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D E C I S I O N
of 18 February 2004

Case Number: T 0473/01 - 3.3.8

Application Number: 90905378.7

Publication Number: 0502845

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Language of the proceedings: EN

Title of invention:
Human high-affinity neurotransmitter uptake system

Patentee:
BAYLOR COLLEGE OF MEDICINE

Opponent:
SmithKline Beecham Plc

Headword:
Neurotransmitter uptake/BAYLOR COLLEGE

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request and auxiliary requests 1 to 4: inventive step (no)"

Decisions cited:
-

Catchword:
-

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Case Number: T 0473/01 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 18 February 2004

Appellant I: (Proprietor of the patent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 9 February 2001 concerning maintenance of European patent No. 0502845 in amended form.

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
S. C. Perryman

Summary of Facts and Submissions

I. The patent proprietor (appellant I) and the opponent (appellant II) each lodged an appeal against the interlocutory decision of the opposition division given at oral proceedings on 16 January 2001 with written reasons posted on 9 February 2001, whereby the European patent No. 0 502 845 was maintained on the basis of the auxiliary request filed with the letter of 15 November 2000. The patent had been granted on European application No. 90 905 378.7 which originated from an international application published as WO 90/06047.

II. The patent had been opposed on the grounds as set forth in Articles 100(a) and (b) EPC that the invention did not involve an inventive step (Article 56 EPC), was not susceptible of industrial application (Article 57 EPC) and was not sufficiently disclosed (Article 83 EPC), and on the ground as set forth in Article 100(c) EPC that the patent contained added matter (Article 123(2) EPC).

III. Basis for the decision under appeal were the main request (claims 1 to 12) and the auxiliary request (claims 1 to 12) both filed on 15 November 2000. The main request was not accepted by the opposition division for lack of sufficient disclosure of the embodiments in relation to cDNA. The auxiliary request, which was limited to embodiments in relation to genomic DNA, was considered to fulfil the requirements of sufficiency and inventive step.

IV. Each appellant filed a reply to the statement of grounds of appeal of the other. Both parties filed new documents.

V. A communication under Article 11 of the Rules of Procedure of the Boards of Appeal presenting some preliminary and non-binding views of the board was then sent to the parties.

VI. In reply to the board's communication, appellant I filed observations with a letter dated 16 January 2004 accompanied by a **main request** and four auxiliary requests. The main request (claims 1 to 12) corresponded to the main request refused by the opposition division while **auxiliary request 1** (claims 1 to 12) corresponded to the auxiliary request it had accepted. **Auxiliary request 2** (claims 1 to 11) corresponded to claims 1 to 11 of auxiliary request 1. **Auxiliary request 3** (claims 1 to 11) was derived from auxiliary request 1 by deleting in claims 1 and 9 thereof the embodiment "transporter for gamma-aminobutyric acid". Finally, **auxiliary request 4** (claims 1 to 11) was derived from auxiliary request 3 by deleting in claims 1 and 9 thereof the embodiment "transporter for glycine".

VII. Claims 1 of the five requests were as follows:

(a) **Claim 1** of the **main request** read:

"1. An in vitro culture of mammalian cells comprising cells transformed with a human DNA encoding a neurotransmitter transporter selected from the group consisting of a transporter for

gamma-aminobutyric acid, serotonin, and glycine, with the provisos that said DNA is heterologous to said cells, and that said neurotransmitter transporter is expressed functionally by said cells."

(b) **Claim 1** of each of **auxiliary requests 1 and 2** differed from claim 1 of the main request in that it contained the further proviso that "said DNA is genomic DNA".

(c) **Claim 1** of **auxiliary request 3** differed from claim 1 of auxiliary request 1 or 2 in that it referred not to three but only two neurotransmitter transporters, namely the **serotonin** and the glycine transporters.

(d) **Claim 1** of **auxiliary request 4** differed from claim 1 of auxiliary request 1 or 2 in that it referred to only one neurotransmitter transporter which was the **serotonin** transporter.

VIII. In the letter of 16 January 2004 appellant I notified the board that it would not be represented at the oral proceedings.

IX. Oral proceedings took place on 18 February 2004. They were attended only by appellant II.

X. The following documents are cited in the present decision:

(D3) Lukas C. Kühn et al., Mol. Biol. Med., Vol. 1, 1983, Pages 335 to 352;

(D4) Moses V. Chao et al., Science, Vol. 17, No. 14, Pages 518 to 521;

(D9) Arlette Franchi et al., Proc. Natl. Acad. Sci. USA, Vol. 83, December 1986, Pages 9388 to 9392; and

(D14) D. R. Thomas et al., Psychopharmacology, Vol. 93, 1987, Pages 193 to 200.

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

In the light of the prior art, the skilled person would not have had a reasonable expectation of success in attempting to express functional neurotransmitter transporters by transfection with human genomic DNA. In particular, document D3 reported the failure to express a desired protein, namely the OKT-10 antigen, in this way, and gave possible reasons for this failure, which were directly applicable also to neurotransmitter transporters. In this respect, neurotransmitter transporters were clearly expressed only in neurons and not ubiquitously in all cells and such differential expression was explicitly mentioned in document D3 as one of the most likely reasons why the OKT-10 antigen could not be expressed in the same way.

XII. The submissions made in writing and during oral proceedings by appellant II, insofar as they are relevant to the present decision, may be summarised as follows:

Reasons of complexity and lack of understanding concerning neurotransmitter transporters and the processes of neurotransmission in general were equally true for other types of transporters as reported for example in document D9 with respect to the Na^+/H^+ antiporter. However, this lack of understanding had not been a barrier to the cloning, expression and functional evaluation of a wide range of transporters and would not have been a technical barrier to the skilled person at the priority date (see eg documents D3, D4 and D9).

