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D E C I S I O N
of 28 April 2005

Case Number: T 0269/03 - 3.3.8

Application Number: 94925144.1

Publication Number: 0778890

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
DNA encoding a human calcium channel alpha-1E subunit

Patentee:
Elan Pharmaceuticals, Inc.

Opponent:
SmithKline Beecham plc

Headword:
Calcium channel/ELAN

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (yes)"

Decisions cited:
T 0111/00, T 0182/03

Catchword:
-

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Case Number: T 0269/03 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 28 April 2005

Appellant: (Opponent)	SmithKline Beecham plc New Horizons Court, Great West Road Brentford, Middlesex TW8 9EP (GB)
Representative:	Bor, Fiona, Dr GlaxoSmithKline Corporate Intellectual Property 980 Great West Road Brentford, Middlesex TW8 9EP (GB)
Respondent: (Proprietor of the patent)	Elan Pharmaceuticals, Inc. 800 Gateway Boulevard South San Francisco, CA 94080 (US)
Representative:	Grund, Martin, Dr Dr Volker Vossius Patentanwaltskanzlei - Rechtsanwaltskanzlei Geibelstrasse 6 D-81679 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 6 December 2002 rejecting the opposition filed against European patent No. 0778890 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
M. B. Günzel

Summary of Facts and Submissions

I. The opponent (appellant) lodged an appeal against the decision of the opposition division dated 6 December 2002, whereby the opposition against the European patent No. 0 778 890 was rejected.

II. The patent had been opposed on the grounds in Articles 100(a) and (b) EPC that the invention did not involve an inventive step and was not sufficiently disclosed.

III. In the decision under appeal it was considered by the opposition division that the claimed subject-matter as a whole involved an inventive step and was sufficiently disclosed.

IV. In the statement of grounds of appeal, lack of inventive step of the subject-matter of claim 1 was the only reason why the decision under appeal was challenged by the appellant. In support of its views the appellant filed seven additional documents. In reply, the respondent (patent proprietor) filed observations.

V. The Board issued a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal containing provisional and non-binding opinions. In reply to the Board's communication both parties filed observations, the appellant submitting with its letter of 23 March 2005 an additional document (to be referred to as D18).

VI. Oral proceedings took place on 28 April 2005.

VII. The set of claims as granted consisted of 10 claims.

Claim 1 read:

"1. An isolated DNA fragment, comprising a sequence of nucleotides that encodes an alpha-1E subunit of a human neuronal calcium channel, and having the sequence presented as SEQ ID NO:1."

Claim 2 concerned an alpha-1E subunit of a human neuronal calcium channel having a given sequence. Claim 3 was directed to a mammalian expression vector containing the nucleotide sequence SEQ ID NO: 1. Claims 4 to 8 concerned cells including the same sequence. Claims 9 and 10 were directed to methods using the cell of claim 7 and the cell of claim 8, respectively.

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

(D1) Tuck Wah Soong et al, Science, Vol. 260, 21 May 1963, Pages 1133 to 1136

(D2) WO-A-93/04083 (published on 4 March 1993)

(D6) Stefan J. Dubel et al., Proc. Natl. Acad. Sci. USA, Vol. 89, June 1992, Pages 5058 to 5062

(D11) Tetsuhiro Niidome et al., FEBS, Vol. 308, No. 1, August 1992, Pages 7 to 13

(D14) D. Randall, J. Membrane Biol., Vol. 161, 1998, Pages 207 to 213

(D18) Patrice Mollard et al., FASEB J., Vol. 2, 1988, Pages 2907 to 2912

IX. The submissions made by the appellant (opponent), insofar as they are relevant to the present decision, may be summarised as follows:

Admissibility into the proceedings of document D18

Document D18 was of *prima facie* relevance since it revealed the existence, before the priority date of the patent in suit, of low voltage-activated calcium channels in human cells.

Inventive step of claim 1

Starting form document D2 (taken as the closest prior art) which disclosed human calcium channel α1A, α1B, α1C and α1D subunits, the technical problem to be solved was the provision of a further human calcium channel α1 subunit. The solution to that problem was the provision of the DNA of claim 1.

A new specific type of calcium channel α1 subunits had been cloned in two mammalians, namely the rat and the rabbit. The rat rbE-II subunit and the rabbit BII subunit which were described in documents D1 and D11, respectively, had ~93% amino acid sequence homology. For the skilled person it would have been obvious to try looking in humans for a homologous sequence. For

this, only routine techniques had to be applied and there was a reasonable expectation of success.

The same approach as taken by the Boards of appeal in decisions T 111/00 of 14 February 2002 and T 182/03 of 23 June 2004 should be followed.

X. The submissions made by the respondent (patent proprietor), insofar as they are relevant to the present decision, may be summarised as follows:

Admissibility into the proceedings of document D18

Document D18, which was late filed, only showed that in certain human cells there were low-voltage-activated and high-voltage-activated calcium channels. Therefore, it was not relevant to the assessment of inventive step for the subject-matter of claim 1.

Inventive step of claim 1

At the priority date, as reflected in particular by document D2, there was a diversity of subunit classes, subtypes and splice variants of different calcium channels that appeared not to fit exactly into defined categories.

Since the rat rbE-II variant of $\alpha 1$ subunit reported in document D1 was structurally more related to the high voltage-activated channels, but functionally more related to the low voltage-activated channels, it was clear that the authors of document D1 did not know exactly what kind of subunit they had found.

