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Datasheet for the decision of 14 December 2012

Case Number: T 1430/08 - 3.3.08

Application Number: 93915447.2

Publication Number: 647275

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Cloning and expression of gonadotropin-releasing hormone receptor

Patentee:
Mount Sinai School of Medicine

Opponents:
Ardana Bioscience Limited
Abbott Products GmbH
AEterna Zentaris GmbH

Headword:
Gonadotropin-releasing hormone receptor/MOUNT SINAI

Relevant legal provisions:
EPC Art. 54, 56
RPBA Art. 13(3)

Keyword:
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
T 0465/92

Catchword:
-

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Case Number: T 1430/08 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 14 December 2012

Appellant: (Opponent 03)	AEterna Zentaris GmbH Weismüllerstraße 45 D-60314 Frankfurt/Main (DE)
Representative:	Polypatent Postfach 40 02 43 D-51410 Bergisch Gladbach (DE)
Respondent: (Patent Proprietor)	Mount Sinai School of Medicine One Gustave Levy Place New York, NY 10029-6574 (US)
Representative:	Jones Day Rechtsanwälte, Attorneys-at-Law, Patentanwälte Prinzregentenstraße 11 D-80538 München (DE)
Party as of right: (Opponent 02)	Abbott Products GmbH Hans-Boeckler-Allee 20 D-30173 Hannover (DE)
Representative:	Bauriegel, Lutz Abbott Products GmbH IP Department (PH-ZP) Hans-Böckler-Allee 20 D-30173 Hannover (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 13 June 2008 concerning maintenance of the European patent No. 647275 in amended form.**

Composition of the Board:

Chairman: M. Wieser
Members: M. R. Vega Laso
R. Moufang

Summary of Facts and Submissions

I. European patent No. 0 647 275 with the title "Cloning and expression of gonadotropin-releasing hormone receptor" was granted on European patent application No. 93915447.2 (published as WO 94/00590). The patent was granted with 36 claims.

II. Three oppositions were filed based on the grounds for opposition of Article 100(a), (b) and (c) EPC, in particular that the claimed subject-matter lacked novelty (Article 54 EPC) and an inventive step (Article 56 EPC), and also extended beyond the content of the application as filed, and that the invention as claimed was not disclosed in the patent in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

III. In an interlocutory decision under Article 101(3)(a) and 106(2) EPC posted on 13 June 2008, the opposition division held that the ground of opposition of Article 100(c) EPC prejudiced the maintenance of the patent in the granted form (main request), but that taking into account the amendments introduced into the set of claims according to auxiliary request I and the adapted description filed at the oral proceedings, the patent and the invention to which it related met the requirements of the EPC.

IV. Claims 1, 2, 5, 6 and 8 of the set of claims filed as auxiliary request I read as follows:

"1. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes:

(a) a polypeptide having the amino acid sequence SEQ ID NO: 2; or

(b) the complement of the nucleotide sequence of (a).

2. The isolated DNA molecule according to claim 1 comprising the nucleotide sequence of SEQ ID NO: 1.

5. An expression vector comprising the nucleotide sequence of claim 1, or 2, operatively associated with a regulatory nucleotide sequence containing transcriptional and translational regulatory information that controls expression of the nucleotide sequence in a host cell.

6. A cell that comprises a recombinant nucleic acid molecule comprising the nucleotide sequence of claim 1.

8. An isolated GnRH receptor comprising the amino acid sequence of SEQ ID NO: 2."

V. The patent proprietor and opponent 03 each lodged an appeal against the interlocutory decision of the opposition division.

VI. Opponent 03 (appellant) duly filed a statement of grounds of appeal and requested, *inter alia*, oral proceedings under Article 116 EPC.

VII. The patent proprietor (respondent) did not submit a statement of grounds of appeal. Its appeal was rejected as inadmissible by an interlocutory decision dated 11 May 2009 (Article 108 in conjunction with Rule 101(1) EPC).

VIII. The respondent replied to the appellant's grounds of appeal, but did not put forward any arguments concerning the substance of the appeal. It requested oral proceedings in the event that the board did not intend to dismiss the pending appeal.

IX. The party as of right (opponent 02) did not make any submissions.

X. The board summoned the parties to oral proceedings. In a communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) attached to the summons, the board expressed its provisional opinion on the issues of novelty and inventive step.

XI. The oral proceedings were re-scheduled upon request by the respondent.

XII. On 17 October 2012, the representative of former opponent 01 informed the board that his client was no longer in existence and so would not be represented at the oral proceedings.

