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Datasheet for the decision of 12 January 2016

Case Number: T 1210/11 - 3.3.04

Application Number: 01202212.5

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Language of the proceedings: EN

Title of invention:
Compounds and methods for inhibiting amyloid beta-protein filament formation and neurotoxicity

Patent Proprietor:
Potter, Huntington

Opponents:
F. Hoffmann-La Roche
Wyeth and Elan Pharmaceuticals Inc.

Headword:
Amyloid beta-protein/POTTER

Relevant legal provisions:
EPC Art. 56

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Inventive step - all requests (no)

Decisions cited:

Catchword:

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Case Number: T 1210/11 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 12 January 2016

Appellant: (Patent Proprietor)	Potter, Huntington 1006 South Moody Avenue Tampa, FL 33629 (US)
Representative:	Sweetinburgh, Mark Roger Sweetinburgh & Windsor Unit 76, Basepoint Metcalf Way Crawley Sussex RH11 7XX (GB)
Appellant: (Opponent 1)	F. Hoffmann-La Roche Grenzacherstrasse 124 CH-4070 Basel (CH)
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Party as of right: (Opponent 2)	Wyeth et al. Five Giralda Farms Madison NJ 07940 (US)
Representative:	Dörries, Hans Ulrich df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstrasse 16 80333 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 17 March 2011 concerning maintenance of the European Patent No. 1172377 in amended form.**

Composition of the Board:

Chairwoman	G. Alt
Members:	A. Chakravarty
	M. Blasi

Summary of Facts and Submissions

I. Appeals by the patentee (appellant I) and opponent 1 (appellant II) were filed against the interlocutory decision of the opposition division maintaining European patent No. 1 172 377, as amended, based on claim 1 (the sole claim) of auxiliary request 11, provided that the conditions laid down in the Implementing Regulations are fulfilled. The patent is entitled "*Compounds and methods for inhibiting amyloid Beta-protein filament formation and neurotoxicity*".

II. Opponent 2 did not file an appeal and is respondent to the appeal of appellant I.

III. Appellant I filed a statement of grounds of appeal together with new auxiliary claim requests 1 to 3. The main request consisted of the claims as granted and auxiliary claim request 4 was the (sole) claim of auxiliary request 11 pending before the opposition division.

IV. Claim 1 of the main request and of auxiliary requests 1 to 4 reads as follows:

"1. An oligopeptide which binds α1-antichymotrypsin, wherein the oligopeptide is $A\beta_{2-9}$"

In the above claim Aβ stands for amyloid-β protein.

V. Both appellant II and the respondent replied to appellant I's statement of grounds and objected *inter alia* to the subject-matter of claim 1 of the main and auxiliary requests 1 to 4 as not meeting the requirements of Article 56 EPC.

VI. Appellant II filed a statement of grounds of appeal to which appellant I replied.

VII. The board summoned the parties to oral proceedings. All parties informed the board that they would not attend the oral proceedings, which took place on 12 January 2016, in their absence pursuant to Rule 115(2) RPC and Article 15(3) RPBA. At the end of the oral proceedings, the Chairwoman announced the decision of the board.

VIII. The following documents are mentioned in the present decision:

D8: WO 92/03474 (published 5 March 1992)

Exhibit A - submitted by appellant I on 8 December 2010 in the course of proceedings before the opposition division.

IX. Appellant I's submissions on inventive step can be summarised as follows:

It was not obvious for the skilled person, starting from the $A\beta_{1-12}$ peptide disclosed in document D8, that the claimed $A\beta_{2-9}$ peptide would be able to inhibit binding of α1-antichymotrypsin (ACT) to Aβ. This was because the claimed peptide lacked amino acid residues 1 and 10 to 12 of the $A\beta_{1-12}$ peptide. The skilled person would have expected that the missing charged amino acids had an important role in the binding ability of the peptide and would not have been able to predict with any certainty that this ability would be retained.
The claimed peptide had an improved ability to cross the blood/brain barrier which was clearly foreshadowed in the patent and the application as filed, both of which

