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Datasheet for the decision of 13 March 2014

Case Number: T 1109/10 - 3.3.08

Application Number: 02731941.7

Publication Number: 1461425

IPC: C12N9/02, C12N15/53

Language of the proceedings: EN

Title of invention:
NOVEL HUMAN HYDROXYLASES AND POLYNUCLEOTIDES ENCODING THE SAME

Patent Proprietor:
Lexicon Pharmaceuticals, Inc.

Opponent:
Max-Delbrück-Centrum für Molekulare Medizin (MDC)

Headword:
Hydroxylases/LEXICON

Relevant legal provisions:
EPC Art. 57

Keyword:
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Decisions cited:
T 0870/04, T 0898/05, T 1450/07

Catchword:

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Case Number: T 1109/10 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 13 March 2014

Appellant: (Opponent)	Max-Delbrück-Centrum für Molekulare Medizin (MDC) Berlin-Buch, Robert-Rössle-Strasse 10 13092 Berlin (DE)
Representative:	Krauss, Jan Boehmert & Boehmert Pettenkoferstrasse 20-22 80336 München (DE)
Respondent: (Patent Proprietor)	Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381 (US)
Representative:	Hewson, Timothy John Abel & Imray 20 Red Lion Street London, WC1R 4PQ (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 18 March 2010 rejecting the opposition filed against European patent No. 1461425 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman: M. Wieser
Members: T. J. H. Mennessier
J. Geschwind

Summary of Facts and Submissions

I. The opponent (appellant) lodged an appeal against the decision of the opposition division dated 18 March 2010, whereby its opposition filed against European patent 1 461 425 with the title "*Novel human hydroxylases and polynucleotides encoding the same*", which had been granted on European patent application No. 02731941.7, published as the international application WO 02/97039, was rejected.

II. The opposition has been filed on the grounds of Articles 100(a) EPC (lack of inventive step (Article 56 EPC) and lack of industrial application (Article 57 EPC)) and 100(b) EPC.

III. The respondent replied to the appellant's statement setting out the grounds of appeal by filing submissions together with two new documents to be referred to as documents D17 and D18.

IV. A communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal, presenting preliminary and non-binding views of the board, was sent to the parties as an annex to the summons. The board informed the parties that, in view of its preliminary opinion with regard to industrial application, it was inclined to set aside the decision under appeal and to revoke the patent.

V. The appellant replied to that communication by filing further submissions.

VI. The claim request on file, i.e. the claims as granted, consists of 12 claims; claim 10 reads as follows:

"10. An isolated protein having the amino acid sequence of the protein shown in SEQ to *[sic]* NOS:2, 4, 6, or 8."

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

(D1) D. J. Walther et al., Science, Vol. 299, 3 January 2003, page 76

(D2) GenBank database record N° AY098914

(D5) J. P. Tipper et al., Archives of Biochemistry and Biophysics, Vol. 315, No. 2, December 1994, pages 445 to 553

(D17) G.-A. Wang et al., Journal of Neurochemistry, Vol. 71, No. 4, 1998, pages 1769-1772

(D18) S. M. Mockus et al., Biochemica et Biophysica Acta, Vol. 1342, 1997, pages 132 to 140

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

According to the sentence bridging pages 2 and 3 of the application, proteins were disclosed which "share[d] structural similarity with animal hydroxylases, and in particular tryptophan hydroxylases".

However, the application was silent as to the degree of identity of the said proteins (NHPs) to specific hydrolases, in particular to tryptophan hydroxylases. No alignment was provided and no structural features

were indicated which would have marked the claimed proteins as being members of the alleged enzyme family.

It was neither derivable from the disclosure of the application which of the four described reading frames was more likely to be expressed *in vivo,* nor was there any experimental data indeed supporting the *in vivo* expression of any one of the claimed sequences.

There was no indication given which could support an association between a specific disease or condition and an increased or impaired expression of any of the four disclosed reading frames.

The disclosure in the application as filed provided conflicting and contradictory structural and functional information that did not fit into the picture of the claimed NHPs being human tryptophan hydroxylases (TPHs): (a) the NHPs had the characteristic signal peptide of secreted or membrane proteins, whereas tryptophan hydroxylases were known to be cytoplasmic localized proteins (page 22, lines 5 to 11) and were thus neither secreted nor membrane localized; b) it was indicated that soluble versions of the NHPs could be produced by removing one or more transmembrane domains (see page 23, lines 31 to 35), whereas hydroxylases did not have any transmembrane domains; and c) reference was made to antibodies which "*bind to a [claimed] NHP domain and competitively inhibit the binding of a [claimed] NHP to its cognate receptor*" (see page 34, lines 16 to 20), whereas tryptophan hydroxylases were catalytic enzymes and not signalling molecules binding to receptors of any kind. Therefore, serious doubts existed whether the claimed NHPs actually were hydroxylases.

