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Datasheet for the decision of 28 June 2011

Case Number: T 0612/08 - 3.3.04

Application Number: 01964677.7

Publication Number: 1294751

IPC: C07K 14/435

Language of the proceedings: EN

Title of invention:
Dermacentor variabilis GABA-gated chloride channels

Applicant:
Merial Limited

Opponent:
-

Headword:
Dermacentor GABA channels/MERIAL LTD

Relevant legal provisions:
EPC Art. 56, 83, 84, 111(1), 123(2)

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request: clarity (yes); sufficiency of disclosure (yes), added subject-matter (no); inventive step (yes)"

Decisions cited:
-

Catchword:
-

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It can be changed at any time and without notice.

Case Number: T 0612/08 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 28 June 2011

Appellant: (Applicant)
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3239 Satellite Blvd.
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Representative:
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 30 October 2007 refusing European patent application No. 01964677.7 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: R. Gramaglia
B. Claes

Summary of Facts and Submissions

I. The appellant (applicant) lodged an appeal against the decision of the examining division on the refusal under Article 97(1) EPC 1973 of the European patent application No. 01 964 677.7 (published as WO-A-01/74884), having the title "*Dermacentor variabilis* GABA-gated chloride channels".

II. In its decision for refusing the present application, the examining division referred to the reasons given in its communication dated 29 August 2007, wherein it raised an objection on the ground of lack of inventive step only.

III. The decision under appeal was based on claims 1 and 2 filed with the applicant's letter dated 08 August 2007, which is now the main request before the board, reading as follows:

"1. A purified polypeptide, wherein said polypeptide comprises an amino acid sequence selected from SEQ. ID. NO. 1, SEQ. ID. NO. 2, and SEQ. ID. NO. 3".

"2. The polypeptide of claim 1, wherein said polypeptide consists of an amino acid sequence selected from SEQ. ID. NO. 1, SEQ. ID. NO. 2, and SEQ. ID. NO. 3",

where "SEQ. ID. NO. 1", "SEQ. ID. NO. 2", and "SEQ. ID. NO. 3" are amino acid sequences of polypeptides

belonging to GABA-gated chloride channels from *Dermacentor variabilis* (a tick species).

IV. The examining division considered document

D1 Henderson J.E. et al., Insect Biochem. Molec. Biol., Vol. 24, No. 4, pages 363-371 (1994)

to represent the closest prior art. Document D1 disclosed the cloning of a GABA receptor from Drosophila melanogaster using two homology probing procedures which made use of degenerate primers designed on conserved motifs in the transmembrane domains M2 and M3. The objective technical problem was formulated as being the provision of a further GABA receptor. The examining division concluded that it would have been obvious for a skilled person to use the strategy disclosed in document D1 to clone the GABA receptor gene of D. variabilis.

V. The following further documents are cited in the present decision:

D2 Ffrench-Constant R.H. et al., Proc. Natl. Acad. Sci. USA, Vol. 88, pages 7209-7213 (1991);

D4 Database TrEMBL online (01 January 1998), Accession no. O18469, from Yuhas D.A. et al., "Multiple isoforms of an rdl homologue in Helicoverpa virescens".

D11 Hosie A.M. et al., British Journal of Pharmacology, Vol. 115, pages 909-912 (1995);

D13 Jongjan F. et al., Rev. Sci. Tech. Off. Int. Epiz., Vol. 13, No. 4, pages 1201-1226 (1994);

D14 Searle A. et al., Aust. Vet. Practit., Vol. 25, No. 3, pages 157-158 (September 1995).

VI. Oral proceedings were held on 28 June 2011, during which the board introduced document D14 into the proceedings.

VII. The submissions by the appellant, insofar as they are relevant to the present decision, can be summarized as follows:

- The closest prior art document D14 might have motivated the skilled person to look for GABA channels in ticks. The problem was how to achieve this goal.

- The present application used a completely different strategy not suggested by the cited prior art to clone the genes (called Rdl^{Dv}) encoding the claimed sequences, since it was not obvious to fish out Rdl^{Dv} by using a part of GluCl1 (a different chloride channel) from another tick species.