disclosed methods of suppressing the formation of neurotoxic Aβ filaments, present in the brain cells of individuals with Alzheimer's disease. No such method could be effective if the peptide were not able to cross the blood/brain barrier. Moreover, the patent and the application as filed disclosed methods for increasing the ability of the peptide to cross the blood/brain barrier and reach the target site. The skilled person would therefore have understood that the claimed peptides already had such an ability (which was to be increased). Thus evidence filed as Exhibit A during the opposition proceedings should be taken into account in the assessment of inventive step. It was true that Exhibit A showed that the peptide $A\beta_{2-9}$ had a lower permeability through the blood/brain barrier than the low permeability control, but a significantly improved level of permeability compared to $A\beta_{1-12}$ was nevertheless demonstrated.

X. The submissions of appellant II and the respondent on inventive step are summarised as follows:

The $A\beta_{1-12}$ peptide disclosed in document D8 represented the closest prior art document for the subject-matter of claim 1 of all pending requests. The difference between the claimed peptide and that disclosed in document D8 was that the former lacked amino acids 1 and 10 to 12 of the latter. The claimed $A\beta_{2-9}$ peptide had the same technical effect (i.e. binding to ACT and inhibiting AP filament formation) as, and no technical benefit over, the $A\beta_{1-12}$ peptide. In view of this difference and the technical effect (or indeed lack thereof) due to it, the objective technical problem was the provision of an alternative Aβ peptide.

Document D8, page 5, lines 16 to 21, disclosed short peptides homologous to the N-terminus of the Aβ-protein, exemplified by the $A\beta_{1-12}$ peptide, as capable of binding to ACT and inhibiting Aβ filament formation. It was therefore evident to the skilled person that short oligopeptides derived from Aβ, other than the $A\beta_{1-12}$ peptide, could also be used for this purpose. The only requirement set out in document D8 for such short synthetic peptides was that they should be sufficiently homologous with the sequence of the binding site of a serine protease or with the N-terminus of amyloid β protein shown in Figure 1. Figure 1 showed that the sequence of the N-terminus of amyloid β protein homologous to the binding site of a serine protease was precisely the sequence "AEFRHDSG", i.e. the claimed peptide $A\beta_{2-9}$. Thus, document D8 prompted the skilled reader to use shorter fragments of the Aβ peptide which matched the binding site of a serine protease, leading the person skilled in the art directly to the claimed $A\beta_{2-9}$ peptide.

The teaching of document D8 did not lead the person skilled in the art to believe that the deletion of the charged amino acids aspartic and glutamic acid might result in a loss of ACT binding activity of the $A\beta_{1-12}$ peptide.

There was also no evidence on file that the claimed peptide exhibited any surprising or advantageous effects compared to the $A\beta_{1-12}$ peptide. With respect to the ability of the $A\beta_{2-9}$ peptide to cross the blood/brain barrier, there was no indication in the application as filed of a direct interference the claimed peptide with Aβ filament formation in the brains of Alzheimer's patients. Thus there was no evidence in the application as filed that the peptide $A\beta_{2-9}$ was an effective

treatment for Alzheimer's disease, for which the ability of the therapeutic agent to cross the blood/brain barrier was a prerequisite. The data from the *in vitro* experiments described in Example 12 could not be extrapolated to conclude this as it did not address the question of whether the peptide $A\beta_{2-9}$ could cross the blood/brain barrier. In fact Example 12 showed that the claimed peptide had only a modest effect (2 to 2.4 fold) in inhibiting ACT induced Aβ filament formation.

The experimental data contained in "Exhibit A" were post-published and related to a type of *in vivo* testing not described in the patent. This evidence therefore could not overcome the fundamental lack of data/evidence in the application as filed regarding delivery to pathogenic tissue in the brain. Moreover, the data in fact showed that the $A\beta_{2-9}$ peptide had an apparent permeability of 0.00086, i.e. about 18 times lower than the "low permeability control", whereas the permeability of $A\beta_{1-12}$ peptide was below the detection limit. Thus, the data demonstrated that neither the $A\beta_{2-9}$ peptide nor the $A\beta_{1-12}$ peptide could cross the blood/brain barrier or exert a therapeutic effect on pathologic tissue in the brain.

