailing opinion that induction of a CTL response against cancer cells was desirable, if not a necessity in order to target many cancer forms.

Decision T 609/02 was not applicable as the underlying case was different. In the case underlying decision T 609/02 there were only theoretical considerations supporting a clinical effect of the drug recited in the claims (*cf.* decision T 609/02, point 5 of the reasons). In the present case the tumour antigens were not functionally defined but had been identified. The patent in suit disclosed preliminary results which demonstrated that the claimed analogues of self-proteins were indeed capable of breaking CTL tolerance.

Pursuant to decision T 792/00, a prophetic example was sufficient as long as it was reproducible. As example 5 indicated that parallel experiments were ongoing at the time of filing of the patent in suit, the respondent could rely on the results from these experiments reported in document (22).

*Auxiliary request 1*

*Admissibility in the appeal proceedings*

The claims had been limited to the subject-matter of claims 39 to 44 and 55 to 81 of the main request. The patentability of the subject-matter of these claims had never been the subject of any attacks set forth in a submission in the opposition and appeal proceedings.

*Amendment of the appellant's case*

Neither novelty, inventive step, sufficiency of disclosure, nor added matter in relation to these claims had been the subject of any discussion, generic or specific, during the opposition and appeal proceedings. The board should therefore exercise its discretion to hold inadmissible any facts, evidence or requests presented by the appellant that related to the subject-matter of these claims.

*Sufficiency of disclosure*

Claim 1 related to a screening method which was a step further away from the subject-matter of claim 1 of the main request. The absence of a demonstration that tolerance can be broken was irrelevant to this claim. The patent in suit provided enough guidance for the skilled person to carry out the steps of the method. The product claims did not require CTL induction but only that the analogue be immunogenic in humans. Immunogenicity could be provided by T<sub>H</sub> epitopes and B-cell epitopes which were present in the analogues.

## **Reasons for the Decision**

### *Main request*

#### *Admissibility of appellant's written submissions of facts under the provisions of Articles 123(2) and 84 EPC*

1. The appellant's statement of grounds of appeal contained submissions of facts regarding alleged deficiencies of claim 1 of the main request under Article 84 and Article 123(2) EPC. These submissions fall into two groups. Firstly, those submissions which had been made by the appellant during the opposition proceedings but had been dropped before the opposition division reached its decision. Secondly, such submissions which could have been made during the opposition proceedings but were not.
2. As regards the first group, the board notes that the appellant had made submissions under Article 84 EPC concerning the feature "introduced in" in its letter dated 20 December 2007 (see pages 2 and 4). In the light of the minutes of the oral proceedings (see section VI, above) it is however established that these submissions were later not pursued further in the first instance proceedings. In that context it is of no consequence that the feature in question was discussed in the context of a claim request which was later abandoned and replaced by auxiliary request 1 (which corresponds to the main request before the board).
3. The appellant's argument that the opposition division would not allow it to present arguments at oral proceedings under Article 84 EPC with regard to the

- term "introduced in" is contradicted by the evidence on file (see section VI, above), and must thus fail.
4. Regarding the features "50%" and "known and predicted CTL epitopes" the board notes that the appellant made submissions under Article 84 EPC concerning these features during the opposition proceedings in its letter dated 23 August 2006. These submissions were however not pursued in the first instance proceedings. Thus, when given the opportunity in the first instance oral proceedings, the appellant refrained from making any submissions under Article 84 EPC in relation to then auxiliary request 1 which corresponds to the main request before the board (see sections VI and VII, above).
  5. By the time the opposition division decided on the auxiliary request 1, the parties and the opposition division had agreed that the amendments to the claims of auxiliary request 1 fulfilled the requirements of Article 84 EPC (see section VII, above). From the file history it is also apparent that the appellant did not object to the content of the minutes or of the decision as notified to it.
  6. From the above the board concludes that the appellant had made submissions of facts under Article 84 EPC relating to the features "introduced in", "50%", and "known and predicted CTL epitopes" of claim 1 in the first instance proceedings but had not pursued them. These submissions were thus not dealt with in the decision under appeal.

7. The purpose of the appeal procedure is to give a judicial decision upon the correctness of a decision taken by a department of first instance. Pursuant to Article 12(4) RPBA it is therefore within the power of the board as a review instance to hold inadmissible facts, evidence or requests which could have been presented in the first instance proceedings.
  
