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Datasheet for the decision of 15 January 2015

Case Number: T 0908/10 - 3.3.04

Application Number: 99921843.1

Publication Number: 1079851

IPC: A61K38/02, A61K38/22

Language of the proceedings: EN

Title of invention:
Use of anti-prolactin agents to treat cancer

Patent Proprietor:
Oncolix, Inc.

Opponent:
Novo Nordisk A/S

Headword:
Prolactin variants/ONCOLIX

Relevant legal provisions:
EPC Art. 56, 83

Keyword:
Inventive step - main request, auxiliary requests 1 to 7 (no)
Sufficiency of disclosure -
main request, auxiliary requests 1 to 3, 5, 7, 8 (no)

Decisions cited:
T 0970/00

Catchword:

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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 0908/10 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 15 January 2015

Appellant: (Patent Proprietor)	Oncolix, Inc. 14405 Walters Rd. - Suite 1008 Houston, Texas 77014 (US)
Representative:	Wright, Simon Mark J A Kemp 14 South Square Gray's Inn London WC1R 5JJ (GB)
Respondent: (Opponent)	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd (DK)
Representative:	Potter Clarkson LLP The Belgrave Centre Talbot Street Nottingham, NG1 5GG (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 26 February 2010 concerning maintenance of the European Patent No. 1079851 in amended form.**

Composition of the Board:

Chairwoman	G. Alt
Members:	R. Morawetz
	K. Garnett

Summary of Facts and Submissions

I. The appeal of the proprietor (hereafter "appellant") lies against the interlocutory decision of the opposition division concerning maintenance of the European patent No. 1 079 851 in amended form. The patent at issue has the title "*Use of anti-prolactin agents to treat cancer*".

II. 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), and under Article 100(b) EPC.

III. The opposition division decided that the subject-matter of claim 1 of the main request lacked an inventive step in view of the teaching of document D1 when combined with that of document D3. In relation to the subject-matter of claim 12 of the main request the opposition division held that the patent did not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. Auxiliary requests 1 to 8 were likewise held not to comply with Article 56 EPC and/or Article 83 EPC for the same reasons as for the main request. On the other hand, the claims of auxiliary request 9 were considered to fulfill the requirements of the EPC.

IV. With its letter dated 6 July 2010 the appellant filed a statement of grounds of appeal, a main request and auxiliary requests 1 to 9. The claim requests were identical to the corresponding requests underlying the decision under appeal. Claims 1, 9, 10, 11 and 12 of the main request read as follows:

"1. Use of a variant of human prolactin having a

substitution of the glycin at position 129 for the preparation of a medicament for inhibiting the proliferation of a breast or prostate cancer cell which expresses a prolactin receptor.

9. A fusion protein comprising a variant of human prolactin which is linked to another protein, wherein the variant has a substitution of the glycine at position 129.

10. A fusion protein according to claim 9, wherein the prolactin variant is linked to interleukin 2.

11. A fusion protein according to claims 9 or 10, wherein the variant has a substitution of the glycine at position 129 with arginine.

12. Use of a fusion protein according to any one of claims 9 to 11 for the preparation of a medicament for treating breast or prostate cancer, wherein said breast or prostate cancer expresses a prolactin receptor."

The claims of auxiliary request 1 are identical to those of the main request except that claims 1 and 9 have been amended to specify that the glycine at position 129 is substituted with valine, leucine, isoleucine, serine, threonine, proline, tyrosine, cysteine, methionine, arginine, histidine, tryptophan, phenylalanine, lysine, asparagine, glutamine, aspartic acid, or glutamic acid.

The claims of auxiliary request 2 are identical to those of the main request except that claims 1 and 9 have been amended to specify that the glycine at position 129 is substituted with arginine, histidine or lysine.

The claims of auxiliary request 3 are identical to those of the main request except that claims 1 and 9 have been amended to specify that the glycine at position 129 is substituted with arginine.

The claims of auxiliary request 4 are identical to those of the main request except that fusion protein claims 9 to 12 have been deleted.

The claims of auxiliary request 5 are identical to those of the main request except that the reference to "prostate" cancer has been deleted from claims 1 and 12.