Even when provided with appropriate alignment tools, a person skilled in the art, finding that the sequence of SEQ ID NO:2 shared 71% identity with the sequence of the known human tryptophan hydroxylase (TPH1) and substantially differed therefrom at its C- and N-terminal ends, would not have concluded that this information was sufficient to establish that a new human tryptophan hydroxylase had been identified.

Post-published documents D1 and D2 were not relevant for the assessment of industrial application.

The disclosure in the application was essentially speculative and did not provide "a sound and concrete technical basis" of industrial application as required in decision T 898/05 of 7 July 2006.

IX. The submissions made by the respondent in writing, insofar as they are relevant to the present decision, may be summarised as follows:

The invention concerned the discovery of a new human tryptophan hydroxylase (TPH2).

A person skilled in the art, being aware that the sequences disclosed in the application were very similar to the known sequence of TPH1 and that the novel sequences were expressed in a number of tissues including those of the CNS, would have realised that the disclosed nucleotide sequence constituted a novel TPH gene, which was of obvious interest and utility for research, diagnosis and treatment of diseases and disorders known to be linked to serotonin metabolism.

The passage on page 2, lines 6 to 10, of the application stating that the novel human proteins

(NHPs) could be used to identify and/or develop agents useful for modulating behavior, was crucial for the positive assessment of industrial application as confirmed by documents D1 and D2. As could be derived in particular from documents D17 and D18, the slight difference at the C-terminal end between TPH1 and the NHP of SEQ ID NO: 2 would not have led a person skilled in the art to think that the latter was not a tryptophan hydroxylase.

The statement on page 23, lines 31 to 35, that soluble or secreted forms of the claimed proteins could be produced by removing transmembrane domains, was qualified by the term "where applicable" and was not therefore in contradiction with the description of a protein lacking transmembrane domains.

The statement on page 34, lines 16 to 20, referring to "antibodies that bind to a NHP domain and competitively inhibit the binding of a NHP to its cognate receptor" was made in reference to novel human proteins (NHPs) in general rather than specifically referring to TPH2. Therefore, it was not in contradiction with the fact that TPH2 was an enzyme and not a receptor having a cognate ligand. In general, passages in the detailed description pointing to no more than minor inconsistencies would not have detracted a skilled person from explicit statements in the summary of the invention.

The contribution of the invention was immediately derivable from the description and moreover obvious from the nature of the invention and the background art. Accordingly, the criteria set forth in decision T 898/05, for an invention to be considered to be industrially applicable, were satisfied.

X. The oral proceedings took place as scheduled on 13 March 2014 in the absence of the respondent, who has not previously informed the board of its intention not to attend.

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

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

Reasons for the Decision

1. Claim 10 is directed to four distinct but closely related proteins. The longest (490 amino acid residues) has the sequence shown in SEQ ID NO: 2. The three other ones are truncated versions thereof which lack four, five or six amino acid residues at its N-terminal end (see SEQ ID NOs: 4, 6 and 8).

2. According to the requirements of Article 57 EPC, each of these four proteins is required to be susceptible of industrial application. The assessment of this requirement of the EPC has to be carried out from the position of a skilled person at the relevant filing date, i.e. without the benefit of hindsight provided by post-published documents. Reference to such documents may be permitted for confirmatory purpose only if industrial application was demonstrated in the patent application (see decision T 1450/07 of 11 February 2009; point 8 of the Reasons).

3. Having read the application as filed (see WO 02/97039), the skilled person would have gathered the following information:

3.1 The four proteins (collectively referred to in the application as "NHPs") shared structural similarity with mammalian tryptophan hydroxylases which were involved in a rate-limiting step in the biosynthesis of neurologically active compounds, including serotonin (see page 1, lines 10 to 13 together with the sentence bridging pages 1 and 2).

3.2 Therefore, the NHPs were expected to be useful for the identification and/or the development of agents useful for modulating behavior (see page 2, lines 6 to 10).In the absence of any experimental proof, the skilled reader would not have interpreted this statement as an affirmation but only as a non-proven expectation.

3.3 However, in view of the sentence on page 2, lines 10 to 14, reading "*[T]he novel human acid nucleic acid (cDNA) sequences described herein encode protein/open reading frames (ORFs) of 490, 486, 485, and 484 amino acids in length (SEQ ID NOS: 2, 4, 6, and 8, respectively)*", it would have become evident to the skilled reader, that the inventors, who had cloned a gene and determined the presence of four different reading frames, at the relevant date, were not in a position to determine which of the reading frames indeed encoded a protein that could be expressed.