XI. Appellant I requested that the decision under appeal be set aside and that the patent be maintained as granted (main request), or alternatively, that the patent be maintained in amended form on the basis of one of the sets of claims filed as auxiliary requests 1 to 3 together with the statement of grounds of appeal, or further alternatively that the appeal of appellant II be dismissed, i.e. that the patent be maintained on the basis of the claim as considered allowable by the opposition division (auxiliary request 4 in the appeal proceedings).

XII. Appellant II and the respondent requested that the appeal of appellant I be dismissed, the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Main request and auxiliary requests 1 to 4

Inventive step - Article 56 EPC

1. Claim 1 of all pending claim requests is identical. Its subject-matter is a peptide consisting of the eight amino acids from positions 2 to 9 of amyloid β peptide (Aβ). Aβ is a 39 to 42 amino acid long peptide derived from an about 700 amino acid amyloid precursor protein (see patent, paragraph [0002]). Although the patent does not disclose the sequence of Aβ, it makes reference to prior art for this, e.g. document D8, Fig. 1. Thus, the sequence of the claimed peptide is AEFRHDSG.

Closest prior art

2. From the specification of the patent (see paragraph [0013]) it can be derived that the purpose of the claimed $A\beta_{2-9}$ peptide is "*for use in the treatment of an individual with Alzheimer's disease. [...] to the use of the oligopeptide $A\beta_{2-9}$ [...] in methods of suppressing the formation of neurotoxic Aβ filaments which are present in brain cells of individuals with Alzheimer's Disease and suppressing the progression of the disease. It further relates to the use of oligopeptide $A\beta_{2-9}$ for suppressing the formation of neurotoxic Aβ filaments.*"

3. Document D8 discloses synthetic peptides having all or a portion of the amino acid sequence of Alzheimer's amyloid protein (Aβ), including "*a peptide corresponding*

to amino acids 1-12 of the N-terminal portion of the Alzheimer β protein" (page 15, lines 7 to 8). These peptides mimic a component of a specific complex between the Aβ and α1-antichymotrypsin (ACT) and interfere with the formation of the complex. They are foreseen as a treatment for an individual in whom such complexes form, e.g. a patient suffering from Alzheimer's disease (see the paragraph bridging pages 3 and 4). The subject-matter disclosed in document D8 therefore was conceived for the same purpose as the claimed invention. In accordance with the established case law of the boards of appeal (see Case Law of the Boards of Appeal of the European Patent Office ("CLBA"), 7th edition 2013, I.D. 3) and in agreement with the findings of the opposition division and with all parties to the proceedings, the $A\beta_{1-12}$ peptide, disclosed in document D8 (see for instance, page 8, line 10), represents the closest prior art for the assessment of inventive step of the subject-matter of claim 1.

The problem and its solution

4. The difference between the $A\beta_{1-12}$ peptide and the claimed $A\beta_{2-9}$ peptide is that the latter is shorter by one amino acid (aspartic acid) at the N-terminal and by three amino acids (tyrosine, glutamic acid and valine) at the C-terminal (cf. document D8, Fig. 1).

5. Accordingly, starting from the disclosure in document D8 and taking into account the difference between the closest prior art and the claimed subject-matter, as well as the description of the patent, the technical problem to be solved is the provision of an alternative agent for the treatment of Alzheimer's disease.

6. Appellant I however, considered that "*Exhibit A*" demonstrated that the structural differences between the claimed $A\beta_{2-9}$ peptide and the $A\beta_{1-12}$ peptide cause the former to have an improved permeability across the blood/brain barrier compared to the latter. Thus, appellant I's position is, in effect, that the problem to be solved by the claimed subject-matter is the provision of an improved agent for the treatment of Alzheimer's disease.

