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Datasheet for the decision of 7 November 2013

Case Number: T 1148/09 - 3.3.04

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Title of invention:
Diagnosing tumorigenicity and determining resistance to anticancer therapy

Applicant:
A & G Pharmaceuticals, Inc.

Headword:
Diagnosis of tumorigenicity/ A & G PHARMACEUTICALS

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2)

Keyword:
"Main and sole request - after amendment: requirements of the EPC met (yes)"

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Case Number: T 1148/09 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 7 November 2013

Appellant: (Applicant)	A & G Pharmaceuticals, Inc. 600 E. Lombard Street, Suite 509 Baltimore, MD 21202 (US)
Representative:	Jappy, John William Graham Gill Jennings & Every LLP The Broadgate Tower 20 Primrose Street London EC2A 2ES (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 10 December 2008 refusing European patent application No. 02741997.7 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: G. Alt
M. Montrone

Summary of Facts and Submissions

I. This is an appeal of the applicant (hereinafter "appellant") against the decision of the examining division of 10 December 2008 to refuse the European patent application No. 02 741 997.7. The reasons for the decision are contained in the examining division's communication of 13 October 2008.

The application has the title *"Diagnosing tumorigenicity and determining resistance to anticancer therapy"*. It was published as the International application WO 02/102229 on 27 December 2002. A corrected version of the original version was published on 10 July 2008 which is referred to in the present decision as the "application" or "application as filed".

II. The term "GP88" is used in the application as a name for a growth factor that was first discovered in the culture medium of highly tumorigenic "PC cells", an insulin-independent variant isolated from the teratoma derived, adipogenic cell line 1246. The term "PCDGF" is sometimes used as a synonym for the term "GP88".

III. The following documents are cited in the present decision:

D1 WO 98/52607

D5 Clinical Endocrinology, vol. 53, 2000, pages 337-344, Turner, H.E. et al.

D6 Cancer Research, vol. 57, 1997, pages 4098-4104, Landry, C.F. et al.

IV. The decision under appeal dealt with one single request.

Its claims 1, 2, 4, 5 and 7 read:

"1. A method for diagnosing tumorigenicity in a human patient, comprising:

i. Detecting PCDGF/GP88 in cells of a biological sample obtained from a patient;

ii. determining the number of PCDGF/GF88 positive cells in that sample; and

iii. determining the ratio of PCDGF/GP88 positive cells to the total number of cells in said biological sample, wherein said ratio is indicative of tumorigenicity.

2. A method according to claim 1, wherein an anti-human PCDGF/GP88 antibody is used.

4. A method of determining whether a human patient is resistant to the antineoplastic effects of antiestrogen therapy, comprising:

i. Detecting PCDGF/GP88 in cells of a biological sample; and

ii. determining the amount of PCDGF/GF88 in said sample wherein the amount of PCDGF/GP88 is indicative of resistance to the antineoplastic effects of antiestrogen therapy; or

iii. determining the ratio of PCDGF/GP88 positive cells to the total number of cells in said biological

sample wherein said ratio is indicative of resistance to the antineoplastic effects of antiestrogen therapy.

5. A method according to claim 4, wherein step (iii) is performed and step (ii) is not performed.

7. The method of any of claims 1, 2 and 4 wherein said biological sample comprises a material selected from the group consisting of blood, serum, plasma, urine, nipple aspirate, cerebrospinal fluid, liver, kidney, breast, bone, testes, brain, colon, lung or ovary."

V. The examining division refused the application because its claims 1, 2, 4, 5 and 7 did not comply with the requirements of the EPC.