8. In this context the board is aware of decision T 390/07 of 20 November 2008 in which it was held that a claim request was inadmissible in appeal proceedings if it had been filed in first instance proceedings and later withdrawn to avoid a decision (decision T 390/07, points 2 and 3 of the reasons and decisions cited therein). It was the purpose of appeal proceedings to review what has been decided at first instance and not to review what has not been decided. The board considers that pursuant to the same rationale, submissions of fact which had been presented but not pursued in the first instance proceedings and which are thus not dealt with in the impugned decision, as in the present case, are inadmissible in appeal proceedings. For these reasons, the board has decided to exercise its power under Article 12(4) RPBA not to admit the first group of submissions under Article 84 EPC in the appeal proceedings.
  
9. As regards the second group (see point 1 above), the appellant has submitted that the feature "introduced in" in claim 1 and the alleged selection from several lists that had taken place in claim 1(a) to (c) of the main request violated Article 123(2) EPC and that removal of the term "and/or addition" violated Article 84 EPC. The appellant has not provided any

reasons why these submissions were not made in the first instance proceedings and no such reason is otherwise apparent, considering that the claims of the main request before the board are identical to the claims of auxiliary request 1 before the opposition division.

10. Since the appellant had been given the opportunity by the opposition division to comment under Articles 123(2) and 84 EPC on the claims in question (see section VI, above) and submissions under these articles could and thus should have been presented in the first instance proceedings, the board decides to exercise its power under Article 12(4) RPBA not to admit these submissions in the appeal proceedings.

*Sufficiency of disclosure*

11. Claim 1 is formulated as a "second (further) medical use" or "Swiss-type" claim and relates to the use of a) polypeptide constructs, b) nucleic acid constructs or c) genetically modified live vaccine constructs for the preparation of an immunogenic composition for treating a tumour (see section V above). These constructs are referred to in the patent as autovaccine constructs or AutoVac constructs (see e.g. paragraphs [0031], [0102], and examples of the patent in suit).
12. The patent in suit discloses (see paragraph [0030]) that:

*"We have based the present invention on our novel theory that self-proteins containing foreign MHC class II epitopes, following exogenous uptake, can gain*

*access into the MHC class I antigen processing pathway of e.g. macrophages and dendritic cells. In this way a strong CTL response against subdominant epitopes in the self-protein could be induced. Alternatively, genes encoding modified tumour antigens could be administrated as nucleic acid vaccines eventually also leading to MHC class II as well as MHC class I mediated immune responses."*

It is further proposed (see paragraph [0031] of the patent in suit) that:

*"Using the autovaccine constructs and vaccination protocol mentioned above the modified tumour antigen could be presented by MHC class I as well as by MHC class II molecules on professional antigen presenting cells. Co-presentation of subdominant self-epitopes on MHC class I and immunodominant foreign epitopes on MHC class II molecules would mediate a direct cytokine help from activated MHC class II restricted T-helper cells to MHC class I restricted CTLs (Fig. 2). This will in our opinion lead to a specific break of the T cell autotolerance towards the tumour antigen and this is exactly what is desired in cancer immunotherapy."*

Figure 2 illustrates the AutoVac concept for inducing a CTL response, i.e. inserted foreign immunodominant T cell epitopes presented on MHC class II activate T helper cells and CTL's recognising subdominant self-epitopes presented on MHC class I are activated by the adjacent activated T helper cell (see Figure 2 and paragraph [0038] of the patent in suit).

13. These disclosures establish that the claimed invention is based on a theory developed by the inventors. This has not been contested by the respondent. The theory finds its basis on the one hand in previous findings of the respondent in the context of experiments relating to autoantibody induction reported in document (1) and on the other hand in a mechanism for CTL activation which has been proposed in the literature shortly before the priority date of the patent in suit (*cf.* paragraphs [0023] to [0029] of the patent in suit).

