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D E C I S I O N
of 23 June 2004

Case Number: T 0182/03 - 3.3.8

Application Number: 94911544.8

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Language of the proceedings: EN

Title of invention:
Human brain phosphodiesterase

Applicant:
SMITHKLINE BEECHAM CORPORATION

Opponent:
-

Headword:
phosphodiesterase/SMITHKLINE BEECHAM

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (yes)"

Decisions cited:
T 0606/89

Catchword:
-

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Case Number: T 0182/03 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 23 June 2004

Appellant: (Applicant)
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 31 May 2002 refusing European application No. 94911544.8 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
V. Di Cerbo

Summary of Facts and Submissions

I. The appeal lies from the decision of the Examining Division dated 31 May 2002 to refuse the European patent application No. 94 911 544.8 published under the international application No. WO 94/20079 with the title "Human brain phosphodiesterase" because of lack of inventive step vis-à-vis document (E18) (see Section III infra).

II. The request on appeal comprises 13 claims which had been filed with letter dated 2 March 2001 and constituted the basis of refusal by the Examining Division. Claim 1 reads as follows:

"1. An isolated nucleic acid molecule encoding human cAMP-specific phosphodiesterase ($PDEIV_B$) polypeptide of SEQ ID NO:2."

Claims 2 and 3 relate to further embodiments of the molecule according to claim 1. Claim 4 relates to an isolated polypeptide consisting of the amino acid sequence of SEQ ID NO:2. Claims 5 to 9 relate to vectors/plasmids comprising the nucleic acid of claim 1 and claims 10 to 13 relate to recombinant host cells comprising the vector of claim 5.

III. The documents mentioned in the present decision are the following:

(D1): WO-A-91/16457,

(E18): Swinnen, J.V. et al., The Journal of Biological Chemistry, Vol. 266, No. 27, pages 18370 to 18377, September 1991,

(E19): Livi, G.P. et al., Molecular and Cellular Biology, Vol. 10, No. 6, pages 2678 to 2686, June 1990.

IV. The Appellant's arguments in writing and during oral proceedings regarding inventive step may be summarized as follows:

In the course of the procedure, the three documents (E18), (D1), and (E19) were successively chosen as starting points for determining inventive step. Depending on which of these documents was taken as the closest prior art, the problem to be solved could respectively be formulated as "to clone the human orthologue of the rat PDE4", "to clone the first example of a splice variant of human PDEIVB" or as "to clone the first example of a variant of human PDEIVA".

There were only three possible reasons why the cloning of an orthologue or variant of an already known gene would be inventive:

– there was no motivation to try the cloning experiment.

– there was motivation but the orthologue/variant had not been found despite repeated efforts such that the general perception of the scientific community was that, in fact, it did not exist.

– the orthologue/variant gene or the protein encoded by it had unexpected properties.

The Examining Division's finding of lack of inventive step over the disclosure in document (E18) of the rat brain PDE4 cDNA was entirely reached with the hindsight knowledge of the present invention that the human orthologue to the rat gene existed.

Document(D1) disclosed the existence of at least four human genes in the PDEIV family (cAMP-specific phosphodiesterases family IV). The skilled person would thus, have had no incentive to look for further human genes.

Document (E19) taught that the human PDE (phosphodiesterase) cDNA cloned from a monocyte library encoded a cAMP PDE (cAMP-specific phosphodiesterase) enzyme which was homologous to the Drosophila enzyme involved in learning and memory (ie in processes occurring in the brain), and which could be of great pharmacological significance. The skilled person aware of this teaching would have thought that the monocyte PDE was the same as the human brain PDE and, therefore, would not have had any incentive to look for a further PDE gene in the human brain, all the more so that document (E19) also disclosed that, contrary to the situation in rats, there might not be multiple PDE genes in humans.
Thus, there was no suggestion in the art that a human brain PDE gene existed nor was there any motivation to look for it. Since the problem solved by the present invention could not be derived in an obvious manner

from any prior art document, inventive step could be acknowledged already on this basis.

Furthermore, the tissue restricted expression of the protein encoded by the claimed gene and its weak degree of sequence conservation compared to the monocytes PDE enzyme were unexpected features which opened up the possibility of specificity of action of the protein which was a virtual pre-requisite for pharmaceutical intervention. In fact, the enzyme encoded by the molecule of claim 1 was a *bona fide* drug target which had served for the isolation of a pharmaceutical product which was already in phase IIIa clinical trials.

V. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 13 as filed with letter dated 2 March 2001.

Reasons for the Decision

1. The only issue to be decided is that of inventive step. As a first step, it is necessary to determine which of the documents (E18), (D1) and (E19) is the closest prior art. The respective teachings of these three documents are summarized in the next paragraphs.

2. Document (E18) is concerned with the properties and hormonal regulation of two structurally related cAMP phosphodiesterases from the rat Sertoli cells. In the discussion,(page 18375), it is disclosed that there are at least four rat genes encoding cAMP PDEs and that

alternate splicing opens the possibility of an even larger number of cAMP PDE proteins. A very scant mention of a cAMP-dependent activation of a PDE from human platelets is found on page 18376 (right-hand column, last par.) No reference is otherwise made to PDE cDNAs isolated from human cells.