4. The board takes the view that the pieces of information contained in pages 1 and 2 of the description (see point 3 above), which are not supported by any experimental evidence, have to be considered as being purely speculative. The fact that two proteins share a

certain structural similarity does not automatically imply that they have the same enzymatic activity. Furthermore, the contention that, in the light of the well-known physiological functions of tryptophan hydroxylases described in the prior art, the claimed proteins, based only on an amino acid sequence comparison, are hydroxylases which can be used to identify and/or develop agents useful for modulating behaviour, is not credible. Document D5, on which the respondent relies, has been considered in the opposition proceedings to represent the closest prior art. It reports the cloning of human brain tryptophan hydroxylase TPH1 but does not mention any correlation between the primary structure and the function of TPH1. Thus, this document would only have allowed the skilled person to perform a comparative alignment of the sequence of TPH1 with the sequences of SEQ ID NOs:2, 4, 6 and 8 but it would have been of no use for establishing that any of the claimed proteins was a tryptophan hydroxylase.

5. No relevant conclusion can be deduced from the indication in the application that the novel proteins can be expressed in a large variety of different cell types, including carcinoma cells. There is no pointer to the central nervous system, including the brain, as a preferred place of expression, which, for an enzyme involved in the synthesis of serotonin, could have rendered it plausible to the skilled person that one or more of the claimed proteins had indeed tryptophan hydroxylase activity.

6. Mammalian trytophan hydroxylases are known to be neither secreted nor membrane proteins, not to comprise one or more transmembrane domains and to be enzymes, a feature which excludes that they are capable of binding

a cognate receptor. Having these well known characteristics in mind, the disclosure on page 22, lines 5 to 11, page 23, lines 31 to 35, and page 34, lines 16 to 20 of the application (see Sections VIII and IX above) would have cast serious doubt on the skilled person that any of the four proteins of claim 10 represents a tryptophan hydroxylase.

7. The term "NHP(s)" seems to be a corporate acronym, used in the application to easily designate the claimed proteins, which means that wherever it is used in the application, it refers to the claimed proteins. Therefore, the board is not convinced by the respondent's contention that the comments on page 34, lines 16 to 20 would not apply to the proteins of claim 10.

8. Also the respondent's contention that the expression "*where applicable*" as used on page 23, line 34 would indicate that the presence of one or more transmembrane domains is not a feature of the claimed proteins is not convincing. Rather, in the board's view, this expression is used to indicate that depending on whether a skilled person wants to prepare the soluble or the secreted form of a given NHP, one or more of the transmembrane domains thereof will have to be removed. The board sees no reason why the skilled person should have ignored such highlighted features which the respondent qualifies as "minor discrepancies".

9. The board reaches the conclusion that the disclosure of the patent in suit, at the most, can be regarded as providing a starting point to undertake a research program with the hope that any of the four amino acid sequences SEQ ID NOs:2, 4, 6 and 8 will be identified as having indeed a useful application. The vague and

speculative indication of the possible use of the claimed proteins, namely to identify and/or develop agents for modulating behavior, as a possible objective that might or might not be achievable by carrying out further research is not sufficient for fulfilment of the requirement of industrial application (see decision T 870/04 of 11 May 2005; point 21 of the Reasons). The speculative nature of the disclosure does not provide such a sound and concrete basis that the skilled person at the filing date would have been in a position to recognise that the contribution of the invention could lead to practical exploitation in industry as required in decision T 898/05 of 7 July 2006 (see point 5 of the Reasons).

10. The respondent has referred to post-published documents D1 and D2, arguing that they were merely confirmatory of the *in vivo* function of the claimed invention as explicitly disclosed in the passage on page 2, lines 6 to 10 of the application stating that "*the described hydroxylases can be used to identity and/or develop agents useful for modulating.behavior*". As already explained in point 3.2 above, this passage only expressed the non-proven expectation that the claimed proteins were susceptible of industrial application. Therefore, documents D1 and D2 cannot be taken into consideration (see point 2, supra).

11. The controversial discussion, whether or not the C-terminal end of mammalian tryptophan hydoxylases was essential for substrate specificity, wherein the respondent has relied on documents D17 and D18, is of no relevance for the assessment of industrial application, as the patent does not contain any evidence to assume a correlation between the structure

of the claimed proteins and their putative enzymatic function.

12. Therefore, the subject-matter of claim 10 is not considered to be susceptible of industrial application. Consequently, respondent's sole request does not meet the requirements of Article 57 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated