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Datasheet for the decision of 24 June 2015

Case Number: T 2168/11 - 3.3.08

Application Number: 94931891.9

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Language of the proceedings: EN

Title of invention:
TRANSGENIC ANIMALS HARBORING APP ALLELE HAVING SWEDISH MUTATION

Patent Proprietor:
ELAN PHARMACEUTICALS, INC.
ELI LILLY AND COMPANY

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

Headword:
Alzheimer's disease beta amyloid peptide mouse model/ELAN ELI LILLY

Relevant legal provisions:
EPC Art. 56
RPBA Art. 12(4)

Keyword:
"Main Request - inventive step (no)"
"Admissibility of first, second and third Auxiliary Requests into the appeal proceedings (no)"

Decisions cited:
T 0918/01, T 0278/03, T 0192/06, T 1127/06, T 1847/06, T 0782/07, T 0361/08, T 1231/09, T 2046/11

Catchword:

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Case Number: T 2168/11 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 24 June 2015

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Respondent: (Patent Proprietor 1)	ELAN PHARMACEUTICALS, INC. 800 Gateway Boulevard South San Francisco, CA 94080 (US)
Respondent: (Patent Proprietor 2)	ELI LILLY AND COMPANY Lilly Corporate Center Indianapolis, IN 46285 (US)
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Party as of right: (Opponent 3)	Bayer AG Konzernbereich RP Patente und Lizenzen 51368 Leverkusen (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 26 July 2011 concerning maintenance of the European Patent No. 0730643 in amended form.**

Composition of the Board:

Chairman M. Wieser
Members: P. Julià
J. Geschwind

Summary of Facts and Submissions

I. European patent no. 0 730 643 is based on European patent application no. 94 931 891.9, published as International patent application WO 95/11968. The patent was opposed by three opponents on the grounds as set forth in Articles 100(a),(b) and (c) EPC. The opposition division considered the Main Request and an Auxiliary Request to contravene Article 54 EPC and, accordingly, the patent was revoked.

II. The patentees lodged an appeal against this first decision of the opposition division. In the decision T 1847/06 of 16 December 2008, this board in a different composition considered a second Auxiliary Request to fulfil the requirements of Articles 123(2), (3), 84 and 54(3),(4) EPC (1973). The case was remitted to the opposition division for further prosecution on the basis of the second Auxiliary Request.

III. In an interlocutory decision dated 26 July 2011, the opposition division considered the second Auxiliary Request filed in appeal (which was made patentees' new Main Request) to be entitled to the claimed priority dates and to meet the requirements of Articles 83 and 56 EPC. Thus, the opposition division maintained the patent in amended form on the basis of this request and a description adapted thereto.

IV. An appeal was lodged by opponent 01 (appellant) against this interlocutory decision. The appellant filed new documentary evidence (documents D41-D45) and requested that the decision under appeal be set aside and that the patent be revoked. As auxiliary request, oral proceedings were requested.

V. In reply to the appellant's Grounds of Appeal, the patentees (respondents) requested, as a Main Request, that the appeal be dismissed. As auxiliary requests, the respondents requested that the decision under appeal be set aside and that the patent be maintained on the basis of one of the newly filed first, second or third Auxiliary Requests. As an auxiliary request, oral proceedings were also requested.

VI. Opponents 02 and 03, parties as of right to the present appeal proceedings, did not file any submissions in this appeal proceedings.

VII. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) annexed to Summons to oral proceedings, the parties were informed of the board's preliminary, non-binding opinion on the issues of the case. In particular, the board considered the Main Request not to fulfil the requirements of Article 56 EPC. The first, second and third Auxiliary Requests were preliminarily considered to be admissible. However, the board noted that no submissions addressing these requests were on file.

VIII. No substantive submissions were filed by the respondents in reply to the board's communication. The respondents informed the board that they would not be represented at the scheduled oral proceedings and they withdrew their request for oral proceedings.

IX. The appellant replied to the board's communication, filed a new document (D46) and, *inter alia*, addressed the admissibility of respondents' Auxiliary Requests.

X. The oral proceedings were cancelled by the board.

XI. Claim 1 of the **Main Request** (claims upheld by the opposition division) read 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,
wherein said agent is administered to said transgenic animal at a dosage of from 1 ng/kg to 10mg/kg, preferably from 10 µg/kg to 1 mg/kg."

Claims 2 to 5 were directed to preferred embodiments of claim 1.

XII. All Auxiliary Requests were identical to the Main Request, except for amendments introduced into claim 1 which read as follows:

a) "1. ... *[as claim 1 of the Main Request]* ...

expresses said APP polypeptide; and
produces detectable quantities of ATF-ßAPP,
wherein said agent is administered ...