In detail, the examining division objected that claim 1 lacked support in the description (Article 84 EPC) and that the disclosure with regard to the invention defined by claim 1 was insufficient (Article 83 EPC), because the application (i) did not disclose the diagnosis of tumours in general, but only that of breast cancer (see point 3.3 of the communication of 13 October 2008), (ii) only disclosed in the experiment of Example 2 that there was a difference in staining between benign and invasive tissue, but neither disclosed the ratio of stained cells to the total cells in the sample nor from which ratio onwards a tissue would be considered as tumorigenic, (iii) only disclosed in Example 2 and Figures 21 and 22 that there was a difference in the GP88 expression between benign and invasive breast tissue and thus only disclosed the detection of existing tumours rather than the potential to develop a tumour, i.e. tumorigenicity (points (ii)

and (iii) above, see point 3.2 of the communication of 13 October 2008).

Furthermore, the examining division considered that claim 1 lacked an inventive step (Article 56 EPC) in view of the teachings in the closest prior art document D1 in combination with the teachings in document D5 or document D6 (see point 3.1 of the communication of 13 December 2008). Document D1 disclosed a method to diagnose the tumorigenicity of breast tissue of a human patient by determining the total amount of GP88 in a sample, either by the determination of GP88-encoding mRNA via Northern Blotting or by the determination of the GP88 protein via ELISA and subsequent comparison of the determined amount to that present in a tissue sample of a healthy subject.

The difference between the disclosure in document D1 and the invention defined in claim 1 was that, instead of using the difference in amounts of GP88 in samples from two different subjects as indicator for tumorigenicity, the method of the invention analysed a single sample of putatively tumorigenic tissue by a cell-based immunohistochemical method and used the ratio of the number of GP88-positive cells to the number of total cells in this sample as an indicator for tumorigenicity. No technical effect other than that the method served for the determination of the tumorigenicity was associated with this difference. The problem to be solved was therefore the provision of an alternative way of determining increased GP88 expression in tumour cells.

Based on the results of an immunohistochemical assay method, document D5 disclosed that several cyclins were over-expressed in pituary adenomas and that the

proportions of cyclin-positive cells in these tumours differed depending on the type of cyclin and tumour sample. Thus, document D5 disclosed that, at least for some cyclins, the number of cyclin-positive cells correlated with the degree of proliferation and tumour presence. Document D6 disclosed results of assays relying on the detection of the number of cells expressing proteolipid protein (PLP)-mRNA versus PLP-non-expressing cells as a measure of the grade of astrocytoma. However, it was also generally derivable from the two documents D5 and D6 that the ratio of *"expressing"* cells to the total number of cells could not be used to diagnose a tumour in cases of all genes which were over-expressed in a certain tumour tissue. Yet the person skilled in the art knew that it was a matter of simple experimentation to find out if this was the case for a particular gene or not.

The subject-matter of claim 4 was held not to comply with the requirements of Articles 54, 56, 83 and 84 EPC and the subject-matter of claims 2, 5 and 7 did not comply with the requirements of Articles 83 and 84 EPC.

Finally, the examining division objected generally to the term "PCDGF/GP88" used in all claims, which, especially when it was read in combination with the word "ratio", was so confusing as to render the claims unclear, contrary to the provisions of Article 84 EPC.

VI. With its statement setting of the grounds of appeal the appellant filed an amended main request and an auxiliary request.

VII. In a communication the board informed the appellant, in particular, about its preliminary views on the issues of inventive step and sufficiency of disclosure.

VIII. Oral proceedings were held on 7 November 2013. The appellant was represented.

At the end of the oral proceedings the appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the sole main request filed at the oral proceedings.

The sole claim of this request read:

"1. A method for diagnosing the tumorigenicity of breast cancer in a human patient, comprising:

i. detecting GP88 in cells of a biological sample obtained from a patient;

ii. determining the number of GP88 positive cells in said sample; and

iii. determining the ratio of GP88 positive cells to the total number of cells in said biological sample, wherein said ratio is indicative of the tumorigenicity of breast cancer, and wherein the biological sample containing cells from said patient is a breast tissue sample; GP88 in said cells of said breast tissue is detected by immunostaining with anti-human GP88 antibody; the number of GP88 positive cells in a said sample is determined by microscopic examination; and a ratio of at least 10% of GP88 positive cells to the total number of cells in said breast tissue indicates the tumorigenicity of breast cancer."