- From the disclosure of document D1, a skilled person would neither know that homologous tick sequences existed nor expect that they could be isolated based on the methods described in document D1. This document would not have been seen by a skilled person as providing suitable probes and cloning strategies for use in isolating the corresponding gene in *D. variabilis*.

- The fact that the sequences obtained using the method of Example 1 of the present application turned out to show homology to the *D. melanogaster* Rdl-like sequences of document D1 was a surprising result which could not have been predicted by a skilled person, in view of the fact that insect and tick species were distantly-related.

- Even if a skilled person turned to document D1, he/she would find no suggestion that the sequences disclosed therein would be useful targets for compounds active against ticks, as document D1 did not even establish a function or use for the sequences it identified, let alone that they were targets for insecticides (as confirmed by the last paragraph of the description on page 370).

- Document D14 did not specifically disclose *D. variabilis* but *Ixodes holocyclus*, which belonged to a huge family of ticks (see document D13, page 1208, lines 1-2 under "Main Genera of Ixodid Ticks").

- The presently claimed GABA receptors were at least an order of magnitude more sensitive to channel blockers than the Drosophila receptors discussed in the prior art documents. This was a further surprising result which could not have been predicted by a skilled person at the priority date.

VIII. The appellant requests that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 and 2 of the main request filed on 11 August 2007 and the amended description filed during the oral proceedings.

Reasons for the Decision

1. The board first turns to the issue of inventive step (see the communication from the examining division dated 29 August 2007).

Closest prior art

2. The claims relate to GABA-gated chloride channel polypeptides useful for identifying molecules to be used for treating or preventing a *D. variabilis* infestation.

Document D1

3. This document aims at identifying sequences in *Drosophila melanogaster* (a species of fruit fly) having homology to vertebrate GABA receptors (see Abstract, first 3 lines on page 363; page 364, l-h column, second

paragraph; and page 368, l-h column, second and third paragraphs of document D1). The discussion of document D1 at pages 368 to 370 relates to a genetic analysis of the identified sequences in comparison to known homologous sequences, without providing any pharmacological characterisation of the identified gene products.

Document D13

4. This document discusses infestation with ticks of the *Dermacentor* genus, including *D. variabilis* (see paragraph 3 on page 1210). This document is also concerned with tick control, including the use of chemical acaricides such as pyrethroids (see page 1218, line 6).

Document D14

5. This document reports that ticks of the family *Ixodes holocyclus* attached to five dogs and one cat could be killed by means of a spray containing fipronil, an insecticide known from document D11 (see page 909, r-h column, lines 5-9) to block GABA-gated chloride channels.

6. The closest prior art for the purpose of objectively assessing inventive step is generally that which corresponds to a similar use requiring the minimum of structural and functional modifications. Document D1 does not address the issue of controlling insects, let alone ticks. Document D13 is concerned with tick control by means of chemical acaricides, such as

pyrethroids, whereas document D14 addresses tick control by means of a GABA-gated chloride channel inhibitor. Applying the above mentioned criterion to these three documents leads to the choice of document D14 as the closet prior art, as also agreed by the appellant.

Problem to be solved

7. The problem to be solved by the present application, as embodied by the subject-matter of present claims 1 and 2 is the provision of novel GABA-gated chloride channel polypeptides useful for identifying molecules to be used for treating or preventing a *D.* variabilis infestation.

8. Examples 1 and 2 of the present application describe the isolation and identification of *D. variabilis* GABA-gated chloride channel amino acid sequences with SEQ. ID. NOs. 1-3. The present application (see example 3 on pages 28 to 29) clearly demonstrates functional expression of these polypeptides in *Xenopus laevis* oocytes. Voltage clamp studies showed the appearance of a rapidly activating current in response to GABA in cell expressing the claimed polypeptides (see page 29, lines 3 to 15 of the application). The GABA-activated current was shown to be blocked by 5 µM fipronil (see Figure 5) and by 10 µM picrotoxinin (see page 29, line 20). Thus the present application provides experimental validation that the claimed polypeptides are functional GABA-gated chloride channels, providing confirmation that they are good targets for pharmacological

intervention. The board is satisfied that the problem as set out has indeed been solved.