[as claim 1 of the Main Request] ..."
(**first Auxiliary Request**)

b) "1. ... *[as claim 1 of the Main Request]* ...
expresses said APP polypeptide; and
produces quantities of ATF-ßAPP which are at least two-fold higher than the quantities of ATF-ßAPP, produced from wild type human ATF-ßAPP in an equivalent transgenic model,
wherein said agent is administered ...
[as claim 1 of the Main Request] ..."
(**second Auxiliary Request**)

c) "1. ... *[as claim 1 of the Main Request]* ...
expresses said APP polypeptide; and
produces detectable quantities of ATF-ßAPP,
wherein said agent is administered ...
[as claim 1 of the Main Request] ...
preferably from 10 µg/kg to 1 mg/kg, and
wherein the effect of the agent on ATF-ßAPP production is measured."
(**third Auxiliary Request**).

XIII. The following documents are cited in this decision:

D1: WO 91/19810 (publication date: 26 December 1991);

D2: M. Mullan et al., Nature Genetics, August 1992, Vol. 1, pages 345-347;

D4: M. Citron et al., Nature, 17 December 1992, Vol. 360, pages 672-674;

D9: WO 94/10569 (publication date: 11 May 1994);

D23: D. Wirak et al., Science, 13 March 1992, Vol. 255, pages 1443-1445;

D24: S. Kawabata et al., Nature, 5 March 1992, Vol.

356, page 23;

D25: J. Marx, Science, 6 March 1992, Vol. 255, pages 1200-1202;

D29: D. Quon et al., Nature, 18 July 1991, Vol. 352, pages 239-241.

XIV. Appellant's arguments, insofar as they are relevant to the present decision, may be summarized as follows:

Main Request
Inventive step (Article 100(a) EPC; Article 56 EPC)
The closest prior art

Document D1 disclosed transgenic mice (the "Cordell's" mice) expressing wild-type ß-amyloid precursor protein (ß-APP), in particular the full-length ß-APP^{751} isoform. In Examples 8-11 (Table 1), the expression vector (ß-APP^{751} with neuronal-specific enolase (NSE) promoter), disclosed in Examples 1 and 5, was used to generate transgenic mice. The brains of the NSE-A751 transgenic mice were histologically analyzed in Example 12 and deposits characteristic for Alzheimer's disease (AD) were identified in these mice but not in control wild-type mice. The generation of transgenic mice with the full-length ß-APP^{695} isoform was also mentioned in Examples 2, 5 and 8. Thus, the transgenic mice disclosed in document D1 produced ß-amyloid protein (ß-AP) and showed characteristic amyloid plaques known to be related to AD. As stated in document D1, these transgenic mice, in particular those harbouring the full-length ß-APP^{751} and ß-APP^{695}, were suitable AD models for use in screening of drugs for AD treatment and/or prevention.

Objective technical problem and proposed solution

Starting from document D1, the objective technical problem was the provision of a further animal AD model for use in drug screening. According to claim 1, this technical problem was solved by the provision of a non-human transgenic animal carrying a human APP with the Swedish mutation and its use for drug screening.

Obviousness

As stated in document D4, only a very limited number of mutant APP were known at the priority date of the patent. While any of these mutants could have been used to produce a transgenic animal AD model for use in drug screening, a mutant with the Swedish mutation disclosed in documents D2 and D4 was the most promising and preferred, since this mutation was the first mutation known to produce increased ß-AP levels (6-8 fold more ß-AP than cells expressing normal ß-APP), establishing a direct link between this mutation genotype and the clinicopathological phenotype. Document D4 disclosed the use of cells transfected by ß-APP with the Swedish mutation for drug screening. It was an entirely logical development to implement the *in vitro* experiments of documents D4 into an *in vivo* setting, i.e. the production of transgenic animals which were at the time usually used for drug screening. Thus, a skilled person would have combined the disclosures of documents D1 and D4 at least with a try-and-see attitude. It only required the replacement of a wild-type ß-APP by an ß-APP with the Swedish mutation in an attempt to improve the "Cordell's" mice AD model provided by document D1.

The broad dosage range in claim 1 was trivial. Such dosages were routinely used in drug screening (even in

neurodegenerative diseases like AD), as acknowledged in the patent and in prior art on file. According to the case law, the mere aggregation of obvious and trivial features did not make a claim inventive.

Reasonable expectation of success

Neither the "Wirak's" nor the "Kawabata's" mice referred to in documents D23 and D24, respectively, expressed the wild-type full-length ß-APP used to produce the "Cordell's" mice disclosed in documents D1 and D29. None of documents D23 and D24 discredited the "Cordell's" mice which, as stated in document D25, were still considered a useful AD model at the priority date of the patent.

The transgenic "Wirak's" mice expressed a short (4kD) ß-amyloid fragment (derived from full-length ß-APP) and formed amyloid-like fibrils that were similar in appearance to those found in brains of AD patients. Later, it was noticed that the mouse line ("C57BL/6 mice") used in these studies was inherently prone to formation of amyloid-like structures, raising questions on the extent to which the transgene contributed to the observed phenotype. However, it could not be deduced from document D23 that the transgenic approach failed as such.

