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**Datasheet for the decision  
of 28 February 2013**

**Case Number:** T 0767/09 - 3.3.08  
**Application Number:** 95939892.6  
**Publication Number:** 792458  
**IPC:** G01N 33/53, G01N 33/537,  
G01N 33/542, G01N 33/543  
**Language of the proceedings:** EN

**Title of invention:**

Methods for aiding in the diagnosis of Alzheimer's disease by measuring amyloid-beta peptide (X- $\geq$ 41) and tau

**Patent Proprietor:**

Elan Pharmaceuticals, Inc.

**Opponent:**

Merck & Co., Inc.

**Headword:**

Diagnosis of Alzheimer's disease/ELAN

**Relevant legal provisions:**

EPC Art. 56

**Keyword:**

"Inventive step (yes)"

**Decisions cited:**

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**Catchword:**

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Case Number: T 0767/09 - 3.3.08

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.08  
of 28 February 2013

**Appellant:**  
(Opponent)

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(Patent Proprietor)

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**Decision under appeal:**

**Decision of the Opposition Division of the  
European Patent Office posted 4 November 2008  
rejecting the opposition filed against European  
patent No. 792458 pursuant to Article 101(2)  
EPC.**

**Composition of the Board:**

**Chairman:** M. Wieser  
**Members:** T. J. H. Mennessier  
C. Heath

## Summary of Facts and Submissions

- I. The opponent (appellant) lodged an appeal against the decision of the opposition division dated 4 November 2008, whereby the opposition filed against European patent No. 0 792 458, which had been granted on European application No. 95939892.6 (published as international application WO 96/15452), was rejected.
- II. The statement of the grounds of appeal was filed on 13 March 2009. With its reply dated 20 August 2008, the patent proprietor (respondent) filed seven auxiliary requests.
- III. On 25 October 2012, the Board issued a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) expressing its preliminary and non-binding view.
- IV. Both parties replied to the Board's communication. The respondent's reply, dated 24 January 2013, was accompanied by an eighth auxiliary request.
- V. At the oral proceedings, which took place as scheduled on 28 February 2013, the respondent withdrew the main request and the first and second auxiliary requests, and made its third auxiliary request its main request.
- VI. The main request consisted of 14 claims, of which claims 1, 7 and 12 read:
- "1. A method useful as a part of a diagnostic procedure for Alzheimer's disease in a patient, said method comprising:

measuring the amount of one or more soluble  $A\beta(x \geq 41)$  in a patient body fluid sample which is cerebrospinal fluid;

comparing the measured amount with a predetermined indicator value of said one or more soluble  $A\beta(x \geq 41)$ , optionally wherein the predetermined indicator value is measured from the same patient at an earlier time and the method provides for monitoring;

assessing patient status based on a difference between the measured amount and the predetermined value; and, wherein a measured amount above the indicator value provides a negative indication in the diagnosis of Alzheimer's disease and a measured amount at or below the indicator value provides a positive indication in the diagnosis of Alzheimer's disease."

"7. A method useful as a part of a diagnostic procedure for Alzheimer's disease in a patient, said method comprising:

measuring the amount of one or more soluble  $A\beta(x \geq 41)$  in a patient body fluid sample which is cerebrospinal fluid;

comparing the measured amount of the soluble  $A\beta(x \geq 41)$  with a predetermined indicator amount of the soluble  $A\beta(x \geq 41)$ ;

measuring the amount of tau in the patient sample;

comparing the measured amount of tau with a predetermined indicator value of tau;

and

assessing patient status based on a difference between the measured amounts and predetermined indicator values of  $A\beta(x \geq 41)$  and tau, wherein a measured amount at or below the  $A\beta(x \geq 41)$  indicator value and at or above the tau value provides a positive indication in the

diagnosis of Alzheimer's disease, and wherein a measured amount above the  $A\beta(x \geq 41)$  indicator value and below the tau indicator value provides a negative indication in the diagnosis of Alzheimer's disease."

"12. A kit comprising an antibody or fragment thereof that binds  $A\beta(x \geq 41)$  but does not bind to  $A\beta(\leq 40)$  and an antibody or fragment thereof that binds to tau, optionally further comprising an antibody or fragment thereof that binds  $A\beta$  or a fragment of  $A\beta$  but that does not bind other fragments of APP."

Claims 2 to 6, 8 to 11 and 13 to 14 were dependent on respectively claims 1, 7 and 12.

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

(D1) J. H. Growdon et al., Soc. Neurosci. Abstracts, Vol. 20, No. 1-2, 1994, Page 1056, Abstract No. 435.9.

(D2) T. Iwatsubo et al., Neuron, Vol. 13, July 1994, Pages 45 to 53.