XIII. By letter dated 17 October 2012, the party as of right informed the board that it would not be represented at the oral proceedings. A few days later a request to record a change of name for the party as of right was filed.

XIV. On 26 November 2012, the respondent withdrew its request for oral proceedings and informed the board that it would not be represented at the oral proceedings.

XV. Thus, at the oral proceedings, which were held on 14 December 2012, only the appellant was represented.

XVI. The following documents are referred to in the present decision:

(3): J. Reinhart et al., 1992, The Journal of Biological Chemistry, Vol. 267, No. 30, pages 21281 to 21284;

(9): S. C. Sealfon et al., 1990, Molecular Endocrinology, Vol. 4, No. 1, pages 119 to 124;

(11): W. C. Probst et al., 1992, DNA and Cell Biology, Vol. 11, No. 1, pages 1 to 20;

(12): M. S. Wright et al., 1992, Acta Endocrinologica, Vol. 126, pages 97 to 104.

XVII. The submissions made by the appellant, orally or in writing, were essentially as follows:

Article 54 EPC - Novelty

Document (9) described the isolation of both pituitary RNA and RNA from cells of the αT_3 cell line (see second full paragraph on page 123). Moreover, it was stated in this document that the αT_3 cell line was a suitable source for the cDNA cloning of the GnRH receptor (see page 122, right-hand column, last sentence). As apparent from paragraph [0067] of the patent in suit, the RNA used as starting material for cloning the claimed nucleic acid molecules was isolated by the same method as described in document (9). cDNA cloning from

isolated mRNA was a standard method at the priority date and within the normal capabilities of a person skilled in the art.

Claims 1 and 2 encompassed both DNA and RNA. Since an mRNA comprising the nucleotide sequence specified in either claim 1 or 2 was contained in the mRNA pool obtained by fractionation of cells of the αT_3 cell line as described in the second full paragraph on page 123 of document (9), a person skilled in the art could isolate it applying standard methods. The term "isolated" characterizing the claimed nucleic acid was not defined in the patent in suit; thus, this term had to be interpreted broadly as meaning that the nucleic acid had been extracted from a cell, further purification not being required. Consequently, the content of document (9) was novelty-destroying.

Since document (9) described expression of the GnRH receptor in oocytes, the oocytes had to contain a nucleic acid encoding the receptor. Thus, the content of document (9) destroyed also the novelty of the subject-matter of claim 6.

Article 56 - Inventive step

Document (9) represented the closest state of the art. The sole difference between the teaching of document (9) and that of the patent in suit was the specific nucleotide sequence. In view of document (9), the objective technical problem to be solved was to obtain the sequence of the GnRH receptor. This technical problem and the solution proposed in the patent in suit,

i.e. how to obtain a cDNA clone, were described explicitly in document (9).

The person skilled in the art would derive from document (9) that a cDNA library for cloning the GnRH receptor gene could be prepared using as starting material either an RNA fraction having a size of 6-7 kilobases isolated from cells of the αT_3 cell line, or a crude mRNA preparation from αT_3 cells. If confronted with a failure using the fraction with an RNA size of 6-7 kilobases for cloning the GnRH receptor, a scientist would try alternative approaches, in particular he/she would use a crude RNA preparation. Thus, following the technical indications given in document (9) and applying methods known in the art and described in documents (12) and (8), a person skilled in the art would be able to isolate the claimed nucleic acid molecule.

Alternatively, the skilled person would try the cloning strategy disclosed in document (12) and use homologous sequences from other members of the G-protein coupled receptor superfamily described in document (11) to screen for a cDNA encoding the GnRH receptor.

Since the skilled person following either approach would arrive at a nucleic acid molecule according to claim 1 or 2 without applying inventive skills, an inventive step should not be acknowledged. The same applied to the expression vector according to claim 5, the cell according to claim 6 and the isolated GnRH receptor according to claim 8.

XVIII. The appellant (opponent 03) requested that the decision under appeal be set aside and the patent revoked.

XIX. The respondent (patent proprietor) requested in writing that the appeal be dismissed.

XX. The party as of right (opponent 02) did not put forward any requests.

Reasons for the Decision

Articles 123(2)(3) and 84 EPC

1. In opposition proceedings, the opponents did not raise any objections under Articles 123(2)(3) and 84 EPC in respect of the claims according to auxiliary request 1, and the opposition division found that these articles were not contravened. In appeal proceedings, the appellant has not put forward any arguments in this respect. Since the board sees no reason to raise any objections of its own motion, the amendments introduced into the claims and the amended claims are regarded as conforming to, respectively, Articles 123(2)(3) and 84 EPC.