Document D24 was a retraction of earlier studies concerning the transgenic "Kawabata's" mice. These mice expressed a C-terminal fragment of ß-APP (which included the 4KD ß-amyloid fragment used in the "Wirak's" mice). In these earlier studies, the overexpression of the C-terminal APP fragment produced extracellular amyloid plaques similar to those found in brains of AD patients. Though the transgenic status of

the mice was confirmed, the earlier reported histopathologically findings could not be reproduced in document D24.

In fact, document D25 summarized the development of the three available transgenic AD models in March 1992. The retractions of the "Wirak's" and "Kawabata's" mice models, both expressing short ß-APP fragments derived from the wild-type full-length ß-APP protein, were seen as disappointing. However, the suitability of the third transgenic animal AD model, namely the "Cordell's" mice disclosed in document D1, the only one expressing the full-length ß-APP (ß-APP^{751} and ß-APP^{695} isoforms), was not challenged and was described as the sole AD model "holding up" at that time.

Admissibility of the Auxiliary Requests

In preparation for the first oral proceedings before the opposition division, the patentees filed requests similar to the actual first and second Auxiliary Requests. These requests were however withdrawn and replaced at these oral proceedings. In its first decision, the opposition division revoked the patent, because it considered the then pending Main and Auxiliary Requests not to be novel. In the subsequent appeal proceedings, the board decided that Auxiliary Request II (now the Main Request), containing a dosage feature, was novel and remitted the case back to the opposition division for further prosecution (T 1847/06, *supra*).

Although the first opposition and appeal proceedings were focused on novelty, extensive submissions on the issue of inventive step were filed by all parties. The same took place before the second oral proceedings

before the opposition division. In fact, an objection for lack of inventive step based on a combination of documents D1 with D2 or D4 was already raised in the notice of opposition. By failing to file the present first and second Auxiliary Requests as a precautionary measure (respectively by withdrawing similar requests then on file), the patentees deprived the opposition division from taking a decision on these requests. Moreover, at the second oral proceedings before the opposition division, the patentees were aware that in the prosecution of a parallel patent application, the competent board had decided that subject-matter corresponding to the present Main Request was not inventive in the light of the same documents (D1, D2, D4) (cf. T 1127/06 of 13 August 2008). Thus, the patentees had a fair chance to file the first and second Auxiliary Requests at that point in time.

No explanations were provided by the patentees why these Auxiliary Requests were not filed or further pursued during proceedings before the opposition division. Admitting these Auxiliary Requests raised completely new issues, such as entitlement to priority, and was thus contrary to procedural economy.

XV. Respondents' arguments, insofar as they are relevant to the present decision, may be summarized as follows:

Main Request
Inventive step (Article 100(a) EPC; Article 56 EPC)
The closest prior art

Document D1 disclosed transgenic mice expressing the wild-type ß-APP, the "Cordell's" mice, and their use for drug testing. A comparison between the amount of ß-amyloid plaques (deposits) formed in brains of

transgenic mice and control animals determined the drug effectiveness. However, it was not clear from document D1 whether the alleged plaques occurred with sufficient size, frequency and reproducibility to form the end point of a drug screening assay. Transgenic "Cordell's" mice expressing wild-type ß-APP would not have been considered by a skilled person a working AD model. There were doubts based on the many different characteristics of the deposits in the "Cordell's" mice relative to the plaques in AD patients, the difficulties in scoring these deposits and the possibility that the deposits in the "Cordell's" mice could be full-length ß-APP as well as or instead of the cleavage ß-AP product. The inconclusive data and the lack of a convincing AD pathology displayed by the "Cordell's" mice did not render them a robust model animal of the AD pathology.

Objective technical problem and proposed solution

Starting from document D1, the technical problem to be solved was the provision of a robust animal AD model for screening of therapeutic agents. The patent provided such model by selecting transgenic animals expressing ß-APP with the Swedish mutation in the ß-APP transgene and producing detectable levels of the amino-terminal fragment of ß-APP (ATF-ßAPP), a cleavage product used as a marker to identify suitable animal AD models at an earlier stage in the life-cycle than would be required for animals to develop the AD pathology.

Obviousness

At the priority date, there was a concern that laboratory (transgenic) animals were inherently incapable of developing AD because they did not so in

nature. Furthermore, scepticism was in the field due to the retraction of two purported animal AD models (*infra*). Indeed, more straightforward options were available to a skilled person, such as to improve existing *in vitro* models or *ex vivo* screening methods using cells from AD patients.