There was no evidence that neurotransmitter transporter proteins as a class had "unique aspects" compared with other transporters such that there would be no reasonable expectation of success that they could be functionally expressed in heterologous cells by procedures already used for *in vitro* expression of other transporter or receptor membrane proteins. The skilled person would have used these procedures in order to solve the problem of providing alternative *in vitro* expression systems for investigating neurotransmitter transporters with a reasonable expectation of success.

XIII. Appellant I requested that the decision under appeal be set aside and the patent be maintained on the basis of either the main request or auxiliary requests 1 to 4 all filed on 16 January 2004.

XIV. Appellant II requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

1. All requests on file have in common that their claim 1 covers the subject-matter of claim 1 of auxiliary request 4, namely an *in vitro* culture of mammalian cells transformed with heterologous human genomic DNA encoding a transporter for serotonin, said transporter being functionally expressed. This embodiment is exemplified in the description (see Examples I and II), the transformation being achieved, in the absence of any information about the gene, by calcium phosphate precipitation of human genomic DNA, prepared as intact chromosomes or as degraded DNA fragments.

2. The question at issue is whether this subject-matter involves an inventive step. If not, then claim 1 of all requests would fail to meet the requirements of Article 56 EPC.

3. The said culture of transformed cells is useful for the investigation of the mechanisms of the serotonin-specific transport (uptake) system and the evaluation of agonists and antagonists thereof (see page 2, lines 36 to 38, in the patent specification).

4. Document D14 is a prior art document which describes a system based on the use of rat synaptosomes to perform such an investigation and evaluation. In this system, the effect of a test drug is evaluated by measuring the uptake of [^{3}H]-serotonin into crude synaptosomes prepared from hypothalamus, cortex or corpus striatum of a rat. The evaluation may be carried out either *in vitro* by adding the drug directly to the synaptosomes

or *ex vivo* by, first, orally administering the drug to a rat and, second, measuring two hours later the uptake of [^{3}H]-serotonin on synaptosomes prepared from the administered and then sacrified rat. This document is considered to represent the closest prior art.

5. Starting from document D14, the technical problem underlying the patent in suit may be considered to be the provision of an alternative *in vitro* cellular means appropriate for the investigation of the mechanisms of the serotonin-specific transport (uptake) system and to the evaluation of potential agonists and antagonists of serotonin uptake useful in the treatment of disorders in the human being believed to be associated with serotonin uptake such as, in particular, depression and anxiety (see page 4, lines 38 to 45, in the patent specification).

6. As solution to said problem claim 1 proposes an *in vitro* culture of mammalian cells (eg murine fibroblasts as used in the examples) transformed with a heterologous human genomic DNA encoding the human serotonin transporter, said DNA being functionally expressed.

7. Synaptosomal **rat** preparations as used in document D14, because they were subcellular fractions (prepared from tissues rich in chemical synapses), suffered from being heterogeneous from one preparation to the other, a condition which was not desirable for a rapid and reliable evaluation of novel therapeutic agents interacting with serotonin-uptake mechanisms. Furthermore, using such preparations only the **rat** serotonin transporter could be investigated.

8. Therefore, the skilled person facing the aforementioned technical problem would have readily looked for another model of serotonin uptake, which was relatively invariant over the time and involved not the rat but the **human** serotonin transporter.

9. At the priority date, a body of information was available which described an approach to prepare *in vitro* invariant cellular systems capable of expressing a protein of interest, in particular a membrane-bound protein, the gene of which was unknown, as was the case for the human serotonin transporter. This approach relied on the transformation of established **murine fibroblast** cell lines with **human genomic DNA**, the cells which had taken up and expressed the gene being identified using a selective technique. It had been proven to be successful in documents D3, D4 and D9, with regard to, respectively, a couple of human cell surface antigens, the human nerve growth factor receptor and the human Na^+/H^+ antiporter that exchanges internal H^+ for external Na^+.

10. Document D3 demonstrated the feasibility of the approach for the expression of human cell surface proteins. Document D4 established that a protein naturally produced in the human neurones could be expressed in murine fibroblasts. Document D9 showed that the approach was appropriate for the preparation of cells functionally expressing a membrane-bound protein involved in a transmembrane transport. It is the board's judgment that, in view of the information conveyed by these documents, there was much incentive for the skilled person to try using the approach

described in documents D3, D4 and D9 to prepare with a reasonable expectation of success murine fibroblasts capable of functionally expressing the human serotonin transporter, a membrane-bound protein involved in a transmembrane transport and naturally expressed in particular in neurones.

11. The argument made by appellant I that there would have been no reasonable expectation of success in trying the said approach, because in document D3 it is reported that using said approach the authors failed to identify expected transformants expressing the OKT-10 antigen, is not persuasive: not only is said protein not involved in a transmembrane transport, but also the precise reason why this protein has not been expressed is unknown (only hypotheses are proposed in document D3; see page 348). The skilled person would not have been put off from using the method proposed in document D13 which apart from this isolated failure for the OKT-10 antigen was otherwise reported as working successfully.

12. Therefore, an *in vitro* culture of murine fibroblasts, transformed with a human genomic DNA encoding a transporter for serotonin, said transporter being functionally expressed, lacks an inventive step. As a result, claim 1 of each of the five requests on file fails to meet the requirements of Article 56 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 L. Galligani