However, as acknowledged in the patent in suit in paragraph [0029]:

*"As mentioned above, CTL's also require specific T cell help, although the mechanism for this is still not clear."*

14. For the requirement of sufficiency of disclosure to be fulfilled it is required that the European patent application or European patent discloses the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC, Article 100(b) EPC). According to established jurisprudence (*cf.* T 609/02 of 27 October 2004, point 9 of the reasons), where a therapeutic application is claimed in the form of the use of a substance or composition for the manufacture of a medicament for a defined therapeutic application, as in the present case, attaining the claimed therapeutic effect is a functional technical feature of the claim. As a consequence, in order to meet the requirements of sufficiency of disclosure, unless this is already known to the skilled person at the relevant date, the

application must disclose the suitability of the product to be manufactured for the claimed therapeutic application. It is required that the patent provides some information in the form of, for example, experimental tests, to the effect that the claimed compound has a direct effect on a metabolic mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se. Post-published evidence may be taken into account, but only to back-up the findings in the patent application in relation to the use of the ingredient as a pharmaceutical, and not to establish sufficiency of disclosure on its own.

15. When assessing the present invention in the above perspective, the therapeutic application is the treatment of a tumour and the mechanism specifically involved in the disease is the T cell autotolerance towards the tumour antigen. It is the aim of the present invention to break this T cell autotolerance by effecting simultaneous presentation by a suitable antigen-presenting cell of at least one CTL epitope and at least one first T<sub>H</sub> epitope by administering an immunogenic composition comprising an autovaccine construct as defined in claim 1 a) to c) and thereby inducing a specific CTL response in the animal against cells carrying the cell-associated polypeptide antigen on their surface or harbouring the cell-associated antigen in their intracellular compartment.
  
16. Example 5 of the patent in suit, which is the only example relating to breaking of T cell autotolerance, discloses that the potential advantage of the invention for induction of self-reactive CTLs was being

investigated in ovalbumin transgenic mice.

Two ovalbumin AutoVac constructs were produced. In these constructs the naturally occurring human T-cell epitope from tetanus toxoid, P30, was inserted into ovalbumin. It was the intention to immunize four different transgenic mouse lines with different ovalbumin expression levels and tolerance, i.e. RIP-OVA<sup>low</sup>, RIP-OVA<sup>int</sup>, RIP-OVA<sup>high</sup> and RIP-mOVA mice, with these AutoVac constructs. In these mice, only P30 would be foreign whereas ovalbumin would be a self-antigen. This situation should therefore constitute a true autovaccination for CTL induction towards ovalbumin.

However, the patent specification reports that preliminary results obtained in RIP-OVA<sup>low</sup> mice having the lowest degree of "peripheral tolerance" to ovalbumin demonstrated that **both** the ovalbumin with inserted P30 and the naturally occurring ovalbumin molecules were capable of inducing CTL responses.

The RIP-OVA<sup>low</sup> mice were thus not tolerant to ovalbumin, as both the ovalbumin with inserted P30 and the naturally occurring ovalbumin molecules were capable of inducing CTL responses in these mice. Indeed, if the mice would have been tolerant, the naturally occurring ovalbumin should not have been capable of inducing a CTL response. No results are reported in the patent in suit for the other mouse models.

17. The board concludes therefore that example 5 fails to show the suitability of the proposed autovaccine constructs for breaking T cell autotolerance and a *fortiori* for the treatment of tumours. No other data

- that would reflect the suitability of the autovaccine constructs for the claimed therapeutic effect are provided in the patent in suit. There is moreover no evidence that the CTL cells, if they were generated, would not be rendered non-responsive or anergic by the tumour (*cf.* paragraph [0015] of the patent in suit).
18. The respondent's contention that example 5 explicitly reported that tolerance towards OVA was successfully broken in the RIP-OVA<sup>low</sup> mouse model using the claimed technology must therefore fail as it is contradicted by the experimental results reported in the patent in suit (see example 5 and point 16, above). Thus, as in the case underlying decision T 609/02 (*supra*), the patent specification provides no evidence at all relating to the invention in claim 1.
19. The respondent's arguments which were based on document (22) must likewise fail because, in a case like the present one, post-published evidence cannot be used to remedy the fundamental insufficiency of disclosure which existed at the effective date of the patent in suit (*cf.* decision T 609/02, *supra*, points 8, 9, and 13 of the reasons). Post-published evidence, such as that provided by document (22), may be taken into account only to back-up the findings in the patent as filed, and not to establish sufficiency of disclosure on its own. As no relevant findings in this respect were contained in the patent in suit, the disclosure of document (22) has to be disregarded.
20. Following the rationale of decision T 609/02 (*supra*, see point 14 above) it remains to be considered if the prior art provides the skilled person with information