Even if a transgenic approach was considered, multiple options were available to a skilled person. Document D1 disclosed several regulatory sequences (neural-specific promoters) and a number of possible ß-APP constructs (A42, A99, A695), but only one (ß-APP^{751}) was tested. A skilled person could have tried any of these, or other, ß-APP isotypes, isoforms or fragments to see if a robust AD pathology was achieved. Further, a number of other APP mutations were also known, of which any could have been selected. There was no objective reason why a skilled person would have specifically selected a ß-APP with the Swedish mutation in a transgenic approach. It was only with the benefit of hindsight of the patent that this combination was apparent.

The Swedish mutation had been identified in a human family (document D2) and reported to be associated with increased processing of ß-APP in human cell culture (document D4). Indeed, document D4 reported that human 293 cells transformed by a cDNA encoding human ß-APP with the Swedish mutation produced higher ß-AP levels than cells expressing wild-type ß-APP. However, this document did not provide an incentive to create a transgenic animal model expressing ß-APP with the Swedish mutation. On the contrary, the conclusion in document D4 actually pointed away from such a model, since it was stated that the transfected cells described therein, or endogenous cells taken from a AD patient with the Swedish mutation, could be useful for

screening and identifying therapeutic compounds. This was in line with document D2 which acknowledged that humans having a ß-APP with the Swedish mutation had a relatively late AD onset and thus, it was unlikely that transgenic animals with this mutation would develop a significant AD pathology. Document D2 taught the skilled person away from a transgenic animal comprising ß-APP with the Swedish mutation as a useful AD model.

Moreover, even if document D4 stated that human 293 cells expressing ß-APP with the Swedish mutation produced higher ß-AP levels than cells expressing the wild-type ß-APP, it was known in the art that, in experiments conducted with wild-type ß-APP, the effects demonstrated *in vitro* frequently were not replicated *in vivo*. The results disclosed in document D4 could not be used to predict the effect *in vivo*. The less so since it was not known whether ß-APP processing would occur in a non-human model and would result in detectable levels of ATF-ßAPP. There was a lack of understanding regarding the cleavage efficiency of human Swedish APP by non-human enzymes and the metabolic stability of ATF-ßAPP generated by such cleavage. Therefore, taking D1 as the closest prior art, document D4 did not provide an incentive for a skilled person to produce a transgenic animal (mouse) expressing ß-APP with the Swedish mutation for screening therapeutic agents.

Reasonable expectation of success

Several efforts to produce an effective animal AD model were made in the years immediately before the priority date. Wirak *et al.* reported transgenic mice expressing and accumulating human ß-AP in their brains and forming amyloid-like fibrils similar to those seen in brains of AD patients. Kawabata *et al.* reported transgenic mice

overexpressing a C-terminal fragment of human ß-APP and forming amyloid plaques and neurofibrillary tangles in their brains which was associated with neuronal degeneration similar to that seen in the brains of AD patients. However, in document D23, Wirek *et al.* reported that the published data did not support the conclusion that the expression of human ß-APP transgene caused the formation of amyloid deposits in the brain of the transgenic mice. In document D24, Kawaba *et al.* acknowledged that the AD pathology identified in the transgenic mice was not reproducible. As stated in document D25, only one transgenic animal AD model was left by these retractions, namely the "Cordell's" mice disclosed in documents D1 and D29, which, however, did not display a robust AD pathology. Indeed, document D25 simply stated that the animal AD model of document D1 was "holding up", without further emphasis or stronger sentiment, thereby showing a lack of confidence in the transgenic mouse approach.

In fact, the transgenic mice disclosed in documents D1 and D29 were not shown to have the characteristic amyloid plaques. Document D29 only stated that there were deposits resembling ß-amyloid structures typically seen in AD patients' brain. A mere resemblance did not establish a robust AD model. The less so since the antibody used to detect the deposits was cross-reactive binding to both the pathogenic ß-AP (generated by ß-secretase cleavage of ß-APP) and the full-length ß-APP. The generation of the pathogenic ß-AP was a prerequisite for an AD model, but it was not even clear whether the transgenic mice disclosed in documents D1 and D29 met this basic requirement. As concluded in document D29, further studies were needed on the quality and quantity of the detected deposits as well as on the display of other AD pathological features, it

was thereby shown that the authors of document D29 were not sure whether the disclosed transgenic mice could develop into a robust AD model.

In view of the confusion in the state of the art and the reported failures of transgenic animal models comprising the wild-type human ß-APP to produce significant AD pathology, a skilled person could not have had a reasonable expectation of success that a transgenic animal expressing a human ß-APP with the Swedish mutation instead of the wild-type ß-APP would have provided a robust AD model or that its use in screening assays to identify therapeutic agents for AD treatment and/or prevention would be meaningful.

According to the case law, a skilled person was cautious, with a conservative attitude, never entering unpredictable areas or technology and performing only routine work within the framework of normal practice of filling gaps in knowledge by applying already existing knowledge. In the present case, the skilled person faced a situation where all previous attempts had failed and there was no guidance as to which direction could generate a successful AD model. It was required to perform scientific research and the outcome was unknown. Thus, inventive step was given.

