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Datasheet for the decision of 16 December 2008

Case Number: T 1847/06 - 3.3.08

Application Number: 94931891.9

Publication Number: 0730643

IPC: C12N 15/00

Language of the proceedings: EN

Title of invention:
Transgenic animals harboring APP allele having Swedish mutation

Patentee:
ELAN PHARMACEUTICALS, INC., et al

Opponents:
F. HOFFMANN-LA ROCHE & CO.
GLAXO GROUP LIMITED
Bayer AG

Headword:
Swedish mutation/ELAN

Relevant legal provisions:
EPC Art. 123(2)

Relevant legal provisions (EPC 1973):
EPC Art. 54(3)(4), 84

Keyword:
"Main request - novelty (no)"
"First auxiliary request - disclaimer offends against Article 123(2) EPC"
"Second auxiliary request - novelty (yes)"
"Remittal for further prosecution"

Decisions cited:
G 0001/03, T 0033/06

Catchword:
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Case Number: T 1847/06 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 16 December 2008

Appellants: (Patent Proprietors)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 13 September 2006 revoking European patent No. 0730643 pursuant to Article 102(1) EPC 1973.**

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
B. Günzel

Summary of Facts and Submissions

I. European patent No. 0 730 643 with the title "Transgenic animals harboring APP allele having Swedish mutation" was granted on European patent application No. 94 931 891.9 (published as WO 95/11968), which was filed as PCT/US94/11827 on 18 October 1994 claiming the priority of two earlier US applications filed on 27 October 1993 and 1 November 1993, respectively.

II. The patent was opposed by three parties on the grounds of Article 100(a) EPC 1973, in particular that the claimed subject-matter lacked novelty (Article 54 EPC 1973) and inventive step (Article 56 EPC 1973), as well as on the grounds of Article 100(b) and (c) EPC 1973.

III. By a decision posted on 13 September 2006, the patent was revoked under Article 102(1) EPC 1973. The opposition division found that the subject-matter of claim 1 of either the main request or the auxiliary request then on file lacked novelty in view of document (9) (*infra*) and that, consequently, the ground of opposition mentioned in Article 100(a) in connection with Article 54(3)(4) EPC 1973 prejudiced the maintenance of the patent.

IV. The patent proprietors (appellants) lodged an appeal against the decision of the opposition division. Together with the statement setting out the grounds of appeal, the appellants submitted a set of amended claims as their main request and re-filed claims 1 to 5 according to the main request in opposition proceedings as their first auxiliary request. In the event that the

board did not consider the subject-matter of the claims according to either request to be novel over document (9), three additional sets of claims were submitted as second, third and fourth auxiliary requests, respectively, for consideration by the board. As a subsidiary request, the appellants requested that oral proceedings be held prior to any adverse decision. In case of a favourable decision on novelty, remittal of the case to the opposition division for consideration of the issues of inventive step and sufficiency was requested.

V. Respondent II (opponent 02) filed observations on the grounds of appeal. A request by respondent I (opponent 01) to extend the term for replying to the statement of grounds of appeal was not granted by the board. Neither respondent I nor respondent III (opponent 03) filed any submissions in response to the statement of grounds of appeal.

VI. The parties were summoned to oral proceedings. In a communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) attached to the summons, the board drew the attention of the parties to some issues in connection with Articles 123(2) and 54 and Rule 80 EPC.

VII. Respondent I replied to the board's communication and submitted additional evidence.

VIII. By a letter dated 17 November 2008 in reply to the board's communication, the appellants filed five sets of amended claims as main request and first to fourth auxiliary requests, respectively, which replaced the

sets of claims previously on file. A further document (renumbered as document (34) in these proceedings) (*infra*) was also filed.

IX. Both respondents filed an additional document in connection with the issue of priority. The appellants requested that these documents be excluded from the proceedings as being late-filed. In the event that the documents were admitted, remittal to the opposition division for discussion of the priority and novelty issues in the light of the new documents was requested.

