Datasheet for the decision
of 17 April 2007

Case Number: T 1190/03 - 3.3.04
Application Number: 96931047.3
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Language of the proceedings: EN
Title of invention: Orphan receptor
Patentee: KARO BIO AB
Opponents: D YOUNG & CO
Akzo Nobel N.V.
CHARLES HARDING
Headword: Orphan receptor/KARO BIO
Relevant legal provisions: EPC Art. 54, 56, 87, 99(1)
EPC R. 66, 67, 56(2), 55(a), 26(2)(c)
Keyword: "Main Request and Auxiliary Request (entitled "Third to Sixth Auxiliary Request"): right to priority (no); novelty (yes); inventive step (no)"
Decisions cited: G 0003/99, T 0025/85, T 0635/88
Catchword: -
Case Number: T 1190/03 – 3.3.04

DECISION
of the Technical Board of Appeal 3.3.04
of 17 April 2007

Appellant: KARO BIO AB
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Composition of the Board:  
Chairman: U. Kinkeldey  
Members: R. Gramaglia  
S. Perryman
Summary of Facts and Submissions

I. European Patent No. 0 792 292 based on European patent application No. 96 931 047.3 (published as WO 97/09348) and claiming priority from GB 9518272 filed on 8 September 1995 (document PD1), GB 9605550 filed on 15 March 1996 (document PD2), GB 9607532 filed on 11 April 1996 (document PD3) and GB 9609576 filed on 8 May 1996 (document PD4) was filed on 9 September 1996 on the basis of 17 claims.

II. Notices of opposition were filed by opponents (O1) to (O3) all requesting the revocation of the European patent on the grounds of Articles 100(a), (b) and (c) EPC. During the oral proceedings before the opposition division the patentee filed inter alia claims 1 to 13 of a new Main Request (Annex II to the decision under appeal), of which claims 1 to 4 read as follows:

"1. An isolated estrogen receptor (called ERβ) having the amino acid sequence of Fig. 1."

"2. An isolated estrogen receptor (called ERβ) having an amino acid sequence which is more than 95% identical to the amino acid sequence of Fig. 1."

"3. An isolated estrogen receptor (called ERβ) consisting of the amino acid sequence of Fig. 13A."

"4. An isolated estrogen receptor (called ERβ) consisting of the amino acid sequence of Fig. 14A."
wherein Fig. 1, Fig. 13A and Fig. 14A illustrated the amino acid sequences of rat ERβ, human ERβ and mouse ERβ, respectively. Claims 5 to 13 related to specific embodiments of the estrogen receptors according to claims 1 to 4, or DNAs encoding them or a drug design method and uses involving these estrogen receptors.

III. The opposition division considered that while claims of the above request pertaining to rat ERβ met the requirements of Article 56 EPC, those relating to mouse ERβ and human ERβ, did not. Hence the patent was maintained on the basis of claims 1 to 8 of the "Auxiliary Request 2" then on file (Annex IV to the decision under appeal), relating to rat ERβ only.

IV. The appellant (patentee) filed an appeal against the decision of the opposition division. The Statement of Grounds of Appeal dated 10 February 2004 included inter alia a Third Auxiliary Request and a Fourth Auxiliary Request. Claims 4 and 5 of Third Auxiliary Request and claims 3 and 4 of the Fourth Auxiliary Request were identical to claims 3 and 4 of the new Main Request (Annex II to the decision under appeal) rejected by the opposition division.

V. With the letter dated 19 March 2007 the appellant filed inter alia a Fifth and a Sixth Auxiliary Requests, of which claims 4 and 5 (Fifth Auxiliary Request) and claims 3 and 4 (Sixth Auxiliary Request) were identical to claims 3 and 4 of new Main Request (Annex II to the decision under appeal) rejected by the opposition division, except for the deletion of "(called ERβ)".
VI. With the Grounds of Appeal, the appellant raised, and maintained throughout the proceedings, the argument that the opposition by opponent (O1) was to be considered as inadmissible because the identity of opponent (O1) was not clearly and unmistakably identified by the end of the opposition period and this deficiency could not subsequently be rectified. The stated opponent, D Young & Co was a partnership and so had no legal personality under English law, and could not be considered as "any person" for the purposes of Article 99(1) EPC. That the opposition division had recognized this opposition as admissible amounted to a substantial procedural violation justifying a refund of the appeal fee. The appellant relied on decisions T 25/85 (OJ EPO 1986, 081), T 635/88 (OJ EPO 1993, 608), and G 0003/99 (OJ EPO 2002, 347).