Admissibility of the Auxiliary Requests

No submissions with regard to this issue were made. In particular the respondents did not react to appellant's submissions objecting to the admissibility of the Auxiliary Requests.

XVI. The appellant requested that the decision under appeal be set aside and that the patent be revoked.

XVII. The respondents requested, as their Main Request, that the appeal be dismissed and the patent be maintained on the basis of the set of claims upheld by the opposition division. As auxiliary request, the respondents requested the maintenance of the patent based on any of their first, second and third Auxiliary Requests.

XVIII. No requests were on file from any of the parties as of right.

Reasons for the Decision

Main Request (identical to claims 1 to 5 of the second Auxiliary Request before the opposition division)

Scope of the appeal proceedings

1. In the statement setting out its Grounds of Appeal, the appellant did not contest the findings of the opposition division as regards the entitlement to the claimed priority (cf. page 2, point 3 of the decision under appeal). Thus, the scope of the present appeal proceedings, as far as it concerns the Main Request, is limited to sufficiency of disclosure and inventive step (Articles 100(a) EPC, in connection with Article 56 EPC, and 100(b) EPC).

Inventive step

2. In the first appeal proceedings, the then competent board considered the dosage feature ("w*herein said agent is administered to said transgenic animal at a dosage of from 1 ng/Kg to 10mg/Kg, preferably from 10 µg/Kg to 1 mg/Kg*") to distinguish the claimed subject-

matter from the disclosure of document D9. Accordingly, novelty was acknowledged (Article 54 (3),(4) EPC; cf. page 15, points 18-20 of the Reasons of T 1847/06, *supra*). Since priority rights of the patent have been acknowledged (cf. point 1 *supra*), document D9 is not relevant for the examination of inventive step (cf. page 6, point 4.3 of the decision under appeal).

The closest prior art

3. In the decision under appeal, document D1 was identified as the closest prior art (cf. page 4, point 4.1 and page 7, point 4.3.2 of the decision under appeal). The board agrees.

3.1 The document discloses the production of non-human transgenic mammals (mice) whose cells contain a transgene construct which results in the expression and production of heterologous (human) APP polypeptides (ß-amyloid precursor protein), such as the human ß-APP^{695} referred to in the document as "A695" (cf. page 8, lines 2-8).

3.2 Using different promoters, such as the promoters of mouse metallothionine-I (MTI) and rat neuronal-specific enolase (NSE) (NSE-A695 and MT-A695; cf. Table on page 26), document D1 exemplifies several fusion constructs expressing and producing ß-APP polypeptides (cf. page 24, point 5.5).

3.3 Examples 1 and 2 disclose fusion constructs with the human metallothionine II (hMTII) promoter (cf. page 42, lines 5-9) and their use for ß-APP expression in mammalian cells (Chinese hamster ovary, CHO-K1 cells; cf. page 42 to page 45). Example 3 refers to specific oligonucleotide probes to distinguish genetic variants

of β-amyloid related proteins (cf. page 15, line 32 to page 16, line 8, pages 45 and 46).

3.4 Examples 5 and 7 disclose the construction of NSE-A695 and MT-A695 transgenic expression plasmids which were proven to express the human ß-APP^{695} protein after transfection into mammalian cells (cf. page 48, lines 32-33 and pages 50-51). Example 8 discloses the production of transgenic mice using these plasmids and standard methods known in the art (cf. page 28, point 5.6 and pages 51-55). Table 1 on page 54 shows the results (% of embryos resulting in live pups, % of live pups who are transgenic, and % of embryos injected resulting in live transgenic animals) obtained with, *inter alia*, the constructs NSE-A695 and NSE-A751.

3.5 Examples 9 to 12 disclose different assays and methods (Southern blot hybridization using an oligonucleotide probe with and without PCR amplification, Western blot and immunocytochemistry using a polyclonal antiserum raised against full-length human A695, and histological analysis using the mAb 4.1 which has as an epitope the N-terminus 10 residues of the β-amyloid protein (ß-AP); cf. pages 59-63).

3.6 The non-human transgenic mammals are described as being useful for testing the effectiveness and efficacy of pharmaceutical drugs for Alzheimer disease (cf. page 9, last paragraph, page 11, lines 9-19, page 12, line 29 to page 13, line 3, page 13, lines 11-17, page 55, lines 1-13, page 64, point 7 and claims 41-44).

The objective technical problem and the proposed solution

4. In the light of the disclosure in document D1, the board considers the technical problem to be the

provision of an appropriate non-human transgenic animal for expression and production of an alternative APP, to be used as an animal model of Alzheimer's disease for screening of therapeutic agents.