- which would allow him/her to conclude that an immunogenic composition comprising autovaccine constructs as defined in claim 1 is suitable for the treatment of tumours.
21. The respondent submitted that tumour antigens were known to the skilled person at the relevant date and the general concept of immunizing against cancer-specific antigens was already well-described in the art in the sense that there was agreement that if an effective immune response could be induced against such antigens, then cancer cells could be directly targeted by the immune system. There was also agreement in the prior art that induction of a CTL response against cancer cells was desirable, if not a necessity, in order to target many cancer forms.
22. That induction of a CTL response would be desirable for the treatment of a tumour is not contested. The argument fails however because there is no evidence on file that at the relevant date the skilled person was aware of information which lead him/her to conclude that it was technically plausible that the autovaccine constructs as defined in claim 1 a) to c) are suitable for inducing a CTL response against cancer cells and thus for the treatment of tumours.
23. Finally, the respondent submitted that pursuant to decision T 792/00 of 2 July 2002, a prophetic example was sufficient as long as it was reproducible. As example 5 indicated that parallel experiments were ongoing at the time of filing of the patent in suit it could rely on the results from these experiments reported in document (22). The board considers that the

rationale of decision T 792/00 is not applicable to the present case as that decision is concerned with sufficiency of disclosure of a product claim and not a second medical use claim in which the therapeutic effect is a functional feature of the claim.

24. In conclusion, the board, having regard to the facts and arguments presented to it, decides that the contested patent does not disclose the suitability of the product to be manufactured for the treatment of a tumour so that there is insufficiency of disclosure (Article 100(b) EPC).

*Auxiliary request 1*

*Admissibility in the appeal proceedings*

25. The appellant objected to the admissibility of auxiliary request 1 as constituting a "fresh case" of the respondent which should have been filed in reply to the grounds of appeal. It held that the respondent had failed to justify the late submission of this request. Although so far appellant's argumentation had focused on claim 1 of the main request, the claim set as a whole had been attacked since revocation had been requested, it was thus not justified to file the claim request at this late stage in the proceedings.
26. This argument did not convince the board. The set of claims corresponding to auxiliary request 1 had initially been filed as a proper and proportionate reaction to observations by the board in its communication pursuant to Article 15(1) RPBA within the time limit set by the board (see sections XI and XIII, above). Pursuant to Article 12(1)(c) RPBA, appeal

proceedings shall be based *inter alia* on any communication sent by the board and any answer thereto filed pursuant to directions of the board. The board regards auxiliary request 1 as a legitimate attempt to remedy the deficiencies under Article 100(b) EPC in respect of the main request, without adding complexity, introducing new deficiencies or unjustifiably delaying the procedure. The set of claims which now constitutes auxiliary request 1 is thus not to be rejected as late filed.

27. The claims of auxiliary request 1 are identical to corresponding claims as granted, and identical also to corresponding claims present in the main request. In particular present claim 1 is identical to claim 46 as granted and claim 39 of the main request, respectively. Auxiliary request 1 differs from the main request only by the deletion of claims 1 to 38 and 45 to 54 with corresponding modification of the back-references. The board concludes therefore that auxiliary request 1 does not create a "fresh case".
28. For these reasons, the board admits auxiliary request 1 into the proceedings.

*Amendments to the appellant's case*

29. Article 13(1) RPBA states that any amendment to a party's case after it has filed its grounds of appeal or reply may be admitted and considered at the board's discretion. The discretion shall be exercised in view of *inter alia* the complexity of the new subject matter submitted, the current state of the proceedings and the need for procedural economy. Furthermore, according to

Article 13(3) RPBA, amendments sought to be made after oral proceedings have been arranged shall not be admitted if they raise issues which the board or the other party or parties cannot reasonable be expected to deal with without adjournment of the oral proceedings.

30. In the present case, the appellant's statement of grounds of appeal contained only arguments as regards claim 1 of the auxiliary request as maintained by the opposition division (which corresponds to the main request before the board). During the written appeal proceedings the appellant failed to raise any specific objections against the patentability of the subject-matter of claims 39 to 44 and 55 to 81 of that request which correspond to claims 1 to 34 of present auxiliary request 1. The allowability of these claims was only challenged in the oral proceedings before the board.
31. This is considered to represent an amendment to the appellant's case. It is thus at the board's discretion to admit and consider it.
32. The appellant's arguments as regards admissibility of the new arguments were not considered persuasive. That new arguments should be allowed because throughout the proceedings all claim requests of the proprietor (now the respondent) had failed following an attack on a single claim, is untenable in view of the fact that the opposition division maintained the patent on the basis of what is now the respondent's main request. The present auxiliary request 1 has been restricted to subject-matter that has not been challenged by the appellant in the grounds of appeal or at any later stage during the written appeal proceedings although

corresponding claims were present in the claims as maintained by the opposition division. There was therefore no justification not to submit arguments against these claims earlier. The board considers that the appellant could, and indeed should, have made its complete case as regards all of the independent claims upheld by the opposition division in its statement of grounds of appeal and should not be allowed to make new attacks on those claims it previously overlooked only because the respondent uses them as a fallback position at a later date.