In a communication dated 31 March 2004, the board indicated its opinion that the opposition by opponent (O1) could be treated as a common opposition by the then partners of D Young & Co at the date of filing of the opposition on 18 May 2000, and exercised its powers pursuant to Rule 66 EPC to invite opponent (O1) to state the full names of the common opponents at the date of filing of the opposition on 18 May 2000, within a period of 4 months from receipt of that communication. This was done by opponent (O1) by letter received 3 June 2004.

VII. Oral proceedings were held on 17 April 2007 in the absence of the appellant, who had previously informed the board that he would not attend.
VIII. The following documents are cited in the present decision:

D1 Koike S. et al., Nucleic Acids Research, Vol. 15, pages 2499-2513 (1987);


D10 Dechering K. et al., Current Medicinal Chemistry, Vol. 7, No. 5, pages 561-576 (2000);


IX. The submissions by the appellant (patentee) in writing, insofar as they are relevant to the present decision, can be summarized as follows:

Admissibility of the opposition by opponent (O1)

- The identity of opponent (O1) was not clearly and unmistakably identified by the end of the opposition period and this deficiency could not subsequently
be rectified. Therefore, the opposition by opponent (O1) had to be considered as inadmissible.

Main Request and the auxiliary requests entitled "Third to Sixth Auxiliary requests"

Inventive step

- Document D4 and document D5 did not unambiguously direct the skilled person towards the human ERβ and mouse ERβ amino acid sequence according to Fig. 13A and Fig. 14A disclosed in the specification. Therefore, it was not obvious to get the specific human ERβ and mouse ERβ amino acid sequence according to Fig. 13A and Fig. 14A disclosed in the specification, since it could not be taken for granted that these specific sequences would have been among the "spectrum" of variants of human and mouse ERβ which the skilled person would pick up upon repeatedly applying various screening procedures.

- Assuming that the skilled person would have accepted that the sequence in document D5 was indeed that of an ERβ, this document would not have provided any motivation to look for alternative sequences to that already disclosed in document D5.

- A further fact dissuading the skilled person from looking for alternative sequences to that already disclosed in document D5, was that this document did not demonstrate (no binding data) that the described polypeptide was a functional ERβ.
Later-published documents D10, D14 and D15 confirmed the doubts expressed by the scientific community about the disclosure by document D5 of a true ERβ nuclear receptor and about the uncertainties about its true N-terminus.

The substitution of a leucine in the claimed sequence for a proline in the sequence of document D5 (position 474) could have implications on the conformation/biological activity of the protein and thus achieve a technical distinction.

X. The submissions by respondents I, II and III (opponents (O1), (O2) and (O3)), insofar as they are relevant to the present decision, can be summarized as follows:

Admissibility of the opposition by opponent (O1)

- It was not necessary to discuss this issue since the patent had been opposed by two other parties (opponents (O2) and (O3)) and the notices of opposition by opponent (O1) and opponent (O2) were substantially identical.

Main Request and the auxiliary requests entitled "Third to Sixth Auxiliary requests"

Inventive step

- It was standard technique to use cDNA such as cDNA encoding rat ERβ (document D4) to design probes to fish out ERβ sequences from other species.

- The only differences between the claimed human ERβ and the disclosure in document D5 were that the ERβ
sequence in document D5 lacked eight N-terminal amino acids and exhibited one different amino acid. This document also provided a clear indication that a longer sequence encoding human ERβ could exist with an upstream (5'-) ATG translation initiation codon. Therefore, it would have been routine laboratory practice for the skilled person to use the sequence given in document D5 to obtain sequence information upstream to the given ATG translation initiation codon.