5. It has not been contested during the proceedings before the opposition division that the claimed subject-matter indeed solves this problem formulated. In view of the evidence on file and the actual scope of the claims (cf. point 11.3 *infra*), the technical problem is solved over the whole breadth of the claims.

Obviousness

6. Document D1 refers to "*ß-amyloid precursor protein*" in general and, indeed, its teachings are exemplified by "*the 751 amino acid sequence* [which] *is the most notable example of a precursor protein*" (ß-APP^{751}) and the 695 amino acid variant (ß-APP^{695}) (cf. page 16, lines 9-16 and page 8, lines 2-8; point 3.1 *supra*). The board agrees with the opposition division that document D1 provides a motivation for a skilled person to produce non-human transgenic mammals expressing other human ß-APP variants (cf. page 7, point 4.3.2 of the decision under appeal).

7. As acknowledged in the patent itself, the ß-APP with the Swedish mutation was already identified in the prior art as an ß-APP causing familial, early onset Alzheimer's disease (cf. page 3, paragraph [0008] of the patent, referring to documents D2 and D4). The relevance of this ß-APP was well-known to a skilled person at the priority date and no inventive effort was required to replace any of the ß-APP forms used in document D1 by such a Swedish ß-APP form. In fact, document D2 concludes by emphasizing the relevance of

the Swedish ß-APP form and by stating that, although difficulties may be encountered, means are also available to solve them, namely "(g)*iven the relatively late age of onset of disease development in humans with either codon 717 or 670/671 variants, it seems unlikely that transgenic animals with any of these mutations would develop significant pathology. An important consequence of the codon 670/671 mutation may be its combination with pathogenic codon 717 variants to increase the likelihood of producing Alzheimer-like pathology in transgenic mice*" (cf. page 347, right-hand column, first paragraph of document D2; emphases added by the board).

8. The board agrees with the appellant that the broad dosage range in claim 1 is well-known and routinely used in the art of drug screening, as shown by the large number of references cited by the appellant in this respect (cf. page 15, point 6.2 of Grounds of Appeal). Indeed, this is also derivable from the patent itself which refers to such dosage in a very general manner (cf. page 9, paragraph [0059] of the patent). No unexpected and/or advantageous effects are shown to be associated with this dosage range which, in any case, is not exemplified in the patent. The respondents do not rely on this feature to support their arguments on inventive step. This feature, thus, provides no contribution to the prior art and is disregarded for the assessment of inventive step.

Reasonable expectation of success

9. In the decision under appeal, the opposition division considered documents D29, D23 and D24 to question the results of document D1 and to render the use of transgenic animals as models of Alzheimer's disease

uncertain and complicated. In particular, reference was made to the "*unclarified cross-reactivity of the different antibodies specific for the β-APP deposits*" shown in document D29 (authored by the present inventor) and to the retraction of documents D23 and D24 (cf. page 7, second and third paragraphs of point 4.3.2 of the decision under appeal).

10. The board, does not agree and considers that none of these documents casts serious doubts on the disclosure of document D1.

10.1 None of documents D23 and D24 concerns the production of transgenic animals comprising a transgene encoding a full-length β-APP. The animals disclosed in these studies comprise a transgene encoding the β-AP. Several β-APP isoforms (ß-APP^{695}, ß-APP^{751} and ß-APP^{770}) and β-AP (A99, A42) were known in the art and differences in their processing and (pathological) physiological effects were also known to exist (cf. page 7, line 35 to page 8, line 30 and page 15, line 15 to page 16, line 31 of document D1; these passages are also referred to in the "Background of the invention" of the patent itself). Accordingly, the board cannot see any reason why these studies would cause a skilled person to seriously doubt the results shown in documents D1 and D29.

10.2 Document D23 states that "(t)*he inclusions in C57BL/6 mice do not resemble the extracellular amyloid deposits that have been reported in transgenic mice that overexpress the entire APP-751 transgene*" (cf. page 1444, right-hand column, third paragraph of document D23). It is thereby explicitly acknowledged that the results obtained with a β-AP transgene are not comparable to these of a β-APP transgene in a

straightforward manner. Although document D24 is a retraction, the transgenic status of the mice and the overexpression of β-AP are both confirmed. The sole matter retracted concerns the histopathological findings which, according to document D25, could have been intentionally manipulated in order to display better results (cf. page 1200, left-hand column, second paragraph document D25). The actual histological findings concerning these transgenic animals are thus unknown and "*remain to be assessed by further study*" (cf. right-hand column, last paragraph document D24). It has to be noted here that document D25 explicitly acknowledges the transgenic model described in documents D1 and D29 to be "*holding up*" (cf. page 1201, right-hand column, last paragraph of document D25).