X. At the oral proceedings, which were held on 16 December 2008, the appellants and respondents I and II were represented. Although it had been duly summoned, respondent III was not represented. At the outset of the oral proceedings, the appellants inverted the order of their main request and first auxiliary request and withdrew their second auxiliary request, the previous third and fourth auxiliary request thus becoming second and third auxiliary request, respectively.

XI. Claim 1 of the **main request** (claims 1 to 5, filed as first auxiliary request with letter of 17 November 2008) reads as follows:

"1. Use of a transgenic nonhuman animal or stem cell to screen an agent for activity in preventing, inhibiting or reversing Alzheimer's disease, wherein said transgenic nonhuman animal or stem cell:

comprises a diploid genome comprising a transgene encoding a heterologous APP polypeptide comprising the Swedish mutation wherein the amino acid residues at positions corresponding to positions 595 and 596 in

human APP^{695} are asparagine and leucine, respectively; and

expresses said APP polypeptide."

Claims 2 to 5 concern various embodiments of the use of claim 1.

XII. Claim 1 of the **first auxiliary request** (claims 1 to 5, filed as main request with letter of 17 November 2008) differs from claim 1 of the main request in that the following negative feature has been inserted an the end of the claim:

"..., provided that said screening does not comprise administering a test compound or compounds to said animal and monitoring the level of soluble ß-amyloid peptide or soluble ß-amyloid peptide fragment in a body fluid of said animal."

XIII. Claim 1 of the **second auxiliary request** (claims 1 to 5, filed as third auxiliary request with letter of 17 November 2008) differs from claim 1 of the main request in that, at the end of the claim, the following feature was inserted:

"..., wherein said agent is administered to said transgenic animal at a dosage of from 1 ng/kg to 10 mg/kg, preferably from 10 µg/kg to 1 mg/kg."

XIV. Claim 1 of the **third auxiliary request** (claims 1 to 5, filed as fourth auxiliary request with letter of 17 November 2008) differs from claim 1 of the main request in that it includes the following additional feature at the end of the claim:

"..., and wherein said animal comprises at least one inactivated endogenous APP allele."

Claims 2 to 5 of each of the auxiliary requests were identical to the corresponding claims of the main request.

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

(9): WO 94/10569, filed on 1 September 1993;

(34): Interlocutory decision of the opposition division concerning European patent No. 0 667 959, dated 10 July 2007.

XVI. The submissions made by the appellants, as far as they are relevant to this decision, may be summarized as follows:

Main request - Novelty

In the decision under appeal, the opposition division found that claim 1 directed to the use of a transgenic nonhuman animal in an *in vivo* screening method lacked novelty over document (9). This finding was inconsistent with the findings of a different opposition division when evaluating the disclosure content of document (9) in the framework of assessing compliance with Article 123(2) EPC (see document (34), paragraphs M2 to M5). In that case, the opposition division was of the opinion that the reference to the use of "other APP isotypes and/or variants" on page 17

of document (9) was not a clear and unambiguous disclosure of using transgenic animals bearing the Swedish mutation in an *in vivo* screening method.

The arguments of the opposition division in that case were adopted by the appellants in the present case. In particular, it was maintained that the term "Similarly", which introduced the passage concerning the transgenic hosts at the top of page 17, did not unambiguously refer back to the features of the APP variants, namely overproduction and cleavage site residues. The term simply referred to the similarity of the described screening methods, ie. *in vitro* cellular models and transgenic animals, with respect to the common βAP monitoring procedure.

First auxiliary request

In view of the opposition division's finding that document (9) disclosed the use of an animal model containing the Swedish mutant form of APP to screen for a specific class of compounds to treat Alzheimer's disease, namely compounds that inhibit soluble βAP production, an amended claim 1 was proposed in order to restore the novelty of the claims by means of a disclaimer.

