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Datasheet for the decision of 26 June 2007

Case Number: T 1384/06 - 3.3.08

Application Number: 99109196.8

Publication Number: 0971033

IPC: C12N 15/00

Language of the proceedings: EN

Title of invention:
Test and model for Alzheimer's disease

Applicant:
ELAN PHARMACEUTICALS, INC.

Opponent:
-

Headword:
Alzheimers's disease/ELAN

Relevant legal provisions:
EPC Art. 123(2), 83
EPC R. 86(3)

Keyword:
"Admissibility of main and first auxiliary request - no"
"Second auxiliary request - added subject-matter - no"
"Sufficiency of disclosure - yes"

Decisions cited:
T 0019/90, T 0315/03

Catchword:
-

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Case Number: T 1384/06-3.3.08

D E C I S I O N
of the Technical Board of Appeal
of 26 June 2007

Appellant: ELAN PHARMACEUTICALS, INC.
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Representative: Lee, Nicholas John
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 5 January 2006 refusing European application No. 99109196.8 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: F. Davison-Brunel
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent application No. 99 109 196.8 published under No. 0 971 033 with the title "Test and model for Alzheimer's disease", filed on 21 January 1992 as a divisional application to the application No. 92 903 304.1 was refused by the examining division for failing to fulfil the requirements of Articles 123(2) and 83 EPC (added subject-matter and lack of sufficient disclosure).

Claims 1 and 2 of the **request refused by the examining division** read as follows:

"1. A transgenic non-human animal comprising a recombinant polynucleotide including a nucleic acid sequence encoding a mutant human amyloid precursor protein (APP) allele that cosegregates with a genetic predisposition to Alzheimer's disease.

2. An animal as claimed in claim 1, wherein the sequence is integrated into the animal's genome."

II. The reasons why the examining division refused the application were as follows:

- The feature of the mutant APP polynucleotide being integrated into the animal genome (claim 2) had originally been disclosed only in relation to the APP polynucleotide sequence mutated in codon 717. Thus, the generalisation of this feature to all mutated APP sequences went beyond the content of the application as filed. Claim 2 was unallowable under Article 123(2) EPC.

- The requirement of sufficiency of disclosure was also not fulfilled:

  - The application did not provide nor suggest any positions in the APP gene other than the valine 717 codon which might be mutated and cosegregate with Alzheimer's disease.

  - In the years following the filing date, it was established that mutations in the APP gene which cosegregated with Alzheimer's disease were rare. In 1998, they had been found to affect fewer than 25 families worldwide (document (3)). It was, thus, undue burden to isolate mutant APP alleles. Otherwise expressed, these alleles could only be obtained by chance.

  - In post-published document (5), it was indicated that transgenic animals such as now claimed could not be used as suitable models for studying the disease.

III. The appellant (applicant) filed a notice of appeal against this decision, paid the appeal fee and submitted a statement of grounds of appeal together with a new main request comprising claims 1 and 2 of the request refused by the examining division (cf. Section I supra) and an auxiliary request.

The claims of the **auxiliary request** read as follows:

"1. A transgenic non-human animal comprising a recombinant polynucleotide including a nucleic acid

sequence encoding a mutant human amyloid precursor protein (APP) allele that cosegregates with a genetic predisposition to early onset familial Alzheimer's disease. (difference with claim 1 of the main request highlighted by the board).

2. An animal as claimed in claim 1, wherein the sequence is integrated into the animal's genome."

IV. The appealed decision was not rectified by the examining division and the case was remitted to the board of appeal (Article 109(2) EPC).

V. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal stating its preliminary non-binding opinion.

VI. The appellant answered this communication and filed a new main request and a new first auxiliary request to replace the requests on file.

Claims 1 and 2 of the new main and first auxiliary requests were respectively identical to claims 1 and 2 as refused by the examining division (Section I, supra) and to claims 1 and 2 of the first auxiliary request filed with the grounds of appeal (Section III, supra). Both requests contained a further claim.

Claim 3 of the main request read as follows:

"3. An isolated polynucleotide, comprising a nucleic acid sequence encoding a mutant human APP allele that cosegregates with a genetic predisposition to Alzheimer's disease."

Claim 3 of the first auxiliary request read as follows:

"3. An isolated polynucleotide, comprising a nucleic acid sequence encoding a mutant human APP allele that cosegregates with a genetic predisposition to early onset familial Alzheimer's disease."(difference from claim 3 of the main request highlighted by the board).