(D4) J. T. Jarrett et al., Biochemistry, Vol. 32, No. 18, 11 May 1993, Pages 4693 to 4697.

(D7) D. J. Selkoe, Trends in Neurosciences, Vol. 16, No. 10, October 1993, Pages 403 to 409.

(D11) M. Tabaton et al., Biochemical and Biophysical Research Communications, Vol. 200, No. 3, 16 May 1994, Pages 1598 to 1603.

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

No objections were raised with regard to Articles 123(3), 123(2), 83, 84 and 54 EPC.

*Article 56 EPC*

Document D7 reported that the progressive deposition of A $\beta$  in the brain was an invariant feature of AD and that A $\beta$  had been detected in CSF of patients with AD and normal CSF. In view of the disclosure in document D7 the technical problem to be solved was the implementation of a precise measurement of A $\beta$  in a patient's cerebrospinal fluid (CSF) to obtain a reliable diagnostic test of Alzheimer's disease (AD).

Document D1 went even further than document D7 as it disclosed that A $\beta$  levels in CSF were significantly correlated both to cognitive and functional measures of dementia severity and that there was a correlation between decreased A $\beta$  and AD.

The statistical analysis at paragraphs [0102 to [0104] on page 17 of the patent specification showed that the problem as defined starting from document D7 was not solved by the method of claim 1. According to Table III (see paragraph [103]) A $\beta$  was found in CSF at a level of  $383 + 76 = 459$  pg/ml in the AD group of patients (see column AD) and of  $632 - 156 = 476$  pg/ml in the normal control group (see column NC). The difference between these two values was not significant and thus CSF A $\beta$

was not an accurate biomarker of AD. This was confirmed by the overlap shown in Table III between the A $\beta$  levels found in CSF of AD patients (383 +/- 76) and in CSF of the patients with other neurological disorders (543 +/- 177; see column ND).

The disclosure of document D7 taught the skilled person to link soluble amyloid- $\beta$  peptide (A $\beta$ ) levels in CSF with AD and it even contained a hint that the levels of soluble A $\beta$  in CSF might decline during the course of the disease.

From the disclosure in document D2 it was obvious for the skilled person to analyse A $\beta$ 42(43) in CSF of AD patients since this was the pathogenic biomarker of interest. Also document D4 taught the skilled person to analyse A $\beta$ (1-42) rather than A $\beta$ (1-40) since this variant was critical to the formation of amyloid plaques. The relevance of documents D2 and D4 was highlighted by a statement on page 1602 of document D11 reading "*The finding that a significant amount of the soluble A $\beta$  present in AD brains extends to amino acid residue 42 is of special interest*". Therefore, the method of claim 1 was obvious over document D7 in combination with either of documents D2 and D4. The main request did not meet the requirements of Article 56 EPC.

IX. The submissions made by the respondent, insofar as they are relevant to the present decision, may be summarised as follows:

The requirements of Articles 123(2), 123(3), 83, 84 and 54 EPC were met.

*Article 56 EPC*

The closest prior art was represented by the disclosure in document D11 which was published in 1994, only a few months before the earliest priority date claimed for the patent at issue, and which was concerned with the identification of a marker of Alzheimer amyloid. It disclosed that soluble A $\beta$  in brain but not in CSF was a marker of Alzheimer amyloid (see the title). The technical problem to be solved starting from document D11 was the provision of a non-invasive method useful in the diagnosis of AD. The solution to this problem was the method of claim 1 relying on the measurement of soluble A $\beta$ (x $\geq$ 41), i.e. A $\beta$  variants and fragments thereof whose carboxyterminus extended beyond amino acid 40, instead of total A $\beta$ , and the detection of a reduction in the measured levels over time. The experimental part of the description demonstrated that the technical problem had been solved by the method of claim 1, as derivable from the statistical analysis in paragraphs [0103] to [0105] of the patent specification.

Since document D11 disclosed (see the paragraph on page 1599 above the 'Materials and methods' Section) that A $\beta$  had not been considered to be a useful marker in a non-invasive assay performed on CSF, it would have dissuaded the skilled person from trying to develop such assays based on the detection of A $\beta$ . Even if the skilled person had nevertheless decided to measure total soluble A $\beta$  in CSF, it would not have been obvious to him/her to measure A $\beta$ (x $\geq$ 41). Neither document D2 nor document D4, which both related to the detection of A $\beta$ 42 in plaques, provided a pointer to such measurement.



Besides claim 1, also claim 7, disclosing a method additionally measuring the level of tau protein, and claim 12, referring to a kit useful for such method, involved an inventive step. The main request complied with the requirements of Article 56 EPC.

- X. The appellant (opponent) requested that the decision under appeal be set aside and the patent be revoked.
  
- XI. The respondent (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 14 of the main request as filed at the oral proceedings of 28 February 2013.