The disclaimer introduced into claim 1 excluded the use of a nonhuman animal bearing the Swedish mutation in a screening method that comprised monitoring the level of soluble βAP or fragments thereof in a body fluid of the animal. The disclaimer was in accordance with the requirements of decision G 1/03 (OJ EPO 2004, 413) since it delimited claim 1 against state of the art

under Article 54(3) EPC 1973, did not remove more than it was necessary to restore novelty and was clear within the meaning of Article 84 EPC 1973.

The use of the expression "does not comprise" in the disclaimer reflected the generic disclosure in document (9). There was nothing in the description of this document that suggested that its technical disclosure was limited to screening methods that consisted solely of the two steps of administering a test compound or compounds to an animal bearing the Swedish mutation and measuring the level of βAP or βAP fragment in a body fluid of said animal, nor was there any technical reason for excluding additional steps. On the contrary, it was clear that the *in vivo* screening methods described in document (9) could include additional steps.

It was apparent from claim 14 as well as from the passages on page 6, lines 32 to 35, and page 17, lines 1 to 13 of document (9) that the disclosure of this document extended beyond a method "consisting" of administering a test compound to a transgenic animal with the Swedish mutation. Unlike the situation in decision T 33/06 of 18 September 2007, document (9) did not contain a specific experimental protocol in the examples that was relevant to the novelty of the claim under consideration.

Second auxiliary request

None of the documents on file disclosed screening agents for activity in preventing, inhibiting or reversing Alzheimer's disease by administering the

agent to a transgenic animal bearing the Swedish mutation at a dosage in the range specified in claim 1.

XVII. The submissions made by the respondents may be summarized as follows:

Main request

As correctly analysed by the opposition division, the subject-matter of claim 1 was not novel over document (9). On page 17, lines 1 to 5 of this document it was made clear that the animal model to be used in screening methods did express the APP isotypes and/or variants mentioned in the preceding paragraph.

First auxiliary request

According to G 1/03 (*supra*), a disclaimer should not remove more than was necessary to restore novelty. However, due to the use of the language "does not comprise", the disclaimer introduced into claim 1 was open-ended, such that the scope of the disclaimer was not limited to just one method of screening an agent for activity in preventing, inhibiting or reversing Alzheimer's disease and, furthermore, had no direct counterpart in document (9). Thus, the disclaimer added matter and was in contravention of Article 123(2) EPC. Moreover, by the inclusion of the open-ended expression "does not comprise" within the disclaimer, claim 1 did not clearly define the protection for which protection was sought.

Second auxiliary request

The feature specifying a given amount of agent to be administered to the transgenic animal could not confer novelty to the claimed subject-matter in light of the fact that document (9) disclosed such amounts/dosages, eg. in page 17, lines 18 to 24 and page 19, lines 19 to 23.

The dose ranges specified in claim 1 were very wide and dosages falling within those ranges were implicit to the teaching of document (9). When screening an agent in a transgenic mouse bearing the Swedish mutation as described in document (9), any skilled person would inherently use a dosage that would fall within the wide ranges specified in claim 1.

XVIII. The appellants (patentees) requested that the decision under appeal be set aside and that the case be remitted to the opposition division for further prosecution on the basis of either the main request filed as first auxiliary request with letter dated 17 November 2008, or the first to third auxiliary requests, in the order, filed respectively as main, third and fourth auxiliary requests with letter dated 17 November 2008.

XIX. The respondents (opponents) requested that the appeal be dismissed.

Reasons for the Decision

Main request - Novelty

1. Claim 1 of the main request presently on file is identical to the corresponding claim of the main request refused by the opposition division on the grounds of lack of novelty under Article 54(3)(4) EPC 1973 in view of document (9).

2. Document (9) is the publication of an International application under the PCT filed on 1 September 1993, ie. before the earliest priority date of the present patent (27 October 1993), for which all requirements of Article 158(2) EPC 1973 have been met. It designates the same Contracting States as the present patent. Thus, the contents of document (9) have to be considered as comprised in the state of the art for the purpose of assessing novelty of the claimed subject-matter in the present case (Article 150(3) in connection with Article 54(3)(4) EPC 1973).