The claims of auxiliary request 6 include all the amendments made to form auxiliary requests 3, 4 and 5.

Auxiliary request 7 is identical to auxiliary request 2 except that claims 9 and 10 have been combined.

Auxiliary request 8 is identical to auxiliary request 2 except that claims 1 to 5 have been deleted and claims 10 to 12 have been renumbered as claims 3, 2 and 1 respectively.

Auxiliary request 9 corresponds to the claims of auxiliary request 9 that were upheld by the opposition division.

V. The respondent received the statement of grounds of appeal but did not file any response.

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

D1 Goffin V. and P.A. Kelly, Journal of Mammary Gland Biology and Neoplasia (1997), vol. 2, pages 7-17

D2 Fuh G. and J.A. Wells, The Journal of Biological Chemistry (1995), vol. 270, pages 13133-13137

D3 Goffin V. et al., The Journal of Biological Chemistry (1996), vol. 271, pages 16573-16579

D6 Goffin V. et al., The Journal of Biological Chemistry (1994), vol. 269, pages 32598-32606

D14 Goffin V. et al., Endocrine Reviews (2005), vol. 26, pages 400-422

D15 US2006/0277614 (2006)

D16 EP1463758 (2009)

VII. The parties were summoned to oral proceedings and were informed about the board's preliminary view in a communication pursuant to Article 15(1) RPBA.

VIII. Oral proceedings before the board were held on 15 January 2015. The respondent was absent, as had been announced by a telephone call to the registrar of the board on 9 January 2015. At the end of the oral proceedings the chairwoman announced the board's decision.

IX. The appellant's arguments submitted in writing and orally may be summarized as follows:

Main request

Inventive step: claim 1

Document D1 represented the closest prior art. Pursuant to decision T 970/00 an *ex-post facto* analysis of the prior art should be avoided. The skilled person reading D1 would have taken the reference to unpublished observations concerning the inhibition of proliferation in breast cancer cell lines with PRL site 2 mutants at face value. The unpublished observations of document D1 amounted to no more than a vague indication of a possible medical use for a chemical compound.

The technical problem was to provide a therapeutic agent for use in the treatment of breast or prostate cancer, wherein the cancer cells express a prolactin receptor (PRLR). The solution resided in the use of a variant of human prolactin (hPRL) having a substitution at glycine 129.

Documents D3 and D6 showed conflicting results as regards the effect of G129R-hPRL on PRLR and the skilled person would place more weight on the disclosure of document D6 than on the disclosure of document D3. A person skilled in the art would thus have been deterred from using the G129R-hPRL variant for treating breast cancer.

Documents D14, D15 and D16 gave insight into how the group that authored documents D1, D3 and D6 viewed their own results as reported there and set out the problems with the possible use of G129R-hPRL as cancer

therapeutic.

Sufficiency of disclosure: claim 12

Claim 12 was drawn up as a second medical use claim and was thus limited to fusion proteins that treated breast or prostate cancer. The opposed patent gave one example of a suitable fusion partner, IL-2, and described in detail how to screen fusion proteins for their ability to inhibit proliferation of breast and prostate cancer cells. Although it was not predictable whether or not a fusion protein possessed the therapeutic effect, the skilled person could design and produce suitable fusion proteins and test them using the assays disclosed in the patent in suit.

Auxiliary requests 1 to 8

No further arguments were submitted relating to these requests.

X. The respondent did not submit any arguments during the appeal proceedings.

XI. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request, alternatively one of auxiliary requests 1 to 9, all as filed with its letter dated 6 July 2010. The respondent did not file any requests during the appeal proceedings.

Reasons for the Decision

Main request

Introduction

1. The patent in suit relates to the inhibition of the cell proliferation-promoting effects of prolactin (PRL) on its receptor. The prolactin receptor (PRLR) is a member of the cytokine receptor superfamily and binds a group of hormones, including not only PRL but also growth hormone (GH) (see e.g. document D2, abstract). PRL and GH possess two binding sites for the receptor, termed binding site 1 and binding site 2. Binding of PRL or GH to PRLR is sequential. First the hormone, e.g. PRL, interacts with the receptor through its binding site 1, forming an inactive complex. The hormone then binds to a second receptor through its site 2, which leads to receptor homodimerisation and formation of an active complex (see e.g. document D1, page 10, left hand column, first full paragraph; Figure 3A).