- As for the substitution of a leucine in the claimed sequence for a proline in the sequence of document D5 (position 474), the appellant has not shown that the claimed allele exhibited advantageous properties compared to the human ERβ described in document D5.

Requests

XI. The appellant had requested in writing that the decision of the Opposition Division in relation to the inventive step of claims 3 to 13 of the Main Request filed during oral proceedings and attached to the minutes of the contested decision as Annex II be set aside and that the patent be maintained on the basis of the request entitled Third Auxiliary Request filed on 10 February 2004 or, in the alternative, on the basis of one request entitled Fourth Auxiliary Request filed on 10 February 2004, or Fifth or Sixth Auxiliary Requests filed on 19 March 2007, and a refund of the appeal fee.

The respondents (opponents (O1) to (O3)) requested that the appeal be dismissed.
Reasons for the Decision

Admissibility of the opposition by opponent (O1)

1. The appellant argues that the opposition by opponent (O1) was to be considered as inadmissible because the identity of opponent (O1) was not clearly and unmistakably identified by the end of the opposition period and this deficiency could not subsequently be rectified. While, as argued by the appellant, it is true that a partnership under English law is not a legal person, for commercial and litigation purposes in England the name of a partnership, here D Young & Co, is accepted as a clear and convenient short identification of the partners acting in common. While strict compliance with Rules 55(a) and 26(2)(c) would require the individual partners to be named, the name of the partnership is considered by the board to clearly and unmistakably identify the opponent. Lack of the full names of the partners is considered by the board to be a deficiency to be treated under Rule 56(2) EPC, which means the opponent has to have failed to comply with an invitation to remedy the deficiency before the opposition can be rejected as inadmissible.

The opposition division did not issue such an invitation, and when the board did so, opponent (O1) remedied the deficiency within good time. Opposition (O1) must thus be treated as admissible.

1.1 The decisions relied on by the appellant do not lead to any different conclusion. In decision T 25/85 (OJ EPO 1986, 081), the facts were different in that the
opposition was explicitly filed on behalf of a third party which was not named until after the end of the opposition period, so that the case is not to the point. In decision T 635/88 (OJ EPO 1993, 608), the board had a legitimate doubt as to the identity of the opponent, and the opponent refused to comply with a request to clarify this doubt. This case is again not to the point, as here the board had no doubt as to the identity of the opponent, and the opponent did provide the further requested details. Enlarged Board of Appeal decision G 3/99 (OJ EPO 2002, 347) recognized that an opposition could be filed in common by a plurality of persons, and laid down conditions none of which the board can see as being violated here.

1.2 That the opposition division did not itself issue an invitation to remedy a perceived deficiency pursuant to Rule 56(2) EPC cannot be regarded as a substantial procedural violation. This argument for inadmissibility emerged clearly only at the appeal stage.

1.3 The board cannot see that there has been a substantial procedural violation on this or any other ground, and in the absence of such, and irrespective of the outcome of the appeal, there is no basis for considering a refund of the appeal fee pursuant to Rule 67 EPC.

**Substantive issues**

2. All the requests before the board (see paragraphs IV and V supra) include claims to the human ERβ (claim 3 of the Main Request filed during oral proceedings before the opposition division and attached to the minutes of the contested decision as Annex II; claim 4 of the
Third and Fifth Auxiliary Requests and claim 3 of the Fourth and Sixth Auxiliary Requests) and to mouse ERβ (claim 4 of the Main Request filed during oral proceedings before the opposition division and attached to the minutes of the contested decision as Annex II; claim 5 of the Third and Fifth Auxiliary Requests and claim 4 of the Fourth and Sixth Auxiliary Requests). For the purpose of the present decision, the board will focus on these claims, which are critical for the outcome of the appeal proceedings.