3. Document (9) relates generally to methods and compositions for detecting soluble βAP (ß-amyloid peptide) in fluid samples, and in particular to screening methods for the identification of inhibitors of βAP production where βAP is detected *in vitro* or *in vivo*, with the aim of finding drugs which, by inhibiting the generation of βAP *in vivo*, are effective in the treatment of Alzheimer's disease, a condition which has been associated with the deposition of βAP as amyloid plaques in the cerebral tissue and in the walls of cerebral and meningeal blood vessels (see page 1, lines 12 to 18 and page 2, lines 29 to 33).

4. In the paragraph starting on page 16, line 9 of document (9), it is described that *in vitro* monitoring of βAP levels in conditioned culture medium from a suitable cell culture may be used for drug screening, and examples for suitable cell lines are provided. In the following paragraph on the same page, it is indicated that cell lines capable of expressing APP (amyloid peptide precursor) variants which overproduce βAP are preferred for use in the described drug screening methods. APP variants having one or several amino acid substitutions directly amino-terminal of the βAP cleavage site are mentioned as particularly preferred variants, and a variant bearing a double mutation (Lys^{595} -> Asn^{595} and Met^{596} -> Leu^{596}) found in a Swedish family suffering from familial Alzheimer's disease is specifically mentioned as an example. It is also described that, when this variant is expressed in a cell culture, approximately six to eightfold more βAP is produced than in cells expressing normal APP (see page 16, lines 33 to 37).

5. As concerns animal models, it is stated in the following paragraph of document (9) (see first paragraph on page 17):

> "*Similarly, in vivo monitoring of βAP in animal models, such as the mouse animal model disclosed in WO 91/19810), [...], and animal models expressing other APP isotypes and/or variants, may also be used to screen compounds for therapeutic effectiveness...*"

6. For its finding of lack of novelty, the opposition division relied on this passage, and in particular on the reference to "*other APP isotypes and/or variants*" which, in its view, clearly encompassed the Swedish mutation mentioned in the passage immediately before.

7. The board sees no reason to deviate from this finding. Even though the passage quoted above does not specifically mention an APP variant bearing the Swedish mutation, the board considers that a person skilled in the art reading the passage would understand that the APP variants mentioned in the preceding paragraph as variants associated with an overproduction of βAP, and in particular the "Swedish variant" are also contemplated as APP variants which can be expressed in animal models for screening compounds for therapeutic effectiveness, as described in document (9).

8. Contrary to the appellant's argument, the board believes that the word "similarly", which links the paragraph quoted above (see point 5) to the previous paragraph on page 16 of document (9), cannot be interpreted as referring solely to the similarity of the screening methods used *in vitro* and *in vivo*. Rather, "similarly" is considered to refer to the APP variants mentioned in the previous paragraph as being associated with an overproduction of βAP, and thus implicitly to the APP variant bearing the Swedish mutation.

9. Consequently, when reading the first paragraph on page 17 in connection with the preceding paragraph on page 16, subject-matter encompassed by claim 1, in particular the use of a transgenic animal bearing the Swedish mutation for screening an agent for therapeutic

activity in Alzheimer's disease is anticipated. Thus, claim 1 lacks novelty over document (9) under Article 54(3)(4) EPC 1973 and, therefore, the main request cannot be allowed.

First auxiliary request - Article 123(2) EPC

10. Claim 1 is identical to claim 1 of the main request, except for the amendment introducing a negative feature to exclude particular subject-matter (see Section XII above) from the scope of the claim.

11. The appellants admitted that the negative feature in question is not disclosed in the application as originally filed. According to G 1/03 (OJ EPO 2004, 413), a disclaimer which is not disclosed in the application as filed may be allowable to restore novelty by delimiting a claim against the state of the art under Article 54(3)(4) EPC 1973 (see G 1/03, Order, points 1 and 2.1), provided that the disclaimer does not remove more than is necessary to restore novelty (G 1/03, Reasons, point 3, last sentence of the second paragraph, and Order, point 2.2).