10.3 Document D29 is the scientific publication of the results disclosed in Example 12 of document D1. These results rely on the monoclonal antibody 4.1, which recognizes an epitope mapped to the N-terminal 10 residues of the β-AP (cf. page 240, left-hand column, third paragraph and Figure 2 of document D29; see also paragraph bridging pages 6 and 7 of document D1), and on antibodies raised against the full-length β-APP. The specificity and cross-reactivity of these antibodies is not fully described in these documents and thus, the actual composition of the identified extracellular β-amyloid immunoreactive deposits is not known with absolute certainty, i.e. whether they contain only β-APP or both β-APP and β-AP. The relevance of specific antibodies was also acknowledged in the art (cf. *inter alia*, page 674, right-hand column, first paragraph of document D4).

Document D29 concludes that the deposits "*seen in the transgenic mice resemble several β-amyloid structures typically seen in the brains of Alzheimer's disease victims*" and expresses the interest to further characterize the properties of these deposits and to assess whether the transgenic "*mice display other pathological features characteristic of Alzheimer's disease*" (cf. page 241, left-hand column, last paragraph of document D29). The presence of at least one characteristic feature of Alzheimer's disease (presence of β-amyloid structures) in the described transgenic mice is thereby acknowledged. This is fully in line with the disclosure of document D1 which proposes the use of these mice to "*test potential therapeutic compounds*" (cf. *inter alia*, page 62, first full paragraph of document D1; point 3.6 *supra*).

11. According to the jurisprudence of the Boards of Appeal set out in several decisions, absolute certainty is not required for a reasonable expectation of success (cf. T 192/06 of 6 March 2007, point 11 of the Reasons; T 278/03 of 18 January 2005, point 13 of the Reasons; T 918/01 of 6 October 2004, point 9.1 of the Reasons; "Case Law of the Boards of Appeal of the EPO", 7th edition 2013, I.D.7.1, page 184). In the present case, based on the evidence on file, such reasonable expectation of success was given. The more so in view of the following considerations:

11.1 Alzheimer's disease was known to have several causes resulting from heterogeneity in the evolution and properties of this disease, such as an early or late onset (cf. paragraphs [0002] and [0003] of the patent). The interest for having several transgenic models was thus evident for a skilled person, as also shown by documents D1 and D29 which refer to the alleged

different properties of the non-human transgenic mammals expressing the ß-APP^{751} or the ß-APP^{695} variant. Thus, the prior art provided a motivation to produce further transgenic mammals expressing other alternative ß-APP variants, such as the known ß-APP with the Swedish mutation (cf. points 6-7 *supra*). In this context, the reference to "*a mutated form of the gene that was recently linked to the disease*" in document D25 (cf. page 1201, right-hand column, last paragraph) is seen as a hint to a skilled person to try the claimed subject-matter for the solution of the technical problem.

11.2 According to a further approach elaborated by the Boards of Appeal, which is relevant for the present case, a skilled person "*would have had either some expectations of success or, at worst, no particular expectations of any sort, but a 'try and see' attitude, which ... does not equate with an absence of a reasonable expectation of success*" (cf. T 1127/06, *supra*, point 13 of the Reasons).

11.3 Moreover, as regards respondents' references to the cleavage and processing of ß-APP and to detectable amounts and stability of ATF-ßAPP, the board notes that according to claim 1 the non-human transgenic animal has to express the ß-APP^{695} variant with a Swedish mutation. No other requirement, such as processing of this ß-APP^{695} variant, any particular degree of efficiency of this processing, or the presence of other ß-amyloid products, is mentioned. The claim is not limited to any specific animal, to the presence of appropriate cleavage enzymes, etc.

According to the established case law, features which are not recited in and are not deducible from a claim

do not limit the scope of said claim and thus, do not have to be taken into account when assessing novelty and/or inventive step (cf. "Case Law", *supra*, II.A. 6.3.4, page 270). It has also been decided that the expectation of success depends on the complexity of the technical problem to be solved. While for very ambitious problems requiring the consideration of all the features relied on by the respondents but not contained in claim 1, important difficulties might *a priori* be expected, less ambitious problems might normally be associated with higher expectation of success (cf. *inter alia*, T 192/06, *supra*, point 11 of the Reasons and T 782/07 of 4 February 2009, point 35 of the Reasons).

12. In consequence, the board decides that the Main Request does not fulfil the requirements of Article 56 EPC.

Admissibility of first, second and third Auxiliary Requests

13. In a communication pursuant to Article 15(1) RPBA, the board expressed a preliminary and non-binding positive opinion on the admissibility of these requests into the appeal procedure. The board also noted that there were no submissions on file addressing these Auxiliary Requests (cf. point VII *supra*).

14. In reply to this communication, the appellant addressed the Auxiliary Requests and provided arguments against their admissibility into the appeal procedure (cf. point IX *supra*). The respondents did not reply to the board's communication or to the appellant's reply thereto. They informed the board that they would not be attending the scheduled oral proceedings and explicitly withdrew their request for oral proceedings (cf. point VIII *supra*).