At the end of the oral proceedings, the chairman announced the board's decision.

IX. The appellant's arguments, as far as they are relevant to the present decision, may be summarized as follows.

The basis for amended claim 1 in the application as filed was found in claim 64, in paragraph [00164] for the feature relating to the cut-off value of "10%", and in the whole application as far as application of the method for the diagnosis of breast cancer was concerned.

The amendments to claim 1 and the deletion of all other claims, respectively, overcame all reasons for refusing the application pursuant to Articles 83 and 84 EPC.

Document D1 was the closest prior art document. It disclosed a method for determining the tumorigenicity of breast cancer tissue by comparing the GP88 protein or GP88 mRNA level of a sample from putative tumorigenic tissue with that of a sample of non-tumorigenic tissue from the same patient or a normal subject. The problem to be solved was the improvement of the detection of GP88 resulting in an improvement of cancer diagnosis. The solution was to calculate the ratio of the number of GP88 positive cells compared to the total number of cells in a single sample suspected to be tumorigenic. This method had two advantages over the method disclosed in document D1. It was simpler because only a single sample was needed and the information about the stage of cancer was made on the basis of stained cells.

A skilled person who wanted to improve the method disclosed in document D1 would, for example, chose to improve the measuring quality of this method, but would not move to a cell-based immunohistochemical method.

This was so in particular because he or she knew that GP88 was a secreted protein, but that an immunohistochemical method did not take account of secretion. The description of the application, for example, disclosed immunohistochemical detection methods only in relation to the detection of proliferation markers which were either nuclear and transmembrane proteins, i.e. Ki-67 or cERB, and not secreted proteins.

Reasons for the Decision

Allowability of amendments (Article 123(2) EPC)

1. Claim 64 of the application as filed reads:

"1. A method for diagnosing tumorigenicity, comprising:

obtaining a breast tissue sample containing cells from a patient;

i. detecting GP88 in said cells of said breast tissue sample by immunostaining with anti-human GP88 antibody;

ii. determining the number of GP88 positive cells in said sample by microscopic examination; and

iii. determining the ratio of GP88 positive cells to the total number of cells in said breast tissue sample, wherein a ratio of at least about 1% indicates tumorigenicity."

and thus recites all features of the method of claim 1 (see section VIII above) either explicitly or

implicitly - that claim 64 relates to a method of diagnosing the tumorigenicity of breast cancer is disclosed by the feature that the detection of GP88 is made in cells of a breast tissue sample.

Claim 64 does not disclose that (i) the patient is "human" and (ii) that it is a ratio of "at least 10%" of GP88-positive cells to the total number of cells in said breast tissue that indicates the tumorigenicity of breast cancer. However, that the method referred to in claim 64 is to be used in relation to samples from human patients is derivable from the application as filed as a whole. In the board's view, this may for example be illustrated by the reference to *"women"* in the statements in paragraph [0008]: *"Breast cancer is a major worldwide cause of morbidity and mortality among women"*, or paragraph [00153]: *"These studies are directly relevant to women's health because they provide analysis of the novel growth factor PCDGF as a potential prognosis marker of breast cancer"*. Moreover, claim 1 of the application as filed which recites the gist of the invention, namely that the ratio of GP88-positive cells to the total number of cells in a biological sample is indicative of tumorigenicity, is directed to *"A method for diagnosing tumorigenicity in a human patient"*. The cut-off value of "at least 10%" for the ratio of GP88 positive cells to the total number of cells in the sample as an indicator for tumorigenicity is disclosed in paragraph [00161] of the application as filed.