12. Thus, having regard to the arguments put forward by the respondents, the issue to be decided in connection with the first auxiliary request is whether or not the negative feature introduced as a disclaimer in claim 1 with the aim of excluding the novelty-destroying disclosure of document (9), extends beyond the content of said disclosure.

13. As stated in connection with the main request (see points 7 to 9 above), the board considers that the

statements in the last paragraph on page 16 and the first paragraph on page 17, when read together, anticipate the use as claimed in claim 1 before the disclaimer was introduced. These paragraphs describe the use of a transgenic animal bearing the Swedish mutation in a screening method, which method consists solely of the steps of administering an agent to an animal bearing the Swedish mutation and measuring the level of βAP or βAP fragment in a body fluid of said animal. Since no further steps of the screening methods are either generally or specifically described in this passage, there is no basis in the cited passage of document (9) for a disclaimer which excludes methods comprising not only the described method steps, but also additional steps not specified in document (9).

14. The appellants pointed to claim 14 of document (9) as a possible basis for disclaiming screening methods comprising further steps. The board is not able to acknowledge such basis. Whereas it is true that in claim 14 the wording "*comprising*" is used, the screening method defined in claim 14 does not provide a basis for the disclaimed methods. It should be noted that, according to claim 14, the animal to which the test compound is administered is not defined as a transgenic animal bearing the Swedish mutation, but only as a "mammalian host".

15. Nor can a basis for the disclaimer be found in the passage on page 6, lines 32 to 36 of document (9), in which neither transgenic animals producing the "Swedish variant" of APP are mentioned nor further method steps are described.

16. For these reasons, the disclaimer introduced into claim 1 extends beyond the disclosure of document (9) and, therefore, does not meet the requirements of G 1/03 (*supra*). Consequently, the amendment to claim 1 by introducing the disclaimer offends against Article 123(2) EPC.

Second auxiliary request

Articles 123(2)(3) EPC and Article 84 EPC 1973

17. No formal objections were raised by the respondents against the introduction of a dosage feature in claim 1 (see Section XIII above) and the board sees no reason to do so of its own motion. The limiting feature has its basis on page 21, lines 30 to 33 of the application as filed. The formal requirements of Article 123(2)(3) EPC and Article 84 EPC 1973 are thus met.

Novelty - Article 54(3)(4) EPC 1973

18. Respondent I maintained that the dosage feature introduced into claim 1 did not impart novelty to the claim because this feature was described on page 17, lines 18 to 24 and page 19, lines 19 to 23 of document (9).

19. On page 17, lines 18 to 24, it is stated that the test compounds will typically be administered **to the culture medium** at a **concentration** in the range from about 1 nM to 1 mM, usually from about 10 µM to 1 mM, and on page 19, lines 19 to 23 possible therapeutically effective doses of **pharmaceutical compositions** to be

administered to patients suffering from Alzheimer's disease are suggested. Hence, neither passage concerns screening methods using nonhuman transgenic animals bearing the Swedish mutation. Moreover, contrary to the respondents' argument, the board is not convinced that a person skilled in the art would seriously contemplate using a concentration suitable for cell cultures, or doses described in connection with therapeutic applications, in screening methods carried out in test animals.

20. Thus, the board concludes that the subject-matter of claim 1 is novel over document (9).

Remittal to the opposition division

21. Since the objections of lack of inventive step and sufficiency of disclosure have not been considered by the opposition division, the case is remitted for further prosecution. The parties have agreed to the additional documents filed at a late stage of the appeal proceedings being part of the proceedings before the opposition division after the remittal of the case. In view of these documents, the validity of the priority claimed in the present patent may have to be considered anew.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division for further prosecution on the basis of the second auxiliary request filed as third auxiliary request with the appellants' letter dated 17 November 2008.

The Registrar: The Chairman:

A. Wolinski L. Galligani