Even assuming that the skilled person was entirely familiar with the nomenclature and literature of calcium channels at the priority date, he/she would not have expected to find a fifth human α1 calcium channel subunit, in addition to the four human α1 calcium channels of types A, B, C and D described in document D2, in a straightforward manner using only routine work and experimentation.

XI. The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 0 778 890 be revoked.

XII. The respondent (patentee) requested that the appeal be dismissed.

Reasons for the Decision

Admissibility into the proceedings of document D18

1. The respondent objected to the admissibility of document D18 into the proceedings as being late filed and not highly relevant to the assessment of inventive step.

2. Document D18 was indeed submitted with the appellant's letter of 23 March 2005 after the time limit fixed by the Board in its communication issued under Article 11(1) RPBA.

3. The Board, exercising its discretion, decides to admit document D18, which essentially describes the electrophysical effects of arginine vasopressin on

human ACTH-secreting pituitary adenoma cells and is of marginal relevance for the decision to be taken.

Inventive step of claim 1

4. Claim 1 is directed to an isolated DNA fragment having the DNA sequence shown in Figure 1 of the patent in suit which encodes a human neuronal calcium channel alpha subunit referred to in the patent as the subunit hα-1E.

5. Document D1 is regarded as the closest state of the art. It describes the primary structure, localisation, and functional characteristics of the rat **rbE-II** protein, a newly identified **rat brain calcium channel α1 subunit**. The authors consider that the properties of rbE-II appear to define a new class of voltage-activated calcium channel α1 subunits which differs from the four classes (A, B, C and D) of voltage-activated calcium channel α1 subunits already identified in the mammalian central nervous system. Furthermore, the authors of document D1 state (see footnote 9 on page 1136) that the rbE-II protein is ~93% identical (in terms of its primary structure) to the **rabbit brain BII calcium channel**.

6. The rabbit brain **BII** protein was disclosed in document D11 which reports the identification and isolation of cDNAs encoding two isoforms thereof (see in particular Figure 1 which shows the deduced amino acid sequence of one isoform and the differences with the sequence of the other isoform).

7. The technical problem to be solved by the invention is regarded as being the provision of a human neuronal calcium channel alpha subunit homologous to the rat **rbE-II** subunit of document D1. The solution to this problem is a DNA fragment having the sequence shown in Figure 1 of the patent in suit.

8. Aware of the existence of the rat **rbE-II** subunit identified in document D1 and of the closely structurally related rabbit **BII** subunit identified in document D11, the skilled person would have indeed been prompted to conceive that the rat rbE-II and rabbit BII subunits might be representatives of a new mammalian class of calcium channel α-1 subunits, and to believe that a corresponding human homologous subunit existed.

9. Therefore, he/she would have regarded it as obvious to try looking for a cDNA encoding a human α1 subunit homologous to the rat **rbE-II** subunit with some hope to succeed.

10. The obvious theoretical approach which the skilled person would have been expected to take was to fish out such a cDNA from a cDNA library prepared from human neuronal cells using a rat probe derived from the cDNA sequence encoding the **rbE-II** subunit as reported in document D1, the underlying idea being that the expected and the known cDNAs would have shared a large number of consensus sequences. However, there is no evidence of any kind on file which shows that such an approach would have indeed resulted in the successful completion of the endeavour.

11. As a matter of fact, in "real life" the inventors have used rat probes derived from a cDNA encoding the rat **rbB-I** subunit of document D6 (see Example 1, paragraph 0055 on page 7 and paragraph 0057 on page 8 in the patent specification). This is not considered a route that the skilled person would have spontaneously chosen, not only for the reason that document D6 does not describe any nucleotide sequence but also for the reason that a cDNA encoding the rat rbB-I protein would not have been regarded as an appropriate starting material to derive therefrom a rat probe, as the rbE-II and the rbB-I subunits which share only 53 to 54% amino acid identity (see the sentence starting with the phrase "Comparison with other classes" in the middle column on page 1133 in document D1) are not closely related.

12. Since the appellant's attack on inventive step was not based on any evidence, showing that the skilled person might have implemented a rat probe derived from the cDNA encoding the rat rbE-II protein described in document D1 by using only routine work and experimentation, it did not discharge the burden of proof resting upon him.

13. The fact that since the priority date it has been demonstrated that mammalian calcium channel subunits, in particular the human neuronal α1-E subunit, exist in several forms (isoforms) as the result of RNA splicing (see the sentence starting with the expression "In addition" in the first full paragraph in the right-hand column of page 209 of document D14, where reference is made to citation 112 the title of which reads "Structure and Functional Characterization of **Neuronal**

α_{1E} Calcium Channel Subtypes") is also an indicator that even using an appropriate rat probe there would have been no certainty that the skilled person would have been in a position to fish out a cDNA having the particular nucleotide sequence of claim 1. This strengthens the Board's view that there was inventive merit in the isolation of the claimed sequence.

14. Decisions T 111/00 and T 182/03 (see Section IX, supra) which have been referred to by the appellant in support of its submissions apply to situations which in a number of aspects are different from the situation in the present appeal. In particular, in each of those decisions the competent Board had to assess whether not a particular DNA molecule but a whole family of nucleic acid molecules (see claim 1 as referred to in Section I of decision T 111/00 which contains the terms "at least 90% identical to" and claim 1 as referred to in Section II of decision T 182/03 which encompasses a family of nucleic acid molecules encoding a particular polypeptide) involved an inventive step. Therefore, these decisions are not relevant for the present discussion.

15. For these reasons, the subject-matter of claim 1 involves an inventive step. As lack of inventive step of claim 1 was the only ground of appeal, it is the Board's judgment that the appeal has to be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

G. Röhn L. Galligani