2. By replacing small side chain residues with amino acids carrying large side chains, PRL and GH analogs whose binding sites 2 are sterically hindered and unable to interact with their receptor are generated. With these hormone analogs receptor dimerisation cannot occur and the hormone analog is inactive. Moreover, since such mutants maintain the ability to bind through their binding site 1, they block the receptor in the inactive 1:1 stoichiometry and thus act as hormone antagonists (see document D1, page 10, right hand column, first full paragraph; Figures 3B and 3C).

Inventive step (Article 56 EPC): claim 1

Closest prior art

3. Claim 1 concerns the use of a variant of human prolactin having a substitution of the glycin at position 129 for the preparation of a medicament for inhibiting the proliferation of a breast or prostate cancer cell which expresses a prolactin receptor.

4. The appellant submitted that document D1 represents the closest prior art and the board sees no reason to disagree. Document D1 discloses that it had recently been reported that the human breast cancer cell line T-47D secretes high amounts of hPRL which, in turn, exerts an autocrine/paracrine effect on cell proliferation. Moreover document D1 discloses that:

> "[w]e and others have shown that GH-(17) and that PRL-(18; Goffin, unpublished observation) site 2 mutants are able to antagonize such lactogen-induced (self-) proliferation of human breast cancer cell lines." (The numbers "17" and "18" in brackets are footnote references.)

5. The appellant said that the skilled person reading document D1 would take the reference to unpublished observations concerning the inhibition of proliferation in human breast cancer cell lines with PRL site 2 mutants at face value. However, that does not mean that the skilled person would have inferred that the unpublished observations represented merely a vague indication that a PRL site 2 mutant might be an antagonist of proliferation of breast cancer cell lines. The board considers that the skilled person would have had no reason to doubt the statement that

PRL-2 site mutants inhibit the proliferation of human breast cancer cell lines despite the absence of supporting experimental data.

6. If the skilled person nevertheless had had doubts about the reliability of the statement in document D1 relating to the effect of PRL site 2 mutants the board considers he would have consulted reference 17 in document D1 for studies carried out on human breast cancer cell lines with another type of PRL receptor antagonist, namely the GH site 2 mutants. Reference 17 is document D2 in the present appeal proceedings and it provides experimental evidence that variants of GH which bind to, but do not dimerize, the hPRL receptor inhibit the growth of various human breast cancer cell lines *in vitro* (see abstract; Figure 3).

7. In view of what was known at the priority date about the inhibition of the PRL receptor (see points 1 and 2 above), the board considers that the evidence provided by document D2 for GH site 2 mutants would be considered by the skilled person to corroborate the findings with regard to PRL site 2 mutants.

8. The appellant also relied on decision T 970/00, in which it was held (see reasons, point 4.1.2) that:

> "... any ex-post facto analysis, and in particular any conclusion going beyond what the skilled person would have objectively inferred, without the benefit of hindsight knowledge of the invention, from the prior art is of necessity at variance with a proper application of the problem-solution approach".

However, the board has already concluded (see points 5 to 7 above) that the skilled person would have inferred from the prior art that PRL site 2 mutants inhibit the proliferation of breast cancer cell lines. No hindsight knowledge of the invention is necessary to arrive at this interpretation of document D1.

Problem to be solved

9. The problem to be solved in view of document D1 is formulated by the board as the provision of a therapeutic agent for use in the treatment of breast or prostate cancer, wherein the cancer cells express a prolactin receptor. The solution consists in the provision of a variant of human prolactin having a substitution of the glycin at position 129.

Obviousness

10. When considering whether or not the claimed subject-matter constitutes an obvious solution to the technical problem, the question to be answered is whether or not the skilled person, in the expectation of solving the technical problem defined in point 9 above, would have modified the teaching in the closest prior art document D1 so as to arrive at the claimed invention in an obvious manner.

11. Document D1 itself does not disclose the nature of the PRL site 2 mutants that are able to antagonise the cell proliferation of human breast cancer cell lines. Accordingly, the claimed solution is not obvious from document D1 alone.