VII. Oral proceedings took place on 26 June 2007. During oral proceedings, the appellant filed a second auxiliary request which differed from the first auxiliary request by deletion of claim 3, thereby being identical to the first auxiliary request filed with the grounds of appeal (section III, supra).

VIII. The documents mentioned in this decision are:

(3): Consensus report of the Working Group on: "Molecular and Biochemical Markers of Alzheimer's Disease, Neurobiology of Aging, Vol.19, No.2 pages 109 to 116, 1998;

(13): Mullan, M. et al., Nature Genetics, Vol. 1, pages 345 to 347, August 1992;

(20): Declaration of Dr. J. Hardy dated 12 February 2004;

(A): Wirak, D.O. et al., Science, Vol. 253, pages 323 to 325, July 1991, cited on page 21 of the application;

(B): Yoshikai, S. et al., Gene, Vol. 87, pages 257 to 263, 1990, cited on page 9 of the application.

IX. The appellant's arguments insofar as relevant to the present decision may be summarized as follows:

Main and first auxiliary requests; claim 3

Rule 86(3) EPC

Claim 3 directed to an isolated polynucleotide had been added as an "precautionary measure" against the possibility that the board may not accept claims 1 and 2. It corresponded to a claim filed in the parental application.

Article 84 EPC; clarity

It could not be denied that the product of claim 3 was defined in functional terms and that, at the filing date, there may not have been a prototype APP gene. Yet, the way the claim was drafted was adequate since it accurately reflected the contribution to the art made by the inventor. Indeed, this had been the first time that a mutation in the APP gene had been associated with the pathology observed in patients suffering from early onset familial Alzheimer's disease. The skilled person would take it as a matter of fact that mutations other than the one at position 717 could be found and, thus, specific technical features needed not be introduced into the claim. The requirements of Article 84 EPC were fulfilled.

Second auxiliary request
Articles 123(2) and 76 EPC

The subject-matter of claims 1 and 2 found a basis in the application as filed and, accordingly, in the parental application on page 4, lines 11 to 16 (DNA encoding mutant APP alleles associated with early onset familial Alzheimer's disease) together with page 27, lines 10 to 18 disclosing transgenic animals carrying this DNA. The requirements of Articles 123(2) and 76 EPC were fulfilled.

Article 83 EPC

- Following the inventor's discovery of two mutations in the APP gene which cosegregated with early onset Alzheimer's disease, it was immediately apparent to the skilled reader that further pathogenic mutations in the APP gene existed which also cosegregated with Alzheimer's disease.

- The identification of these mutations did not constitute an undue experimental burden. Indeed, it did not depend on chance but, on the contrary, only required that routine steps be carried out such as selecting families with a history of Alzheimer's disease and sequencing the APP gene. Finding these families could be done simply by advertising in medical journals. At the filing date, it would have been no burden to sequence either the whole of the APP gene or the portion of this gene known to be encoding the amyloid peptide found in Alzheimer's patients.

- It was true that eg. document (3) disclosed that mutations in the APP gene were rare. Yet, in document (20), Prof. Hardy attested that they were not so rare as originally thought. Furthermore, how rare they were was largely irrelevant insofar as the skilled person would have expected them to exist and had at his/her disposal the necessary means to identify them.

- Producing transgenic animals was within the capability of the person skilled in the art at the priority date, taking into account the common general knowledge and the teaching of the present application which outlined the strategy and described in detail exemplary methods for producing a transgenic animal of the invention (page 20, line 8 to page 21, line 22, Example 4).

- Finally, it had to be kept in mind that document (13) published some two years after the filing date of the application described the isolation of further mutants in the APP gene which cosegregated with early onset familial Alzheimer's disease, by the same methods as were described in the application as filed.

For these reasons, the requirements of Article 83 EPC were fulfilled.

X. The appellant requested that the decision under appeal be set aside and that the case be remitted to the first instance for further prosecution on the basis of either the main or the first auxiliary request, both filed on

24 May 2007, or on the basis of the second auxiliary request filed during the oral proceedings.

Reasons for the decision:

Main and first auxiliary requests; claim 3
Rule 86(3) EPC; Article 84 EPC

1. Rule 86(3) EPC states that:

"After receipt of the first communication from the Examining Division the applicant may, of its own volition, amend once the description, claims and drawings provided that the amendment is filed at the same time as the reply to the communication. No further amendment may be made without the consent of the Examining Division."