Inventive step

9. The appellant admitted that the teaching in document D14 that a spray containing fipronil (an insecticide known to block GABA-gated chloride channels) was able to kill ticks (see point 5 supra), might have motivated the skilled person to look for GABA-gated chloride channels in ticks. The appellant maintained that it was not obvious how to achieve this goal.

10. The only issue left is thus whether isolating the genes ("Rdl^{Dv}") encoding the claimed GABA-gated chloride channel polypeptides was obvious or not.

11. The appellant maintains that the present application used a strategy not suggested by the cited prior art to clone the claimed sequences, as there was no incentive to use as a probe a part of GluCl1 (a different chloride channel) from another tick species, in order to fish out the claimed Rdl^{Dv} genes, as described in the present application.

12. Whilst the board agrees with the appellant that no prior art suggested to turn to the approach adopted by the inventors of the present application, the question whether other obvious methods were available to the skilled person for isolating the genes encoding the claimed polypeptides, cannot be left unanswered.

13. In its communication dated 29 August 2007, the examining division came to the conclusion that it would have been obvious for a skilled person to use the strategy disclosed in document D1 to clone the GABA receptor gene of *D. variabilis*. The reasons given did not go beyond the sentence "Document D1 discloses the cloning of a GABA receptor from *Drosophila melanogaster* [using] two homology probing procedures which make use of degenerate primers designed on conserved motifs in the transmembrane domains M2 and M3".

14. In the board's judgement, the authors of document D1 in fact used three PCR probing procedures:

(i) A "single site" PCR procedure (see page 364, first paragraph bridging l-h and r-h column, under the heading "DNA amplification") involving three 512-fold degenerate oligonucleotide primer pools (TP1a, TP1b and TP1c in Table 1) corresponding to the motif TTVLTMTT found in the second transmembrane domain M2. The second primer site was provided by digesting first the *D. melanogaster* genomic DNA with BamHI or BglII and ligating an oligonucleotide adaptor comprised of a tailed linker and an anchor template (see also Table 1).

(ii) A "classical" PCR (see page 364, r-h column, second paragraph) using one of TP1a, TP1b or TP1c (see Table 1) as the first primer and a 252-fold degenerate probe (TP2 in Table 1) as the second primer, corresponding to the motif CFVFVF found in the third transmembrane domain M3.

(iii) A further "classical" PCR (see page 366, l-h column, end of second paragraph) using one of TP1a, TP1b or TP1c (see Table 1) as the first primer and a probe corresponding to the motif ATVNYFT found in the third transmembrane domain M3 of all vertebrate GABA α-subunits, as the second primer.

15. Applying procedure (i) above revealed LCCH1 and LCCH2 (see Figure 1) having > 40% identity (based on the amino acid sequence) with vertebrate ligand-gated chloride channels (see page 366, l-h column, first paragraph).

However, it is also stated on page 368, l-h column, end of the second full paragraph of document D1 that the "single site" PCR procedure (i) used by the authors of document D1 was **limited** to the amplification of only those genes exhibiting a BglII or a BamHI restriction site downstream of the signature motif TTVLTMTT, whereas any other DNA not having these restriction sites could not be identified.

In view of this limitation, the board must conclude that the skilled person wishing to pick up the GABA receptor gene of ***D. variabilis*** would not have turned to strategy (i) disclosed in document D1, if only for the sole reason that he/she could not know in advance whether the ***D. variabilis*** gene looked for had a BglII or BamHI restriction site downstream of the signature motif TTVLTMTT.

16. Applying procedure (ii) above led to the identification of **only** LCCH3 exhibiting both the TTVLTMTT and CFVFVF motifs (see Figure 1 and page 366, l-h column, second paragraph of document D1).

    However, in the board´s view, the information on page 366, l-h column, lines 8-10 of the second paragraph of document D1 that no amplification occurred with probes TP1a or TP1c used together with probe TP2 (based on the CFVFVF motif) would not have encouraged the skilled person to adopt this approach.