### **Reasons for the decision**

#### Article 123(2) and (3) EPC

- 1. The main request differs from the claims as granted in that (i) in claim 1 the patient body fluid has been limited to the cerebrospinal fluid, (ii) claim 2 has been amended accordingly by deleting the superfluous clause reading "*the patient sample is cerebrospinal fluid*", and (iii) previous claims 3, 8, 11, 15 and 16 have been deleted while the rest of claims has been renumbered accordingly. These amendments do not extend beyond the content of the application as filed and do not extend the protection conferred by the patent. Therefore, the main request complies with the requirements of Article 123(2) and (3) EPC.

Articles 84, 83 EPC and 54 EPC

2. No objections under Article 84 EPC (clarity), Article 83 EPC (sufficiency) and Article 54 EPC (novelty) have been raised by the appellant. The Board is satisfied that the claims are clear and supported by the description, that the claimed subject-matter is sufficiently disclosed and that none of the cited prior art documents discloses either a method according to claim 1 or 7, or a kit according to claim 12. Thus, the requirements of Articles 84, 83 and 54 EPC are met.

Article 56 EPC

3. The assessment of inventive step will be based on the problem-solution approach as developed in the case law of the Boards of Appeal. As a first step, the document considered to represent the closest state of the art with respect to claim 1 will be selected and the technical problem faced by the skilled person starting from that document will be defined.
4. At the oral proceedings the appellant relied on document D7 as closest state of the art. With regard to document D1, whose availability at the first priority date is a matter in dispute between the parties (see decision under appeal, point (3) of the reasons on pages 4 to 6), it took the view that it would be an even better candidate for this role. The respondent relied on document D11 as closest state of the art.
5. A review of the content of these three documents leads to the following remarks:

5.1. Document D7 discloses that the progressive deposition of A $\beta$ , a proteolytic fragment of the  $\beta$  amyloid precursor protein ( $\beta$ APP), in the brain is an invariant feature of AD. A $\beta$  had been detected in CSF of patients with AD and in CSF of normal, healthy individuals (see page 404, right-hand column, second last sentence of the first full paragraph). The document is a review article published one year before the earliest priority date and discusses the physiological production of A $\beta$  and the mechanism of AD with particular attention to the implications linked to the detection of A $\beta$  in biological fluids. On page 405 (see point (2) in the right-hand column) it is stated that "*(T)he ability to detect and quantitate the principal protein constituent of an invariant histopathological lesion of AD in CSF and perhaps plasma opens up new avenues towards identifying a laboratory marker to support a clinical diagnosis and perhaps monitor progression of the pathology.*" The penultimate sentence of the same paragraph reads: "*The possibility that the levels of soluble A $\beta$  in CSF might actually decline during the course of progressive  $\beta$  amyloid deposition must also be borne in mind.*"

5.2 Document D1 is an abstract for a meeting which began the day before the earliest priority date claimed for the patent at issue. It presents the results of a study conducted in 19 patients with Alzheimer's disease (AD) to investigate the relationship of *apoE* genotype with brain metabolism of the amyloid  $\beta$ -protein precursor (APP). CSF levels of amyloid  $\beta$ -protein (A $\beta$ ) and of secretory N-terminal APP derivatives were measured. It was found that CSF levels of A $\beta$  were inversely correlated with severity of dementia in AD. This led

the authors to conclude that measurements of CSF A $\beta$  provided a useful biochemical marker which paralleled dementia severity in AD but was independent of *apoE* genotype.

- 5.3 Document D11 discloses the results of an investigation involving nine AD subjects, three neurologically normal subjects and two subjects with non-AD dementia. Three soluble A $\beta$  peptides (all extending beyond residue 40, namely 4 kD, 3 kD and 3,7 kD) were identified in AD but not in control brains. Analysis of CSF from the same subjects confirmed the presence of only 4 kD A $\beta$  in comparable amounts in AD and controls. The authors came to the following conclusion: *"Finally, the lack of correlation between presence and forms of A $\beta$  in CSF and brain parenchyma suggests that the A $\beta$  present in CSF derives from sources other than brain tissue, such as the meninges and choroid plexi. This finding raises questions concerning the usefulness of the CSF for monitoring the events leading to amyloid formation in Alzheimer's brains."* (see page 1602, last paragraph).
6. Thus, while document D7 offers some guidance for AD diagnosis such information cannot be found in document D11. Document D1, a very short abstract of 15 lines only, does not contain technically relevant information that cannot be derived from document D7, which discloses that CSF levels of A $\beta$  are a useful biomarker of AD and contains a direct link that declining levels of soluble A $\beta$  in CSF might be an indication of progression of AD (see point 5.1 *supra*). The Board, therefore, does not see any reason to be engaged in the complex issue of the availability of document D1, but

considers document D7 to represent the closest state of the art.