2. In the present case, the appellant amended the claims a first time, of its own volition, during examination procedure (submissions of 31 January 2005). Then, a first auxiliary request was forwarded with the grounds of appeal. Finally, an amended main request and an amended first auxiliary request were submitted after the board's communication under Article 11(1) RPBA, each of them containing a new claim 3. No reasons were given in writing for the introduction of this last claim. When asked at oral proceedings, the representative declared that claim 3 had been added as a precautionary measure in case the board would not accept claims 1 and 2.

3. This explanation is simply not sufficient to trigger the board's consent to the amendment. Indeed, any potentially acceptable amendment would have had to be carried out to

take into account specific objections or remarks made by the board. Here, the communication under Article 11(1) RPBA clearly indicated the board's concerns that the isolation of transgenic animals comprising polynucleotides mutant APP alleles may be undue burden **precisely because** of the difficulty in isolating such polynucleotides (point 6 of the communication). The addition of claim 3 directed to the polynucleotides per se is, thus, certainly not in answer to the board's concerns. In fact, it appears to be purely gratuitous. For this reason, the main and first auxiliary requests comprising claim 3 are not allowable on procedural grounds.

4. A further remark must be made. The subject-matter of claim 3 of both the main and first auxiliary requests is defined solely in functional terms. Whereas mutant alleles are claimed as a product, no technical information is given as to their nature. It is mentioned in the application as filed that the term APP covers more than one form of the same protein. Furthermore, it is difficult to fathom the technical features corresponding to the term: "co-segregating with a genetic predisposition". Thus, had the board consented to the introduction of claim 3 in the main and the first auxiliary requests, these would nonetheless have had to be refused for lack of clarity ie. for failing to fulfil the requirements of Article 84 EPC.

Second auxiliary request
General considerations

5. This request contains two claims which are both directed to transgenic non-human animals. In accordance with the case law relating to the application of Article 53 EPC (e.g. T 315/03, OJ EPO 2006, 15), it must be investigated whether such subject-matter falls within the category of exceptions to patentability. Obviously, this should be done as the first step in the examination because there is absolutely no point in assessing whether or not a subject-matter which is decided to be an exception to patentability fulfils the requirements for patentability.

6. This first step was, however, omitted by the examining division which refused the corresponding claims 1 and 2 relating to transgenic non-human animals under Article 123(2) and 83 EPC. A possible logical course of action would certainly be to send the case back to the first instance for examining whether or not the claimed subject-matter is primarily suited for patent protection. However, taking into account that it is the board's duty under Article 106(1) EPC to review the decision under appeal and without wanting to prejudice in any way the decision which the examining division may want to make under Article 53 EPC, the issues of added subject-matter and sufficiency of disclosure will be considered below.

Articles 123(2) EPC and 76 EPC

7. The passage on bridging pages 2 and 3 of the application as filed reads as follows:

"..., the present invention provides a transgenic nonhuman animal that harbors at least one integrated copy of a human DNA sequence that encodes an amyloid precursor protein (APP) isoform or fragment that has an amino acid other than valine at the amino acid position corresponding to amino acid residue position 717 of APP770."

Furthermore, it is mentioned on page 4:

"The invention also relates to an isolated nucleic acid encoding such a polypeptide and to uses and applications of such nucleic acid as are described above in relation to the specific embodiment of the invention which involves an amino acid substitution at position 717 (as defined in relation to APP770)."

Finally, on page 27:

"Alternatively, homologous recombination may be used to insert an APP mutant sequence into a host genome at a specific site, for example, at a host APP locus... Homologous recombination may be used to produce transgenic non-human animals..."

This information is given in the context of investigating early onset familial Alzheimer's disease. The same passages are found in the parental application.

8. In the board's judgment, these passages provide a clear and unambiguous formal basis for the subject-matter of claims 1 and 2 - transgenic, non-human animals carrying/having integrated a mutant APP allele into their

genomes. Thus, it is concluded that the requirements of Articles 123(2) and 76 EPC are fulfilled.