12. However, reference 18 in document D1 indicates PRL site 2 mutants that inhibit the proliferation of human

breast cancer cell lines (see point 4 above). Reference 18 in document D1 is document D3 in the present appeal proceedings. Therefore, the skilled person, being aware of the teaching of document D1, would turn to document D3 in order to get information about the PRL site 2 mutants. Document D3 discloses two binding site 2 mutants of hPRL, namely A22W-hPRL and G129R-hPRL. As summarised in Table 1 of document D3, both are able to antagonize the action of wild type PRL, with G129R hPRL being the more potent antagonist than A22W hPRL in the bioassay used (see paragraph bridging pages 16577 and 16578; Table 1). Document D3 thus prompts the skilled person faced with the problem formulated above to try and use the G129R-hPRL site 2 mutant in order to provide a solution to the problem. In view of the disclosure of document D1 (see points 4 and 5 above), he would also have had a reasonable expectation of success.

13. The appellant submitted that at the priority date of the opposed patent (i) documents D3 and D6 disclosed different effects for PRL site 2 variants, (ii) the skilled person would have placed more weight on the disclosure of document D6 than on the disclosure of document D3 (because document D6 used the Nb2 cell proliferation assay which was considered to be the gold standard for assessing the activity of PRL agonists and antagonists) and (iii) a person skilled in the art would thus have been deterred from using the G129R-hPRL variant for treating breast cancer.

14. The board is unable to accept this line of argument, for the following reasons:

(a) Although it is correct that document D6, published in 1994, shows an agonistic effect of G129R-hPRL in Nb2

rat lymphoma cells, document D3, published in 1996, and thus 2 years later, reports that G129R-hPRL shows antagonistic properties on PRLR in an artificial system in which HEK-293 cells are transiently transfected with human and rat PRLR and luciferase under the control of a lactogenic hormone response element. In fact, the experiments of document D3 were carried out because the results obtained in document D6 were considered to be unexpected and paradoxical by the authors of D3, who were also the authors of D6. Moreover, D3 offers an explanation for the observed inconsistencies. Thus, document D3 proposes (see the abstract) that the agonistic/antagonistic properties of human prolactin analogs are species-specific.

(b) Although it is correct that document D6 used the rat Nb2 cell proliferation assay, which was considered to be the gold standard for assessing the activity of PRL agonists and antagonists at the time, document D3 questions its appropriateness for assessing agonistic/ antagonistic properties of PRL/GH analog mutants at binding site 2, especially if human hormones are considered (see document D3, page 16578, right hand column, at the end of the first paragraph).

(c) Document D1 reports that PRL-site 2 mutants are able to antagonize the proliferation of human breast cancer cells. The skilled person, when faced with the problem set out above (see point 9), would have considered these results, which were obtained in human breast cancer cell lines, more relevant than any results obtained in either the Nb2 rat lymphoma assay of document D6 or in the transient Hek-293 cell transfection assay of document D3.

For these reasons, the appellant's argument that the person skilled in the art would have been deterred from using the G129R-hPRL variant for treating breast cancer cannot be accepted.

15. The board is also unable to accept the appellant's argument that the authors of documents D1, D3 and D6 considered G129R-hPRL to be unsuitable as a cancer therapeutic. In this context, the appellant relied on statements made by the authors of documents D1, D3 and D6 in their later publications, namely documents D14 to D16. However, documents D14 to D16 were published after the filing date of the patent in suit. Therefore, any statements made therein were not available to the skilled person at the effective date of the patent in suit, the relevant date for the assessment of inventive step, and could thus not play any role in the considerations of the skilled person.

16. Accordingly, the board comes to the conclusion that the subject-matter of claim 1 is rendered obvious to a person skilled in the art by the combined teaching of documents D1 and D3.

17. In view of the above considerations, the subject-matter of claim 1 of the main request lacks an inventive step and the request is therefore for this reasons alone not allowable.

Sufficiency of disclosure (Article 83 EPC): claim 12

18. In view of the fact that the main request is in any event not allowable for lack of inventive step, it is strictly not necessary for the board to say anything about the Article 83 EPC objection against claim 12 of the main request. However, the board's view on this

issue has consequences for the auxiliary requests and so it is convenient to deal with the issue here.