Article 83 EPC - Sufficiency of disclosure

2. The appellant did not contest the opposition division's finding that the invention claimed according to the auxiliary request I fulfils the requirements of Article 83 EPC (see decision under appeal, page 6, last paragraph under the heading "Auxiliary request I (AR1) as filed during the oral proceedings"). The board does

not see any reason to disagree with the findings of the opposition division in this respect. Thus, the requirements of Article 83 EPC are considered to be met.

Article 54 EPC - Claims 1, 2 and 6

3. In the decision under appeal, the opposition division held that with regard to document (9) the subject-matter of claims 1 and 2 was novel. In the view of the opposition division, document (9) described only pools of mRNAs, but no isolated nucleic acid molecule with the particular nucleotide sequence specified in claims 1 and 2 (see page 7, first paragraph of the interlocutory decision). The appellant has contested this finding.

4. Having considered the arguments put forward by the appellant (see paragraph XVII above), the board is not convinced that, in view of content of document (9), the subject-matter of claims 1 and 2 lacks novelty. It is well established in the jurisprudence of the Boards of Appeal that, for the subject-matter of a claim to lack novelty, it must be clearly and directly derivable from a document that forms part of the state of the art as defined in Article 54(2) or (3) EPC (see e.g. T 465/92, OJ EPO 1996, 32). In the present case, document (9) describes the fractionation of total RNA obtained from cells of the αT_3 cell line by applying the RNA onto a sucrose gradient and, after centrifugation, collecting one-millilitre fractions (see page 123, left-hand column, paragraph under the heading "RNA isolation and Fractionation"). Contrary to appellant's view, the disclosure of either an RNA pool obtained from cells of the αT_3 cell line, or the fractions obtained after

gradient centrifugation of the RNA pool cannot be regarded as the disclosure of **each** of the (thousands of) individual RNAs present in the RNA pool or the gradient fractions, let alone as the disclosure of a particular mRNA having the features specified in claim 1 or 2, i.e. comprising either the nucleotide sequence of SEQ ID NO: 1 or its complement, or a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO: 2. Since - as the appellant admitted - further steps would be required to isolate and characterize a specific nucleic acid molecule as claimed, neither the subject-matter of claim 1 nor that of claim 2 can be regarded as being **directly** derivable from document (9). In this aspect, the board, in line with established case law, disagrees with the appellant's broad interpretation of the term "isolated" (see paragraph XVII above). Thus, the content of document (9) is not considered to be prejudicial to the novelty of the claimed subject-matter.

5. Also the subject-matter of claim 6 is considered to be novel with regard to the disclosure in document (9), because a cell that comprises a **recombinant** nucleic acid molecule comprising the nucleotide sequence of claim 1 is not directly and unambiguously derivable from the document in question.

Article 56 EPC - Inventive step

6. The appellant agreed with the opposition division's finding that document (9) represents the closest state of the art and the appropriate starting point for the assessment of inventive step. So does the board.

7. Document (9) describes the use of a bioassay for the characterization of the rodent GnRH receptor in *Xenopus* oocytes, and suggests that the described bioassay may serve as a tool for cloning a cDNA encoding the GnRH receptor protein (see page 122, right-hand column, last sentence). Oocytes injected with either pituitary RNA or RNA isolated from the gonadotroph αT3 cell line isolated from transgenic mice were shown to develop a response to gonadotropin-releasing hormone (see Figure 1). Since the latter cell line was considered to be potentially an excellent source for cloning the GnRH receptor using oocyte expression, the expression of the GnRH receptor in oocytes injected with αT3 RNA was studied and the apparent size of the mouse GnRH receptor mRNA was determined by sucrose gradient fractionation (see paragraph bridging pages 119 and 120). The maximal response to GnRH was obtained in oocytes injected with RNA from a sucrose gradient fraction corresponding to an mRNA of approximately 6-7 kilobases (see page 121, right-hand column, first full paragraph; Figure 6; and page 122, right-hand column, first sentence of the third full paragraph).

8. In the appellant's view, the sole difference between the subject-matter of claims 1 and 2 and the content of document (9) is the absence in the latter of a specific nucleotide sequence. The board does not share this view. As stated above in connection with the issue of novelty, document (9) does not disclose an **isolated** nucleic acid molecule with the features specified in either claim 1 or claim 2. Thus, starting from document (9) the problem to be solved cannot be regarded solely as the provision of the specific nucleotide sequence, but rather as the provision of an isolated nucleic acid

molecule having a nucleotide sequence that encodes the murine gonadotropin-releasing hormone receptor (GnRH receptor).

9. The appellant has not disputed that this problem is solved by a nucleic acid molecule according to claim 1 or claim 2. Thus, the sole issue to be decided is whether or not the solution provided in claim 1 or claim 2 was obvious to a person skilled in the art at the relevant date.

10. In the board's view, having regard to the statements in passage on page 121, right-hand column, last paragraph of the chapter "Results" of document (9), which are based on the results shown in Figure 6, the skilled person seeking to isolate the gene encoding the murine GnRH receptor would regard the RNA fraction showing the maximum response in oocytes, i.e. fraction 6 in Figure 6, as the most promising starting material for preparing a cDNA library. According to document (9), this fraction corresponds to a RNA size of approximately 6-7 kilobases.

11. Thus, the obvious approach for a skilled person was to try to clone the receptor by preparing a cDNA library from the fraction of the sucrose gradient containing RNA with a size of 6-7 kb. Methods for constructing a complementary DNA library (cDNA library) of a size such that the probability of containing a given receptor protein existing in a cell line exceeds 99%, were well known in the art (see, e.g., document (12), paragraph bridging pages 97 and 98). Contrary to appellant's view, the board is unable to see any reason why a person skilled in the art would have disregarded the

statements in document (9) indicating the likely size of the GnRH receptor mRNA, and would have used a "crude" RNA sample as starting material for the preparation of the cDNA library, instead of the RNA fraction corresponding to a size of 6-7 kb.

12. As stated by the opposition division in the decision under appeal, there is no evidence on file credibly showing that the murine GnRH receptor gene could be isolated from such a cDNA library. In fact, neither in opposition nor in appeal proceedings has the appellant put forward any evidence showing that the 6-7 kb RNA fraction may contain murine GnRH receptor RNA from which the corresponding cDNA could be obtained by reverse transcription. The evidence in the patent itself and in document (3), which was published after the first priority date, suggests the contrary. It is stated in the patent that the insert in the cDNA clone WZ25 corresponding to the murine GnRH receptor mRNA was **1.3 kb** in length (see paragraphs [0068] and [0069] of the patent in suit), and according to document (3) expression of murine GnRH receptors was observed upon injection of fractions from a gradient containing poly(A)$^+$ RNA of **~2 kb** in *Xenopus* oocytes (see document (3), paragraph bridging pages 21281 and 21282 and first full paragraph on page 21282).

13. During the oral proceedings, the appellant alleged that the 6-7 kb RNA fraction might contain GnRH receptor RNA which has not yet been spliced and includes intron sequences that account for the difference between the putative size indicated in document (9) and the actual size of the mRNA as specified in the present patent. However, the appellant failed to provide any evidence

in support of its allegation, in particular evidence showing that the **genomic** sequence encoding the murine GnRH receptor has in fact a length of 6-7 kilobases and includes intron sequences.

14. Hence, like the opposition division, the board concludes that, relying on the technical information provided in document (9), either alone or combined with document (12), the skilled person would not have arrived at a nucleic acid molecule as claimed in claim 1 or 2. Confronted with a failure, the skilled person would have had to devise a new strategy for cloning the murine GnRH receptor gene, for which he/she did not found any guidance in document (9).

15. At the oral proceedings, the appellant put forward a second line of argument based on a combination of documents (12) and (11) (see paragraph XVII above). Document (12) outlines various cloning strategies for peptide hormone receptors, and document (11) describes a sequence alignment of the G-protein coupled receptor (GPR) superfamily. It is stated in the latter document that the compilation of all the available amino acid sequences of the members of this family should prove useful for designing cloning strategies for other GPRs (see page 1, right-hand column, first sentence of the second paragraph).

16. Apart from the fact that this argument was submitted at a very late stage of the proceedings, the appellant failed to provide any convincing evidence that a person skilled in the art would be able to derive from the sequence alignment described in document (11) a specific sequence that could be successfully used to

isolate the murine GnRH receptor gene. In the absence of such evidence, the appellant's argument cannot be accepted.

17. In sum, the board concludes that the solution proposed in claims 1 and 2 involves an inventive step within the meaning of Article 56 EPC. The same is true for the invention as claimed in claims 5 and 6, which relies on the nucleic acid molecule of claims 1 or 2.

18. The board decided not to admit into the proceedings a further objection of lack of inventive step against claim 8. This objection was raised for the first time at the oral proceedings. Since the objection could not be dealt with without adjournment of the oral proceedings and, possibly, remittal to the opposition division, the board decided to disregard it in accordance with Article 13(3) of the Rules of Proceedings of the Boards of Appeal.

Conclusion

19. In view of arguments put forward by the appellant, the board sees no reason to set aside the decision under appeal.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Vottner M. Wieser