15. In its reply to the board's communication, the appellant drew the board's attention to the earlier procedural history of the case.

15.1 In preparation of the first oral proceedings before the opposition division, the patentees/respondents, on 27 January 2006, filed a Main Request and a First Auxiliary Request. Claim 1 of these requests comprised technical features ("*produces detectable quantities of ATF-ßAPP*", Main Request; "*produces quantities of ATF-ßAPP which are at least two-fold higher than the quantities of ATF-ßAPP produced from wild type human ßAPP in an equivalent transgenic animal*", First and Second Auxiliary Requests) which are identically contained in claim 1 of respondents' first, second and third Auxiliary Requests, newly submitted in the present (second) appeal procedure (cf. point XII *supra*).

These requests, however, were withdrawn at the beginning of these first oral proceedings, held on 29 March 2006 before the opposition division. They were replaced by a new Main Request and First Auxiliary Request that did not contain any of the above mentioned technical features (cf. *Minutes of the oral proceedings before the opposition division*, issued on 8 May 2006, page 1, point 2 and Annexes 1 and 2). The newly filed requests were considered by the opposition division not to fulfil the requirements of Article 54 EPC (cf. *Minutes*, *supra*, page 3, points 17 to 23).

According to page 4, point 24 of the *Minutes* (*supra*), the patentees/respondents "*announced that no further requests would be submitted*".

15.2 The decision of the patentees/respondents to withdraw certain requests at the beginning of the oral proceedings deprived the opposition division from the opportunity to examine the subject-matter of these requests and to assess whether the technical features, mentioned in point 15.1 above, provided a technical contribution over the prior art, i.e. whether the withdrawn requests fulfilled the requirements of Article 54 EPC and Article 56 EPC.

15.3 The patentees/respondents lodged an appeal against the first decision of the opposition division, whereby the patent was revoked (cf. point II *supra*). During this appeal proceedings, they filed several new Auxiliary Requests, first, with their statement of Grounds of Appeal on 23 January 2007 (Main Request and Auxiliary Requests 1-4) and then, on 17 November 2008 in reply to the board's Summons to oral proceedings (Main Request and Auxiliary Requests 1-4). None of these Requests contained the technical features mentioned in point 15.1 above.

In their third Auxiliary Request, which was made patentees/respondents' second Auxiliary Request during the oral proceedings, and which was remitted to the first instance for further prosecution, the patentees/ respondents introduced a new feature. This new feature was completely unrelated to the features referred to above and related to a dosage of the agent to be tested to the transgenic animal (cf. point XI *supra*).

Thus, the patentees/respondents, at this stage of the proceedings, had a further opportunity to re-file a request containing the features referred to above which would have allowed the Board of Appeal to decide on it.

15.4 In the Summons to the second oral proceedings before the opposition division, issued on 25 November 2010, the facts and submissions were summarized and a preliminary, non-binding opinion was given to the Main Request (former second Auxiliary Request) on entitlement to the claimed priority and on inventive step. At the end of these Summons, the opposition division stated that "(i)*t is foreseen that full consideration of inventive step, focusing principally on the documents mentioned above and employing, if possible, a correctly applied problem-solution approach, will take place at the upcoming oral proceedings. At that time, sufficiency and all other outstanding matters are also to be discussed*".

Thus, the opposition division left it open whether the Main Request fulfilled the requirements of Articles 56 and 83 EPC. Also at that point in time the patentees/ respondents did not consider it necessary to file an Auxiliary Request containing the technical features referred to in point 15.1 above, which, for the second time deprived the opposition division of the opportunity to decide on such a request.

15.5 Only with their letter dated 16 April 2012, which was sent in reply to appellant's statement of Grounds of Appeal, the respondents filed Auxiliary Requests containing the features mentioned in point 15.1 above (cf. point V *supra*). In the light of the history of the case, these Auxiliary Requests have been filed at a very late stage of the procedure. No reasons have been given to explain the filing of these requests only at this late point in time.

New substantive issues, such as the entitlement to priority rights, which have not been examined yet,

neither by the opposition division nor by the board, may well arise due to the re-introduction of the features mentioned in point 15.1 above, which counteracts procedural economy. According to the established case law of the Boards of Appeal, the purpose of an appeal procedure is not to give the patent proprietor the opportunity to recast its claims as it sees fit and to have all its requests admitted into the appeal proceedings (cf. *inter alia*, T 361/08 of 3 December 2009, T 1231/09 of 12 December 2012, point 1.3 of the Reasons, T 2046/11 of 13 April 2015, point 2.1 of the Reasons).

16. The board, in exercising its discretion (Article 114(2) EPC), governed by the principles laid down in Article 12(4) RPBA, decides not to admit the respondents' first, second and third Auxiliary Requests into the appeal procedure.

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