19. Claim 12 of the main request concerns the use of a fusion protein comprising a variant of human prolactin which is linked to another protein, wherein the variant has a substitution of the glycine at position 129 for the preparation of a medicament for treating breast or prostate cancer, wherein said breast or prostate cancer expresses a prolactin receptor.

20. Claim 12 is drafted as a second medical use claim and thus attaining the claimed therapeutic effect, namely treating breast or prostate cancer, is a functional technical feature of the claim. The relevant question to be addressed in the context of Article 83 EPC is whether or not the patent in suit provides enough guidance for the skilled person to manufacture fusion proteins which also show the claimed therapeutic effect without undue burden or rather whether the skilled person is faced with a research program for which no guidance is forthcoming.

21. The sole disclosure in the patent as regards fusion proteins is to be found in paragraphs [0017] and [0027]. Paragraph [0017] discloses a fusion protein comprising a PRL variant having a substitution of the glycine at position 129 linked to another protein while [0027] reads as follows:

"In yet other embodiments, a prolactin variant having a substitution of the glycine at position 129 is linked to another protein as part of a fusion protein. As one specific embodiment, the prolactin variant may be linked to interleukin 2. One nonlimiting example of such an embodiment is a G129R variant of human

prolactin linked to interleukin 2."

22. These paragraphs thus disclose the linkage of hPRL variants, e.g. of the G129R-hPRL variant, to other proteins, e.g. to interleukin 2, but are silent as regards the type of linker used, the location of the linkage on the prolactin variant, or any other suitable fusion partner of the prolactin variants wherein the resulting fusion protein will have the effect of treating breast or prostate cancer.

23. According to the patent, the treatment of breast or prostate cancer relies on the inhibition of the cell proliferation-promoting effects of PRL on its receptor (see paragraphs [0001], [0018]). The patent is silent as regards the mechanism underlying this inhibition. From the prior art it is however clear that the prolactin variants act as antagonists by binding to the hPRL receptor through their binding site 1 while at the same time not dimerizing it, due to changes in their binding site 2 (see point 2 above). In order to function as an inhibitor of cell proliferation the fusion protein must thus retain the ability of the prolactin variant to bind to the hPRL receptor through binding site 1. The board considers it likely that the size of the fusion partner and the location of the linkage on the prolactin variant have an influence on the binding of the prolactin variant to the hPRL receptor by virtue of, e.g., changes in the three dimensional conformation of the protein and/or steric hindrance.

24. Without any information in the patent as regards the effect of the linker, the fusion partner or the location of linkage on the binding site 1 of the prolactin variant, the skilled person has to produce

and test each and every fusion protein by a trial and error in order to determine whether or not the particular choice of linker, fusion partner and location of linkage provides a fusion protein having the claimed therapeutic effect.

25. This was not contested by the appellant, who conceded that without testing a particular fusion protein it was not predictable whether it would possess the claimed therapeutic effect.

26. The board considers that in the present case, in view of the lack of technical guidance and details in the patent, the production and the testing of fusion proteins showing the claimed therapeutic effect amounts to a research program which represents an undue burden for the skilled person.

27. The board concludes from the above that the subject-matter of claim 12 of the main request fails to meet the requirement of Article 83 EPC.

Auxiliary requests 1 to 7: inventive step (Article 56 EPC)

28. In the board's judgment the board's conclusions under Article 56 EPC for the subject-matter of claim 1 of the main request (see points 3 to 17, above) apply, *mutatis mutandis*, to the corresponding claims of auxiliary requests 1 to 7. These requests are therefore, for this reason alone, not allowable.

Auxiliary request 8: sufficiency of disclosure (Article 83 EPC)

29. In the board's judgment the board's conclusions under Article 83 EPC for the subject-matter of claim 12 of the main request (see points 18 to 27, above) apply,

mutatis mutandis, to the corresponding claim of auxiliary request 8 (and indeed of auxiliary requests 1, 2, 3, 5 and 7), so that auxiliary request 8 is for this reason alone not allowable.

Auxiliary request 9

30. Auxiliary request 9 corresponds to the claims as allowed by the opposition division. Since the proprietor is the sole appellant, nothing further needs to be said about this request.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated