Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 31 March 2017

Case Number: T 0284/12 - 3.3.08

Application Number: 03763065.4

Publication Number: 1576113

IPC: C12N15/63, C07K5/00, A61K38/00

Language of the proceedings: EN

Title of invention:
TUMOR ANTIGENS BFA4 AND BCY1 FOR PREVENTION AND/OR TREATMENT OF CANCER

Applicant:
Aventis Pasteur, Inc.

Headword:
Tumor antigens/AVENTIS PASTEUR

Relevant legal provisions:
EPC Art. 83, 84

Keyword:
Main and sole request - sufficiency of disclosure (no);
Main and sole request - clarity (no)

Decisions cited:

G 0010/93, T 0019/90, T 0609/02, T 1329/04, T 0433/05, T 1685/10

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0284/12 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 31 March 2017

Appellant: (Applicant)	Aventis Pasteur, Inc. Discovery Drive Swiftwater, PA 18370 (US)
Representative:	Cole, William Gwyn Avidity IP Broers Building Hauser Forum 21 J J Thomson Avenue Cambridge CB3 0FA (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 20 September 2011 refusing European patent application No. 03763065.4 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	M. R. Vega Laso
Members:	P. Julià
	R. Winkelhofer

Summary of Facts and Submissions

I. European patent application No. 03 763 065.4 with the title "Tumor antigens BFA4 and BCY1 for prevention and/or treatment of cancer" was published as international patent application WO 2004/005463 (hereinafter "the application"). The examining division of the European Patent Office found that both the main request and the auxiliary request did not fulfil the requirements of Article 56 EPC and, accordingly, refused the application under Article 97(2) EPC by decision posted on 20 September 2011.

II. Together with the statement setting out the grounds of appeal, the applicant (appellant) filed new documentary evidence (document (5)) and a sole claim request identical to the auxiliary request before the examining division. As subsidiary request, the appellant requested oral proceedings.

III. The appellant was summoned to oral proceedings. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), the board informed the appellant of its provisional, non-binding opinion on some issues to be discussed at the oral proceedings. In particular, the board raised several objections under Articles 83 and 84 EPC and introduced new documentary evidence (document (6)) into the appeal proceedings. The appellant was also informed that the appeal was likely to be dismissed.

IV. Without submitting substantive arguments, the appellant informed the board that it did not intend to attend the scheduled oral proceedings.

V. Oral proceedings were held on 31 March 2017 in the absence of the appellant.

VI. Claim 1 of the main and sole request reads as follows:

"1. A tumor antigen for use in a method of preventing or treating cancer in an animal, said method comprising administering a medicament comprising an expression vector encoding the tumor antigen to the animal wherein an immune response to the tumor antigen is induced upon administration of the medicament to the animal, and wherein said tumor antigen is a polypeptide consisting of the sequence SEQ ID NO: 4."

Dependent claims 2 to 11 relate to specific embodiments of claim 1.

VII. The following documents are cited in this decision:

(1): WO 02/059377 (publication date: 1 August 2002);

(2): WO 02/102235 (publication date: 27 December 2002);

(5): WO 01/30847 (publication date: 3 May 2001);

(6): K. Buchet-Poyau *et al.*, Nucleic Acid Research, 2007, Vol. 35, No. 4, 1289 to 1300.

VIII. The appellant's submissions in its statement of grounds of appeal concerned only Article 56 EPC. The appellant did not make any submissions with regard to the objections under Articles 83 and 84 EPC raised by the board in its communication.

IX. The appellant requests to set aside the decision under appeal and to remit the application to the examining

division for further prosecution and issuance of a communication pursuant to Rule 71(3) EPC.

Reasons for the Decision

Article 113(1) EPC

1. In the decision under appeal, the examining division decided in substance only on Article 56 EPC.

2. According to decision G 10/93 (OJ EPO 1995, 172), "*In an appeal from a decision of an examining division in which a European patent application was refused the board of appeal has the power to examine whether the application or the invention to which it relates meets the requirements of the EPC. The same is true for requirements which the examining division did not take into consideration in the examination proceedings or which it regarded as having been met. If there is reason to believe that such a requirement has not been met, the board shall include this ground in the proceedings*". In its communication pursuant to Article 15(1) RPBA attached to the summons to oral proceedings, the board informed the appellant that, for the reasons given therein, it had serious doubts whether the requirements of Articles 83 and 84 EPC were fulfilled.

3. By its decision not to attend the scheduled oral proceedings and not to submit substantive arguments in reply to the board's communication, the appellant has deprived itself of the opportunity to present its comments on the reasons given by the board in its provisional opinion. This has been done even though, as stated above, the board was of the provisional, non-binding opinion that the appellant's main request does

not fulfil the requirements of Articles 83 and 84 EPC and that, therefore, the appeal was likely to be dismissed.

4. The present decision on Articles 83 and 84 EPC is based on the same grounds and evidence on which the board's provisional opinion as expressed in the communication pursuant to Article 15(1) RPBA was based. The requirement of Article 113(1) EPC is thus fulfilled.

Main and sole request
Articles 83 and 84 EPC

5. Claim 1 of the main request is directed to the BCY1 polypeptide of SEQ ID NO: 4 (400 amino acids) for use as a tumor antigen in a method of prevention or treating cancer in an animal. According to the case law of the Boards of Appeal, sufficiency of disclosure (Article 83 EPC) must be plausibly established at the claimed relevant (priority) date from the technical content of the application. For second medical use claims, like claim 1 here, attaining the claimed therapeutic effect is a functional technical feature of the claim (cf. *inter alia*, T 609/02 of 27 October 2004, point 9 of the Reasons for the decision; T 1685/10 of 6 June 2011, point 3 of the Reasons for the decision, and "Case Law of the Boards of Appeal of the European Patent Office", 8th edition 2016, II.C.6.2, 347).

6. The appellant argues - in the context of Article 56 EPC - that claim 1 is presented in a second medical use format in order to reflect the contribution to the art made by the inventors, namely the demonstration of a technical effect that identifies BCY1 (SEQ ID NO: 4) as an antigen suitable for a cancer vaccine (cf. page 5, point 4.1 of appellant's grounds

of appeal). Allegedly, the results in Example 2 of the application show that the BCY1 polypeptide has the relevant technical effect.

7. The board does not share this view. Example 2 of the application does not provide any experimental evidence that the BCY1 polypeptide as such functions as a tumor antigen and elicits an immune response. In sections B and C of Example 2, Table VIII discloses a list of 100 nonamer peptides derived from the BCY1 polypeptide used as immunological reagents for binding to autologous HLA-A*0201 dentritic cells (DC) and activation of cytotoxic T-lymphocytes (CTL) (Example 2, part B). Table IX shows peptide pools consisting of 7-10 peptides which were pulsed onto HLA-A*0201 DC and used to activate autologous T-cell enriched PBMC preparations. According to Example 2, part C, only "*peptide groups 1, 2, 3, 4, 5, 6, and 7 were found to be immunoreactive in these assays*". A subsequent deconvolution of the single peptides from each group tested separately "*revealed a number of individual strongly reactive peptides from the BCY1 protein recognized by human T cells. Many of these single peptides also induced CTL activity killing peptide-loaded human T2 lymphoma cell targets*" (cf. page 46, Example 2, part C of the application). No further information is provided in the application and none of the specific peptides that induced CTL activity is identified therein.

8. Claim 1 does not specify any of the single peptides tested in Example 2, but "*a polypeptide consisting of the sequence SEQ ID NO: 4*" (in contrast to claim 39 of the application directed to "*a method for immunizing a host against the tumor antigen BCY1 comprising administering to the patient* ***a peptide shown in Table***

VIII or IX ..."; emphasis added by the board). An extrapolation of the results obtained using the single peptides to the complete polypeptide is not straightforward. It is common general knowledge in the art that not all possible (linear) epitopes derived from the amino acid sequence of a protein turn out to be actual epitopes of this protein when said protein is found in a native or *in vivo* conformation. There is no evidence on file showing that any of the specific single peptides listed in Table VIII or IX is an actual (linear) epitope of the BCY1 polypeptide under conditions used for administration as a vaccine. Nor is there any evidence on file showing that the BCY1 protein is processed *in vivo* in such a way as to result in the production of any of these single peptides. Whilst it is stated in Example 2 of the application that single peptides (which are not disclosed specifically in the patent application) induced CTL activity, this is not the case for the BCY1 polypeptide itself.

9. It is also common general knowledge in the art that an epitope may be shared by several proteins and that, the shorter a peptide, the higher is the chance that its sequence is shared by several (otherwise unrelated) proteins. Since the sequences of the single peptides disclosed in Example 2 of the application have only nine residues, it cannot be excluded that the epitope(s) present in these sequences are also shared by - or have a high identity/homology to - other proteins fully unrelated to the BCY1 polypeptide. These other proteins (which might or might not be known in the art) may also have an *in vivo* effect/function completely unrelated to that of the BCY1 polypeptide. Since there is no information in the application on the amino acid sequences of the specific peptides that

induced CTL activity, it is not possible for a skilled person to determine the specificity of these peptides.

10. The activation of CTL may well be necessary for an epitope to have a possible therapeutic use, but it is certainly not enough. Both the specificity and the efficiency of the immune CTL response are highly relevant. Indeed, epitopes shared among several proteins which are not associated specifically to any pathologic and/or disease conditions, may not be of therapeutic applicability. Likewise, even if a protein is associated specifically to a pathologic and/or disease conditions, epitopes of this protein may not be of therapeutic applicability as vaccines if their use as antigen does not result in the desired target cells being efficiently destroyed or lysed. In other words, the immune CTL response must be capable of an epitope-specific killing of the desired target cells, in the present case cancer cells. There is, however, no information in the application as regards this issue.

11. The efficiency of a tumor-associated antigen is also closely related to the conformation and amount of antigen expressed on the surface of the (cancer) target cell (cf. page 3, first full paragraph of the application). If the antigen is present only in low or non-significant amounts or in a non-accessible conformation when located on the membrane surface of the target cells, the immune CTL response may not result in an efficient lysis of the (cancer) target cells. As stated in point 10 above, the application fails to provide any evidence as regards this issue.

12. In this context, the content of post-published document (6), cited as an expert opinion and introduced by the board into the appeal procedure in its communication,

is highly relevant. This document describes the identification and characterization of four related human Mex-3 proteins (encoded by the MEX3A-D genes; "*muscle excess*") which are described as a novel (sub)family of evolutionary conserved RNA-binding phosphoproteins shuttling between the nucleus and the cytoplasm and showing different localization to cytosolic foci identified as sites of mRNA storage, translation regulation and degradation (processing bodies, P-granules) (cf. *inter alia*, abstract, page 1290, left-hand column, third paragraph). The amino acid sequences of the four hMex-3 phosphoproteins are shown in Figure 1B.

13. Starting at the amino acid residue at position 122 of the hMex-3A sequence, the amino acid sequence is identical to SEQ ID NO: 4 of the BCY1 polypeptide except for the substitution of a threonine residue for an alanine residue (hMex-A, Thr; BCY1, Ala) at position 513 (see, however, peptide CLP-2950 in Table VIII, page 44 of the application) and for the additional presence of a N-terminal methionine in SEQ ID NO: 4 of the BCY1 polypeptide. Thus, the BCY1 polypeptide disclosed in the application is a N-truncated form of the hMex-A protein, starting in the middle of a first nuclear localization signal (NLS) and having two tandemly repeated K homology (KH) domains (type I) (responsible for interacting with, or binding to, RNA) and a carboxy-terminal RING finger domain (function as an ubiquitin-protein E3-like ligase).

14. In view of the function and cellular localization of the hMex-A phosphoprotein described in document (6), there are serious doubts whether the BCY1 polypeptide disclosed in the application (truncated hMex-A protein) is expressed on the surface of any (cancer) target

cells. There is no evidence in the application that this is actually the case. Therefore, serious doubts, substantiated by verifiable facts (cf. *inter alia*, T 19/90, OJ EPO 1990, 476, point 3.3 of the Reasons for the decision), arise as to whether the BCY1 polypeptide actually falls within the definition of a tumor-associated antigen given in the application (cf. page 3, first full paragraph), and whether it can be used efficiently as a (tumor) antigen for treating, let alone preventing cancer in an animal.

15. It follows from the above that, as regards the therapeutic effect of the BCY1 polypeptide as such (SEQ ID NO: 4), the disclosure in the application is insufficient (Article 83 EPC).

16. According to the established case law of the Boards of Appeal, post-published documents can only confirm or support the technical teaching of the application, but they cannot overcome deficiencies in the disclosure of the application (cf. *inter alia*, T 609/02, *supra*, point 9 of the Reasons for the decision; T 1329/04 of 28 June 2005, point 12 of the Reasons for the decision; T 433/05 of 14 June 2007, point 28 of the Reasons for the decision).

17. In the light of the considerations in paragraphs 8 to 14 above, the claimed therapeutic effect, i.e. that the BCY1 polypeptide consisting of the sequence SEQ ID NO: 4 when administered in the form as recited in claim 1 may be suitable for treating or preventing cancer in an animal, cannot be considered to be plausibly achieved, even in view of the observations that a mRNA of a (BCY1) protein is up-regulated or over-expressed in a pathologic/disease condition (as derivable from documents (1) and (2), for breast and ovarian cancer,

respectively), and that the amino acid sequence of said (BCY1; SEQ ID NO: 4) protein contains short subsequences which, as such, provide an immune CTL response (as disclosed in the application without providing the sequence of any of these subsequences).

18. Although the findings on sufficiency of disclosure above already justify the dismissal of the appeal, the following additional deficiencies under Articles 83 and 84 EPC are noted:

18.1 Claim 1 refers to the prevention or treatment of cancer in an animal. In view of the biological function of the Mex-A protein (*supra*) and the fact that the BCY1 polypeptide of sequence SEQ ID NO: 4 is a human protein, the reference to an animal in general is too broad (cf. page 25, last paragraph of the application, with reference to "*patients, including humans and other mammals*"). Moreover, the evidence provided in the application does not support a technical effect for "*cancer*" in general. If at all, there is only a formal reference to "*BCY1 breast cancer antigen*" in the application (cf. page 42, Example 2, part B), although no experimental evidence is provided (such as mRNA up-regulation/over-expression in breast cancer and in different types of cancer cells).

18.2 The conditions required for "*preventing*" a disease may be fully different from those required for "*treating*" the same disease. There is no information in the application as regards this issue. In particular, there is no evidence to support that the administration of a BCY1 polypeptide of sequence SEQ ID NO: 4 provides an effect for preventing any specific type of (breast) cancer, let alone cancer in general. Such therapeutic

applicability is only speculative and not based on technical facts.

19. Thus, in view of all the above considerations, the main and sole request does not fulfil the requirements of Articles 83 and 84 EPC.

20. Therefore, the appellant's requests cannot be granted.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

A. Wolinski M. R. Vega Laso

Decision electronically authenticated