17. Moreover, a closer scrutiny of the amino acid sequences LCCH1, LCCH2 and LCCH3 in Figure 1 of document D1 shows that LCCH1 and LCCH2, unlike LCCH3, include the "wrong" TTVLTMTT/CFV**M**VF combination. Therefore, it is not surprising that a PCR using the probe combination TTVLTMTT/CFV**F**VF according to procedure (ii) did not reveal LCCH1 and LCCH2. By implication, in the board´s view, the skilled person applying procedure (ii) would also have missed the genes encoding the claimed *D. variabilis* GABA-gated chloride channels having the amino acid sequences SEQ. ID. NO. 1, SEQ. ID. NO. 2 and SEQ. ID. NO. 3. This is because these polypeptides also include this "wrong" TTVLTMTT/CFV**M**VF signature (see page 24, lines 17-18 and 30-31 and page 25, lines 8-9 of the patent application).

18. PCR procedure (iii) for identifying the GABA α-subunit did not yield any amplified product.

    In the board's view, this would further confirm to the skilled person that it could not be taken for granted

that he/she would necessarily get the genes encoding the claimed polypeptides, departing from homologous sequences and using complementary probes as done in document D1.

19. In summary, the skilled person would not have applied the three PCR probing procedures described in document D1. But even if he/she had adopted these techniques, there is no evidence before the board that the genes encoding the claimed polypeptides could have been isolated. Rather, the contrary is true for at least techniques (ii) and (iii). Thus, it not reasonable to conclude that the skilled person would have necessarily arrived at the claimed subject matter in the light of document D1.

Document D2

20. Document D2 (see page 7212, l-h column, under "Isolation and Sequencing of GABA cDNA") discloses the isolation of a ***Drosophila*** GABA cDNA (termed "NB14.1") encoding a polypeptide having sequence homology to $GABA_A$ receptor subunits. The applied strategy was using a 10 kb EcoRI fragment of "cosmid 6" as a probe to screen an embryonic cDNA library.

There is no evidence before the board that the skilled person was in a position to repeat the isolation of "cosmid 6" and reproduce the same procedure described in document D2, let alone that he/she would be successful in isolating the genes encoding the claimed polypeptides, once he/she screened a ***D. variabilis*** library with this "cosmid 6" probe.

Documents D4 and D11

21. These documents do not disclose any cloning strategy.

22. In view of the foregoing, the question set out under point 12 supra as to whether other obvious methods were available to the skilled person for isolating the Rdl^{Dv} genes encoding the claimed polypeptides, has to be answered in the negative.

23. In view of this finding of the board, no need arises to consider the appellant's argument that the presently claimed GABA receptors are at least an order of magnitude more sensitive to channel blockers than the *Drosophila* receptors discussed in the prior art documents.

24. The claims of the main request thus satisfy the requirements of Article 56 EPC.

25. The subject-matter of the claims is also novel. This has been acknowledged by the examining division (see paragraph 1 of the communication dated 29 August 2007), and the board sees no reasons to dispute this finding.

26. The decision under appeal does not give any opinion on the requirements of Articles 123(2), 84 and 83 EPC. The board has therefore considered remitting the case to the first instance for further prosecution in accordance with Article 111(1) EPC, last half sentence, but decided not to do so for reasons of procedural efficiency.

27. Thus, in accordance with Article 111(1) EPC, first half of its second sentence, the board finds, firstly, that the amended subject-matter of claims 1 and 2 of the main request does not extend beyond the content of the application as filed. A basis is found in page 8, lines 6 to 8 of the published version of the International application.

28. Secondly, the board considers that the wording of the claims is clear and that the claimed subject-matter is supported by the description as required by Article 84 EPC.

29. Thirdly, in view of the general description of the invention, disclosing in particular all the DNA sequences SEQ. ID. NO. 28, SEQ. ID. NO. 4, SEQ. ID. NO. 5 and SEQ. ID. NO. 6, which can be used by the skilled person for designing probes for picking up the genes encoding the claimed polypeptides, the board considers that the claimed subject-matter is disclosed in a manner sufficiently clear and complete for it to be carried out, so that the requirements of Article 83 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 claims 1 and 2 of the main request filed on 11 August 2007, description pages 1, 1a, 2 to 29 as filed during the oral proceedings, figures and sequence listing as published.

The Registrar: The Chairman:

B. Atienza Vivancos C. Rennie-Smith