7. In the light of the disclosure of document D7, the technical problem underlying the present application is seen in the actual provision of a non-invasive diagnostic method for AD using A $\beta$  as a marker. The solution to this problem proposed by the patent is the method according to claim 1, relying on the measurement in a patient CSF sample of one or more of the soluble peptides or fragments thereof globally referred to in the patent as A $\beta$ (x- $\geq$ 41) (see paragraph [0039] on page 8 of the patent specification).
8. In view of the results presented in Table III in the experimental part of the description of the patent specification (see paragraph [0103]), the appellant contends that the technical problem has not been solved at all. The Board disagrees. The appellant, although having doubted the statistical relevance of the data provided, has not put forward any expert's report in support of its contention. In the absence of such evidence, there is no reason for the Board not to trust the comments made in paragraph [0104]. Therefore, the Board considers that the results provided in Table III show that the CSF A $\beta$ (x- $\geq$ 41) levels were found to be significantly lower in AD patients relative to controls, whereas total A $\beta$  levels were not (see in Table III the 5th line and the 7th line, in which A $\beta$ 42 stands for A $\beta$ (x- $\geq$ 41)). The Board concludes that the technical problem is solved by the method of claim 1.
9. It remains to be answered whether, starting from the disclosure of document D7 and in view of the prior art

- documents on file, a skilled person would have arrived at the claimed solution in an obvious way.
10. The opponent has argued that each of documents D2 and D4, when read in combination with document D7, would have suggested the skilled person to concentrate its investigations on A $\beta$ 42 (A $\beta$ (x- $\geq$ 41)) in CSF and to look for a decline of these values, being indicative of a progression of AD in a patient.
  11. Document D2 reports on an investigation conducted to learn about the carboxyterminal extent of A $\beta$  composition of senile plaques in the brain affected with AD. Two monoclonal antibodies, one specific for the carboxyterminus of A $\beta$ 40 and the other specific for the carboxyterminus of A $\beta$ 42(43) were developed. Whereas a strong correlation between A $\beta$ 40 positivity and mature plaques was found, it was shown that diffuse plaques, representing the earliest stage of A $\beta$  deposition, were exclusively positive for A $\beta$ 42(43), but completely negative for A $\beta$ 40.
  12. Document D4 is concerned with in vitro kinetic studies of aggregation by three naturally occurring A $\beta$  variants (A $\beta$ 1-39, A $\beta$ 1-40 and A $\beta$ 1-42) and four model A $\beta$  peptides (A $\beta$ 26-39, A $\beta$ 26-40, A $\beta$ 26-42 and A $\beta$ 26-43) in an attempt to understand the accelerated in vivo amyloidogenesis which is associated with AD.
  13. Neither of documents D2 and D4 addresses the issue of AD diagnosis. Both are exclusively concerned with the understanding of amyloidogenesis which gives rise to the formation of senile plaques in AD patients. They do not give any hint as to the measurement of any of the

A $\beta$  peptides and fragments thereof, referred to in the patent as A $\beta$ (x- $\geq$ 41), in CSF, let alone any incentive to assess how CSF A $\beta$ (x- $\geq$ 41) values vary with the progression of AD. The remark made on page 1602 of document D11, saying that a significant amount of soluble A $\beta$  present in AD brains extends to amino acid residue 42, does not have any influence on the relevance of the disclosure in documents D2 and D4 for the present patent. Indeed, document D2 itself, published four months before the first priority date of the patent in suit, states on page 50 (see second sentence in the right-hand column) that A $\beta$ (1-40) was considered to be the major A $\beta$  species in CSF.

14. The Board concludes that the skilled person trying to solve the technical problem underlying the patent, would not have found any suggestion in document D2 or D4 to measure peptides and fragments encompassed by the term A $\beta$ (X- $\geq$ 41) in CSF and to compare the measured amount with a predetermined indicator value for the diagnosis of progression of AD. Therefore, he/she would not have arrived at the method of claim 1 in an obvious way.
  
15. Thus, the method of claim 1 involves an inventive step. The same applies to the method of claim 7 which in addition to the measurement of CSF A $\beta$ (X- $\geq$ 41) requires the measurement of CSF tau protein and to claim 12 referring to a kit comprising antibodies or fragments thereof especially developed to carry out the methods of claims 1 and 7, as well as to the subject-matter of the dependent claims 2 to 6, 8 to 11, 13 and 14. Therefore, the main request complies with the requirements of Article 56 EPC.

**Order**

**For these reasons it is decided that:**

1. The decision under appeal is set aside.
  
2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of claims 1 to 14 of the main request filed at the oral proceedings on 28 February 2013, and a description to be adapted thereto.

The Registrar

The Chairman

A. Wolinski

M. Wieser