3. Document (D1) is concerned with detecting mammalian DNAs encoding proteins which can function in micro-organisms, examples being in particular directed to human cAMP PDE cDNAs. In the background part of the description (page 7), the importance of cAMP in the regulation of a variety of metabolic processes is emphasized as well as the difficulties of using the cAMP-specific phosphodiesterase as target for development of drugs modulating cAMP levels, due to the very many isoforms of this enzyme, which furthermore are synthesized by most tissues. Human cAMP PDE cDNAs are isolated from two different human cDNA libraries (human glioblastoma cells: example 1,C and human temporal lobe: example 2). In example 4, these cDNAs are re-grouped in a family identified as the PDEIV family. This family comprises four classes of cDNAs (PDEIV 1-4), each class of cDNAs being derived from a different genomic locus. In anyone class, the cDNAs are not precisely identical in sequence, the deviations being attributed to different splicing patterns or true polymorphisms in humans.

4. Document (E19) describes the cloning and expression of a cDNA encoding a human cAMP PDE from a monocytes cDNA library. It discloses on page 2684, right-hand column that there might be at most one cAMP PDE locus in the genome in addition to the gene encoding the mRNA

corresponding to this cDNA. The following statement is made at the end of the article: "...cAMP PDEases, which function primarily to regulate cellular levels of cAMP, may also be intimately involved in the neurobiochemical processes that control information transfer in the brain. Thus, further study of the recombinant human enzyme may be of great pharmacological significance in terms of our understanding of the mechanisms involved in the biochemical regulation of mood and human behaviour."

5. In accordance with the case law (see for example, T 606/89 of 18 September 1990), the closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common.

6. Here, the claimed invention comprises a cDNA encoding a cAMP specific phosphodiesterase ($PDEIV_B$) isolated from human brain tissue. Document (E18) which is not concerned with human cAMP PDE cDNAs and which does not suggest any aim or purpose for the rat cAMP PDE cDNAs which it describes, is considered to be the prior art furthest away from the claimed subject-matter. Document (D1) and (E19) both teach human cAMP PDE cDNAs. The earlier discloses their isolation from human brain tissue but also, as above mentioned, emphasizes the difficulties in using the cAMP PDEase enzyme for drug targeting. The latter does not disclose a cDNA from a human brain library but from a monocyte library, yet the intimate involvement of the cAMP PDE enzymes in neurobiochemical processes is emphasized with special

reference to the potential pharmaceutical significance of the recombinant form of the enzyme obtained in said document. In the Board's judgment, the disclosures of these two documents are equally suited to serve as closest prior art. The following reasoning is carried out starting from document (E19).

7. Starting from the teachings of document (E19), the problem to be solved can be defined as isolating an alternative cAMP PDE encoding cDNA.

8. The argument was presented (point IV, supra) that the formulation of this problem was per se inventive because the skilled person would understand from document (E19) that the genomic gene corresponding to the cDNA already isolated from monocytes was probably the only human cAMP PDE encoding gene. Alternatively, he/she would understand from document (1) that all human PDE genes had already been cloned from brain tissue. In both cases, he/she would have no motivation to look for a further cAMP PDE gene.

9. The Board cannot agree with this argument for the following reasons. The number of cAMP PDE genes in humans does not bear any relevance to the claimed subject-matter which does not relate to a human **cAMP PDE gene** but to a human **cAMP PDE cDNA**. Document (D1) makes it clear that for each human gene, there exists many cDNAs because of alternative splicing; indeed several such cDNAs are described. In the same manner, in document (E19) (introduction), it is stated that the mammalian PDE enzymes can be regrouped in families of **isozymes**. In the Board's judgment, both these teachings, one at the DNA level, the other at the protein level,

would leave the skilled person open-minded as to the number of cAMP PDE cDNAs which might still be found.

10. The solution provided is a cDNA resulting from the reverse transcription of the cAMP PDE mRNA as transcribed in human brain tissue. Document (E19) alone makes this tissue an obvious starting material for the cloning since it points out the relevance of the cAMP PDE enzymes in neurobiochemical processes that control information transfer **in the brain**. Of course, the combination of the teachings of documents (E19) and (D1) makes this starting material all the more obvious since, as already mentioned, document (D1) provides the further evidence that for each human gene, one can isolate several cDNAs starting from **brain** tissue.

11. At oral proceedings, the Appellants did not challenge the Board's conclusion that at the priority date, the cloning of cAMP-PDEase cDNAs could be done as a matter of routine. The question remains whether this would have led the skilled person in a straightforward manner to the particular sequence which is claimed.

12. Under these circumstances, inventive step could nevertheless be acknowledged on the basis of unexpected findings or properties regarding/characterising the specifically claimed cDNA or the corresponding protein. The Appellant argued (see point IV supra) that the claimed cDNA encoded a cAMP PDE with unexpected properties, it being structurally divergent from other PDEs and its expression being restricted to specific tissues. It was pointed out that these properties made it particularly suitable for drug targeting and that a drug had de facto been developed using the enzyme as a

target. The Board is not aware of any data refuting these arguments. They, in turn, warrant acknowledgement of inventive step irrespective of whether document (E19) or document (D1) is taken as closest prior art. For this reason it is concluded that the requirements of Article 56 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 first instance with the order to grant a patent on the basis of claims 1 to 13 filed with letter of 2 March 2001 and a description to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski L. Galligani