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

Sufficiency of disclosure/ Clarity, support
(Articles 83 and 84 EPC)

3. Generally, the analysis of tissue sections by staining of the cells with antibodies, a so-called immunohistochemical analysis, is known. Specifically, the application describes in paragraphs [00157] to [00159] the preparation of tissue sections and anti-human GP88 antisera and the staining procedure. Cell counting by microscopic examination and the calculation of the ratio of the total number of cells versus the stained cells are known to the skilled person on the basis of his or her common general knowledge. Thus, technically, the skilled person can carry out the claimed method.

4. The last phrase of claim 1 describes the effect to be achieved by the claimed method: "and a ratio of at least 10% of GP88 positive cells to the total number of cells in said breast tissue indicates the tumorigenicity of breast cancer." In other words, if the ratio has a value as indicated, the tissue is qualified as "tumorigenic", which means that it is a tumour and - as the case may be - also has the potential to proceed into more advanced tumor stages. Thus, the claimed method does not aim at grading of tumors, but to determining whether or not there is a tumour.

4.1 As to evidence in the application for this effect, the application discloses in Example 2, paragraph [00161] and Figure 21 that there is a difference in the staining of cells from benign breast tissue and tissue from an advanced-stage breast tumour – invasive ductal carcinoma. The former tissue does not stain for GP88, while the cells of the latter *"display a very positive*

staining" (see paragraph [00161]. It is also derivable from paragraph [00161] that less than 5% staining is considered as *"negative"*, i.e. the sample is non-tumorigenic, whereas a sample with 10-25% positive staining is considered as weakly and with more than 50% positive staining as strongly tumorigenic. Thus, the description of the staining as *"very positive"* indicates that the tissue is tumorigenic, i.e. that there is a tumor and, in the board's view also, that the examined sample is strongly tumorigenic which matches with it being derived from invasive ductal carcinoma which is a known advanced stage of breast cancer. Hence, there is evidence in the application that the claimed method achieves the intended effect.

5. The sole claim of the present request is restricted to the use of breast tissue for the diagnosis of breast cancer and indicates the ratio from which onwards a tissue would be regarded as tumorigenic. Hence, the two objections (i) and (ii) (see section V above) raised against claim 1 pursuant to Article 83 EPC and Article 84 EPC – insufficient disclosure and lack of support- no longer apply.

The examining division's third objection against claim 1 pursuant to Article 83 EPC and Article 84 EPC (i.e. objection (iii) in section V) - that the application does not make it plausible that the claimed method is suitable to determine "tumorigenicity", i.e the potential to develop a tumour but that it is only suitable to detect the presence of a tumour - is not convincing for the reasons given in points 4 and 4.1 above.

6. The sole request on file only has a single claim. It is derived from claim 1 of the request dealt with in the

decision under appeal. Thus, the objections in the decision under appeal pursuant to Articles 83 and 84 EPC and concerning claims 2, 4, 5 and 7 are not relevant in respect of the present request.

7. The terminology PCDGF/GP88 is not used in the amended claim 1 anymore. Hence, this objection of lack of clarity pursuant to Article 84 EPC is moot.

8. The board therefore concludes that the requirements of Articles 83 and 84 EPC are fulfilled.

Novelty (Article 54 EPC)

9. There were no objections in the decision under appeal and the board has no objections either.

Inventive step (Article 56 EPC)

10. The decision under appeal correctly defines document D1 as the closest prior art document. The document discloses on page 58 under the heading *"Diagnostic test for tumorigenicity"*:

"In teratoma and in breast cancer, an increase in the tumorigenic properties is associated with an increase in GP88 expression or an increase in GP88 responsiveness.[...] Accordingly, increase of GP88 level can be used as a diagnostic approach to detecting tumor. In human tumor biopsies, a change (increase) in GP88 expression when compared to the level of GP88 in normal corresponding tissues is indicative of the state of tumorigenicity or malignancy of the tissue biopsy analysed. Increase in expression of GP88 can be measured at the mRNA level or at the protein level. GP88 mRNA expression can be measured either by Northern

blot analysis, RNAse protection assay or RT-PCR. GP88 protein expression is quantitated by ELISA, EIA or KIA using an anti-GP88 antibody. The ability to measure GP88 expression in tissue extracts in comparison to corresponding tissues from normal subject can be used to predict the degree of tumorigenicity of a particular cancer or to determine whether this particular cancer will be responsive to anti-GP88 therapy."

Thus, document D1 discloses a method for diagnosing the tumorigenicity of breast cancer based on a comparison of the total amount of GP88 in a sample suspected to stem from tumorigenic tissue with the total amount of GP88 in a reference sample stemming from normal tissue.

11. The claimed method differs from that disclosed in document D1 in several features. One is that the claimed method assigns the tumorigenicity on the basis of the ratio of numbers of GP88-expressing versus the total number of cells in a sample. Another one is that the claimed method requires only the withdrawal and analysis of one single sample instead of two. Undeniably, because of at least this latter feature, the handling of the claimed method is more convenient than that disclosed in document D1. An increase in the convenience of the handling of a method of diagnosis is an improvement and the board sees no reason why this effect should not be taken into account when formulating the problem to be solved.

Thus, the board considers that the problem to be solved is to be formulated as the provision of a more convenient GP88-based method for diagnosing the tumorigenicity of breast cancer.

The solution is provided by the subject-matter of claim 1. It follows from the board's observations in points 4 and 4.1 above that the claimed method solves the problem formulated above.

12. In its assessment of the obviousness of the claimed subject-matter the examining division relied on a combination of the closest prior art document D1 with documents D5 and D6.

In the board's view the claimed subject-matter cannot be considered as obvious from a combination of the teaching in document D1 with that in either of documents D5 or D6.

A first reason is that none of the two documents discloses the claimed method as such. Document D5 determines the tumorigenicity by calculating the ratio of the number of stained cells to non-stained cells and not, as claimed, by calculating the ratio of the number of stained cells to the total number of cells (see page 339, second column, first full paragraph, lines 6 to 11). Document D6 is even less related to the claimed subject-matter because it detects positive cells by hybridization of mRNA with a DIG-labelled antisense cRNA and subsequent incubation with an anti-DIG antibody coupled to alkaline phosphatase subsequent for color development and not by binding of an antibody to a protein (see page 4099, first column, "*In situ Hybridization Histochemistry*", first paragraph).

A second reason is - and this was also the view of the examining division - that it is derivable from documents D5 and D6 that over-expression of a protein in a tumor alone is not sufficient to conclude that the ratio of expressing cells is an indicator for

tumorigenicity. Hence, it cannot be inferred from the teaching in documents D5 or D6 that GP88 could be used as a marker in an immunohistochemical assay such as the one claimed.

13. Moreover, the board is convinced by the appellant's argument submitted at the oral proceedings, that because GP88 was known to be a secreted protein, the skilled person would not have envisaged to detect it by immunohistochemistry. The board notes that document D5, for example, discloses immunohistochemistry for the detection of cyclins and Ki-67 which are both nuclear proteins.

14. The examining division held that the claimed subject-matter was obvious because it was *"a matter of simple experimentation"* to find out, if GP88 was a tumour marker that could be detected by immunohistochemistry.

According to the case law the skilled person is in a "try and see situation" only if he or she has, in view of the prior art, already clearly envisaged entities to be tested and then determined by routine tests whether or not such entities have the desired effect (see Case Law of the Boards of Appeal, 6th edition 2010, I.D.6., 6th paragraph). However, as outlined above, the conclusion that the skilled person would have envisaged GP88 as a possible candidate for immunohistochemical detection cannot be drawn. Thus, the examining division's argumentation is not convincing.

15. The subject-matter of claim 1 involves an inventive step. The requirements of Article 56 EPC are fulfilled.

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 grant a patent on the basis of the main request filed on 7 November 2013 at the oral proceedings and a description and figures to be adapted thereto.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith

Decision electronically authenticated