33. For the above reasons, the board decided to exercise its discretion under Articles 13 RPBA to admit only such of the appellant's submissions on these claims as were raised in the grounds of appeal and to the extent that its arguments had already been brought forward in relation to the claims of the main request.

*Auxiliary request 1*

*Sufficiency of disclosure*

34. Claim 1 relates to a method for selection of an immunogenic analogue of a cell-associated polypeptide antigen which is weakly immunogenic or non-immunogenic in an animal, the immunogenic analogue being capable of inducing a CTL response in the animal against cells displaying an MHC Class I molecule bound to an epitope derived from the cell-associated polypeptide antigen.
35. The patent in suit provides detailed instructions as to how the steps of the method can be carried out. Thus, the CTL epitopes can be identified by using methods for

predicting the presence of CTL epitopes that are well known in the art (see paragraph [0071] of the patent in suit) or by performing a literature search (see paragraph [293] of the patent in suit). Useful T-cell epitopes are disclosed in paragraphs [0082] to [0087], and paragraph [0300] of the patent in suit. Paragraphs [0147] to [0159] provide detailed instructions as to how steps a) and b) of the method are to be carried out. The examples provide further guidance on step c), e.g. in paragraphs [0262], [0322] to [0326], [0393] to [0400] and [0435] to [0443].

36. It can therefore reasonably be assumed that a skilled person, following the guidance provided in the patent in suit would be in a position to prepare appropriate immunogenic analogues, to test them and to select those analogues which are verifiably capable of inducing a CTL response in the animal.
  
37. The appellant's argument that claim 1 should be held to be insufficiently disclosed for the same reasons for which the main request was held to be insufficiently disclosed did not convince the board. Claim 1 of the main request is formulated as a "second (further) medical use" or "Swiss-type" claim whereas claim 1 of auxiliary request 1 relates to a method of screening. The rationale of decision T 609/02 (*supra*) which relates to claims wherein attaining the claimed therapeutic effect is a functional feature of the claim is thus not applicable to the claim under consideration. The fact that the patent in suit provides no evidence that T cell autotolerance can be broken, has no consequence for auxiliary request 1.

38. The further argument that the skilled person had no reasonable expectation of success to select an immunogenic analogue when carrying out the method of claim 1 because the patent in suit had not shown that the method worked did not persuade the board either. There is no documentary or experimental evidence before the board that the steps cannot be carried out as claimed or that the skilled person would not be able to select an immunogenic analogue.
39. Finally, the appellant argued that independent claims 7, 11 and 14 suffered from the same problem as claim 1. The board was not convinced by that argument either. Claim 7, 11 and 14 are product claims directed to immunogenic analogues of human PSM, human Her2 and human/murine FGF8b, respectively. The claims do not require that these analogues are capable of breaking T cell autotolerance. The board is convinced that these analogues are immunogenic in humans already due to the mere presence of foreign T<sub>H</sub> epitopes.
40. According to established case law of the boards of appeal the objection based on lack of sufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts (*cf.* decision T 19/90 OJ EPO 1990, 476, point 3.3 of the reasons). The board considers that the arguments raised by the appellant are not supported by facts or evidence and thus not sufficient to meet the standard applied by the case law of the boards of appeal when deciding sufficiency of disclosure. The board concludes that no case of lack of sufficiency of disclosure has been made. Accordingly auxiliary request 1 can be accepted under Article 100(b)

EPC.

41. No other objections were raised in respect of auxiliary request 1 by the appellant.

## **Order**

### **For these reasons it is decided that:**

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of claims 1 to 34 of auxiliary request 1 filed during the oral proceedings and a description and figures to be adapted thereto.

The Registrar:

The Chairman:

P. Cremona

C. Rennie-Smith