Article 83 EPC; sufficiency of disclosure

9. The scope of claims 1 and 2 extends to transgenic non-human animals as model systems for studying early onset familial Alzheimer's disease, carrying an altered APP gene irrespective of the kind of alterations involved or of their localisation within the gene. In contrast, it cannot be denied that the entire thrust of the application is towards providing a model system of Alzheimer's disease which comprises a DNA sequence encoding an APP protein that has an amino acid other than valine at position 717 (application as filed, page 2, lines 17 to 21). In this framework, the application teaches that one should start with "a specimen removed from a subject" suffering from Alzheimer's disease (page 13, lines 24 and 25), then one should detect whether a base change has occurred in the APP gene, isolate the mutated gene and transfer it to animals. The necessary techniques are described on pages 15 to 19 and in the examples (use of small oligonucleotide probes, PCR possibly followed by RFLP analysis, PASA, producing transgenic animals). In the absence of any evidence to the contrary, there is no reason to challenge the feasibility of reproducing this teaching as regards mutants in the valine 717 codon. The key issue is rather whether or not the invention is enabled over the scope of the claim.

10. Identifying families with a history of Alzheimer's disease belongs to the traditional activities of clinical genetics. Furthermore, the application teaches on page 30,

lines 15 to 19 that the detection of the mutated versions of the APP gene is simplified by the fact that an easily detectable chromosomal marker (D21S210) close to APP cosegregates with Alzheimer's disease. Obtaining a "specimen" and finding the altered APP gene - whichever the mutation might be - can, thus, be carried out without undue burden.

11. For the skilled person, identifying the specific mutations involved would inevitably mean that the sequence of the altered APP gene be determined, at least to some extent, and be compared with that of the wild-type APP gene which had already been investigated at the filing date (document (B), Yoshikai et al., cited on page 9 of the application). Without any evidence to the contrary, the board is prepared to accept that the sequencing task, although possibly heavy, does not amount to undue burden. Finally, transgenic animals carrying the mutated APP allele need to be produced. In this context, it is noted that two lines of transgenic mice expressing human wild type amyloid β protein in the brain had already been described at the filing date (see document (A), Wirak et al., cited on page 21 of the application, published between the first and second priority dates).

12. Admittedly, the scope of the claims is not limited to mice but covers transgenic, non-human animals. The situation is, thus, analogous to that encountered in the earlier decision T 19/90 (OJ EPO 1990, 476) dealing with a case where a transgenic, non-human animal was claimed whereas the invention had only been illustrated with transgenic mice. The then competent board decided that "the mere fact that a claim is broad is not in itself a ground for considering the application as not complying

with the requirement of sufficient disclosure under Article 83 EPC. Only if there are serious doubts, substantiated by verifiable facts, may an application be objected for lack of sufficient disclosure." (see point 3.3 of the decision). The board sees no reason to depart from this rationale in the present case.

13. The examining division came to a conclusion of lack of sufficient disclosure for the reasons which are given in Section II supra. The board does not find any of them convincing. Whether or not a given technical achievement is "suggested" is an issue which may have to be taken into account when considering a piece of prior art within the framework of assessing inventive step. As far as sufficiency of disclosure is concerned, the relevant question is whether or not the technical achievement may be reproduced without undue burden on the basis of the information provided, which appears to be the case here (see points 10 to 12, supra).

14. The rarity of APP mutants is apparently linked to the rarity of families with a predisposition to Alzheimer's disease: in 1998, only 120 families worldwide were known to carry deterministic mutations; 21 of them carrying mutations in the APP gene (document (3), page 111). This, of course, implies that the opportunities of studying the predisposition to Alzheimer's disease are few and far between. However, it does not alter the fact that neither the identification of the families nor the further work required for obtaining the now claimed subject-matter are, per se, undue burden. The fact that there are only a very small number of such families does not make the process of identification one of random selection by trial and

error because, however few, they are nonetheless identifiable.

15. The last of the examining division's concerns - the unsuitability of transgenic animals as models for Alzheimer's disease - does not, in fact, affect reproducibility of the transgenic animals.

16. For these reasons, it is concluded that the requirements of Article 83 EPC are fulfilled.

17. The case will be remitted to the first instance for further prosecution. It is important to remember that, as established in the case law (T 19/90, supra), in case of genetic manipulations of animals, there are compelling reasons to consider the provisions of Article 53(a) EPC in relation to the question of patentability. This has been done in, for example, T 315/03 (supra), which indicates a possible practical approach to the issue. If the claimed subject-matter does not fall within the category of "exceptions to patentability" pursuant to Article 53(a) EPC, compliance with all further requirements for patentability (e.g. Articles 54, 56, 57 and 84 EPC) will, of course, also have to be investigated.

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 for further prosecution on the basis of the second auxiliary request filed during oral proceedings.

The Registrar The Chairman

A. Wolinski L. Galligani