Entitlement to priority and relevant state of the art (Articles 87 and 54(2) EPC)

3. In the decision under appeal (see paragraphs 4.1 to 4.4), the opposition division found that the amino acid sequences of Figures 13A and 14A, relating to human and mouse ERβ, respectively, were not directly and unambiguously disclosed in any of the priority documents PD1 to PD4. In fact, priority documents PD1 and PD2 only dealt with the amino acid/DNA sequence of rat ERβ, while priority document PD3 provided the amino acid/DNA sequence of a "human ERβ" missing at least 130 residues and having 30 substitutions compared to the amino acid sequence of Fig. 13A. As for mouse ERβ, none of the priority documents PD1 to PD4 dealt with cloning ERβ from mouse. Consequently, the board sees no reason to diverge from the conclusion arrived at by the opposition division that the priorities claimed in the patent in suit are not considered to be valid in respect of subject-matter relating to the amino acid sequences of Figures 13A (human ERβ) and 14A (mouse ERβ).
4. It follows from the above that the effective date in the context of determining the state of the art relevant to assessment of novelty and inventive step of subject-matter relating to the amino acid sequences of Figures 13A (human ERβ) and 14A (mouse ERβ) is the filing date, i.e., 9 September 1996. Hence the relevant state of the art also comprises the content of intermediate documents D4 and D5, published before the filing date of the patent in suit.

Novelty (Article 54(2) EPC)

5. The respondents did not raise any objection of lack of novelty in respect of claims directed to human ERβ having the amino acid sequence of Fig. 13A and to mouse ERβ having the amino acid sequence of Fig. 14A. Having regard to prior art documents presently on file, the board concludes that these claims fulfil the requirements of Article 54 EPC.

Inventive step (Articles 56 EPC)

Mouse ERβ

6. Insofar as the claims cover mouse ERβ having the amino acid sequence of Fig. 14A (claim 4 the Main Request filed during oral proceedings before the opposition division and attached to the minutes of the contested decision as Annex II; claim 5 of the Third and Fifth Auxiliary Requests and claim 4 of the Fourth and Sixth Auxiliary Requests), document D4 is considered to be the closest prior art because it already discloses the cloning of rat ERβ. The difference between the claimed subject-matter and the disclosure in said closest prior art document is that the ERβ sequence is derived from
mouse. Thus the objective technical problem faced by
the patent in suit is the provision of the mouse ERβ
amino acid sequence. The proposed solution is the
provision of the specific sequence shown in Figure 14A
of the patent in suit.

7. It thus needs to be assessed whether the skilled person
starting from document D4 would have arrived in an
obvious way at the sequence of Fig. 14A to solve the
above problem. In the board's view, once the sequence
of a receptor from one species is known, it is normally
straightforward to identify and isolate the
corresponding gene from a cDNA library of another
mammalian species, using probes based on the known
sequence. For example, the rat ERα cDNA was cloned by
screening a rat uterus cDNA library with three probes
based on the known human ERα sequence, using standard
techniques (see document D1, pages 2500 and 2501, under
the headings "Preparation of rat uterus cDNA library"
and "Screening procedures"). Another approach was using
degenerate PCR primers designed on the basis of
conserved regions within the DNA and ligand binding
domains of nuclear receptors (see document D7).

8. Turning to the circumstances of the present case,
document D4 not only postulated the existence of a
mouse homologue of rat ERβ (see page 5930, first full
sentence: "...ERβ protein expressed in granulosa cells
of mice...") but also taught that rat ERβ was expressed
in the prostate and ovary. Hence, there was an
incentive for targeting mouse ERβ sequences from these
mouse tissues. Moreover, as regards the probes, rat DNA
probes were "less distant" from the mouse cDNA library
to be screened than were the probes in the situation
described in document D1, where human probes were used for screening a rat cDNA library. The board thus concludes that, once the key information represented by the rat ER\(\beta\) DNA sequence of Fig. 1 of document D4 was available to the public, it was within the reach of the skilled person to arrive in an obvious way, via the DNA, at the mouse ER\(\beta\) amino acid sequence of Fig. 14A. Consequently the mouse ER\(\beta\) of claim 4 of the Main Request filed during oral proceedings before the opposition division and attached to the minutes of the contested decision as Annex II, claim 5 of the Third and Fifth Auxiliary Requests and claim 4 of the Fourth and Sixth Auxiliary Requests lacks an inventive step in view of document D4 and the common general knowledge of the person skilled in molecular biology techniques.

9. The appellant contests this argumentation by stating that it was not obvious to get the specific mouse ER\(\beta\) amino acid sequence according to Fig. 14A disclosed in the specification. In the appellant's view, it could not be taken for granted that this specific sequence would have been among the "spectrum" of variants of mouse ER\(\beta\) which the skilled person would fish out upon repeatedly applying various screening procedures. The board accepts that various mouse ER\(\beta\) sequences may exist and that the skilled person could get sequences displaying some differences compared with the specific sequence disclosed in the patent in suit. This can be ascribed to the choice of a cDNA library from a different source or to selecting different screening tools or to point mutations/alternative splicing/incomplete splicing or post-translational further processing, etc.
10. However, the decisive question to be answered is whether or not the specific mouse ERβ sequence according to Fig. 14A disclosed in the specification was "hidden" in the sense that it could only be arrived at by selecting, among a great number of parameters, very specific and exotic tools/techniques (tissue, library, probes, biological activity test, etc) or in the sense that there were unforeseeable difficulties requiring an inventive effort to be solved. For example, if significant differences existed between the particular domains referred to in document D4 (see page 5925, r-h column, lines 4-8) and those in the mouse ERβ looked for, or if one or more of these domains was/were completely absent, a screening strategy designed on the basis of the sequence information provided in document D4 would have, most probably, failed. Yet there is no evidence before the board that one or more of the above hindrances actually affected the skilled person's route to the specific sequence of Fig. 14A. Hence, the board must conclude that the skilled person using the key information represented by the rat ERβ DNA sequence of Fig. 1 of document D4 supplemented by the common general knowledge would have arrived in an obvious way at, among other variants, the specific mouse ERβ amino acid sequence according to Fig. 14A disclosed in the specification.

_Human ERβ_

11. Insofar as the claims cover human ERβ having the amino acid sequence of Fig. 13 (claim 3 the Main Request filed during oral proceedings before the opposition division and attached to the minutes of the contested decision as Annex II; claim 4 of the Third and Fifth
Auxiliary Requests and claim 3 of the Fourth and Sixth Auxiliary Requests), document D5 is considered to be the closest prior art because it already discloses the cloning of another human ERβ. The differences between the claimed subject-matter and the disclosure in said closest prior art document are that the ERβ sequence in document D5 lacks eight N-terminal amino acids and exhibits one different amino acid (proline instead of leucine) at position 474 (see Fig. 1(B) of document D5). Thus the objective technical problem faced by the patent in suit is the provision of a further human ERβ. The solution proposed is the provision of the specific sequence shown in Figure 13A of the patent in suit.

12. The relevant question is whether or not the skilled person starting from document D5, would have arrived in an obvious way at the sequence of Figure 13A to solve the above problem.

13. In the board's opinion, the conclusions of points 7 and 8 supra that the skilled person would have arrived in an obvious way at the mouse ERβ amino acid sequence according to Fig. 14A, also apply, mutatis mutandis, to the cloning of a further human ERβ using probes based on the known sequence of another human ERβ (see Fig. 1A of document D5). The skilled person was able to work under even more favourable conditions compared with picking up the mouse ERβ amino acid sequence, since both species were the same (human vs. human) and no need arose to use degenerate probes, unlike the case of the mouse ERβ sequences (see point 7 supra) or the case described in document D1 (human vs. rat). As for the cDNA library to be screened, document D5 disclosed the tissue
distribution of human ERβ (see page 52, passage bridging l-h and r-h columns).

14. The appellant argues that, assuming that the skilled person would have accepted that the sequence in document D5 was indeed that of a human ERβ, this document would not have provided any motivation to look for a further human ERβ, alternative to that already disclosed in document D5. However, the board observes that the clones that have been picked up by the authors of document D5 did not contain the complete reading frame (see page 51, l-h column: "large part"). Thus there was still an incentive for the skilled to pick up the full-length sequence of the human ERβ gene, which would have brought clarity about the ambiguous 5'-end (and N-terminal residue of the protein) described in document D5. Fishing out the full-length sequence would also have rendered superfluous the troublesome technique used by the authors of document D5 for obtaining nucleotide sequence information downstream (3'-) to the anomalous splice site.

15. A further fact dissuading the skilled person from looking for alternative sequences to that already disclosed in document D5, in the appellant's opinion, was the failure by document D5 to demonstrate that the described polypeptide was a functional ERβ. But even if some doubts arose about the true nature of the protein encoded by the sequence disclosed in document D5, in the board's opinion, the skilled person was able to establish an "alignment report" (as done in Fig. 12 of the patent in suit) between the rat ERβ of document D4 and the protein cloned in document D5. The very high percent homology would have convinced the skilled
person that the protein cloned in document D5 encoded a human homologue of the rat ERβ described in document D4.

16. It is also the appellant's view that it was not obvious to get the specific human ERβ sequence disclosed in the specification, as this specific sequence might not have turned up among the "spectrum" of $2.56 \times 10^{10}$ possible variants of human ERβ which the skilled person could potentially pick up upon repeatedly applying various screening procedures.

17. Again, the decisive question to be answered is not how many variants of human ERβ might theoretically exist, but rather whether or not the specific and concrete human ERβ sequence according to Fig. 13A disclosed in the specification was "hidden" (among $2.56 \times 10^{10}$ theoretical variants or otherwise) for one or more of the reasons emphasised under point 10 supra. There is, however, no evidence before the board that one or more of the above hindrances actually affected the skilled person's path leading to the specific sequence of Fig. 13A. On the contrary, since no significant differences existed between the known sequence and the sequence looked for, picking up variant human ERβ sequences based on an already known human ERβ sequence cannot be compared to the case where some domain (either in the known sequence or in the sequence looked for) was completely absent. Hence, the board concludes that the skilled person using the key information represented by the human ERβ DNA sequence of Fig. 1A of document D5, supplemented by the common general knowledge would have arrived in an obvious way at, among other variants (considerably fewer than $2.56 \times 10^{10}$, because nature "retains" only useful variants),
the specific human ERβ amino acid sequence according to Fig. 13A disclosed in the specification.

18. The appellant also cited post-published documents D10, D14 and D15 as confirming the doubts about the disclosure by document D5 of a true ERβ nuclear receptor, or for illustrating the uncertainties about its N-terminus. However, it is not permissible to take these documents into account because they do not reflect the skilled person's view at the filing date of the patent in suit.

19. Finally, the appellant maintains that the substitution of a leucine in the claimed sequence for a proline in the sequence of document D5 (position 474) could have implications for the conformation/biological activity of the protein and thus achieve a technical distinction. However, the appellant has not shown that the claimed allele exhibits advantageous properties compared to the human ERβ described in document D5. No inventive step can thus be acknowledged in view of a possible technical distinction.

20. Nor can an inventive step be acknowledged on the grounds that the invention consists in a "selection invention" where one specific mouse or human ERβ are selected out of several possible variants belonging to the mouse or human ERβ families. To assume a selection in the present case presupposes that, at the filing date, mouse ERβ having the amino acid sequence of Fig. 14A and human ERβ having the amino acid sequence of Fig. 13A were part of the state of the art, from which the inventors, in the expectation of a particular technical effect, selected these particular
polypeptides. But no advantageous properties have been shown for the claimed alleles (see previous point), so that they cannot be regarded as inventive because they enable any particular technical effect to be achieved.

21. In summary, none of the appellant's claim requests before the board can be allowed.

Reimbursement of the appeal fee

22. Since, according to Rule 67 EPC, a reimbursement of the appeal fee is only possible if the board of appeal deems the appeal allowable, which is not the case here, there is no legal reason to allow this appellant's further request.
Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:  The Chair:

P. Cremona     U. M. Kinkeldey