7. In accordance with the case law of the boards of appeal, reformulation of the problem to take a technical effect into account is only allowable if the new problem can be deduced from the patent. In the same vein, the case law of the boards has consistently held that post-published evidence to support that the claimed subject-matter solves the technical problem underlying the invention, is taken into account only if it is already credible from the disclosure in the patent that the problem is indeed solved (see CLBA, *supra*, I.D. 4.4.1, 4.4.2 and 4.6). In other words, a subsequently invoked technical effect cannot be taken into account when determining the problem underlying the invention if it cannot be deduced from the patent by the person skilled in the art.

8. The board notes that "*Exhibit A*" and the experimental evidence contained therein was submitted during the proceedings before the opposition division. This submission was the first time that the contents of the document were made available to the public. In other words, "*Exhibit A*" is a post-published document.

8.1 The board cannot identify any disclosure in the patent that would allow the skilled person to deduce the technical effect documented in "*Exhibit A*". Although, as submitted by appellant I, the patent "*relates to methods*

of suppressing the formation of neurotoxic Aβ filaments which are present in the brain cells of individuals", the board is not persuaded that this disclosure allows the skilled person to deduce that the claimed peptide is better at crossing the blood/brain barrier than that disclosed in document D8. In fact, neither the patent nor document D8 disclose any information about the ability of any of the disclosed peptides to cross the blood/brain barrier. Indeed, the patent teaches that the peptides of the invention need to be modified to allow them to cross the blood/brain barrier (see paragraphs [0049] and [0059]).

8.2 The disclosure of "*Exhibit A*" is therefore not taken into account in the assessment of the inventive step of the claimed subject-matter and the problem to be solved remains that set out in point 5., above.

8.3 The issue of whether the evidence presented in "*Exhibit A*" actually demonstrates the advantage for the claimed peptide alleged by appellant I therefore need not be decided.

Obviousness

9. The question to be answered by the board is therefore whether or not the skilled person, starting from the $A\beta_{1-12}$ peptide disclosed in document D8 and seeking a solution to the technical problem, formulated in point 6. above, would have arrived at the claimed $A\beta_{2-9}$ peptide without inventive effort.

10. Document D8 teaches that the "*serine protease inhibitor (ACT) interacts specifically with a serine protease-like target protein (Alzheimer β-protein) at a region of the latter which bears striking sequence homology to the*

active site of serine proteases, resulting in formation of a stable ACT-Aβ-protein complex." This finding was thought "*a reasonable molecular mechanism for formation of the insoluble protein filaments that comprise the amyloid deposits of Alzheimer's disease*" and allowed "*design... [of] compounds which are useful to interfere with (reduce or prevent) this ACT-β-protein interaction*" (see page 11, lines 30 to page 12, lines 7 and 10).

10.1 A compound particularly useful for this was a "*synthetic peptide which has an amino acid sequence sufficiently homologous to all or a portion of the amino acid sequence of the region of Alzheimer's β-protein represented in Figure 1 that it binds to ACT is homologous with amino acids 1-12 of Figure 1 [...]*" (see claim 9).

10.2 Figure 1 of document D8 shows the region of Aβ aligned with the active sites of five serine proteases. This homologous region begins at position 2 (alanine) and extends to position 9 (glycine) of the $A\beta_{1-12}$ peptide. Position 10 of $A\beta_{1-12}$ peptide is the amino acid tyrosine, while in the other serine proteases shown, it is glycine.

11. Taking the above disclosure into account, the board considers that the attention of the skilled person seeking a solution to the technical problem was drawn to amino acids 2 to 9 of the N-terminal region of Aβ, and therefore the claimed peptide was an obvious choice.

12. The opposition division held that the deletion of the charged amino acids, aspartic and glutamic acid from the $A\beta_{1-12}$ peptide would have made the skilled person uncertain that the $A\beta_{2-9}$ peptide would retain the

ability of the longer $A\beta_{1-12}$ peptide to bind ACT and hence to prevent the polymerisation of the Aβ into neurotoxic filaments.

13. Whilst the board recognises that the common general knowledge of the skilled person included the knowledge of the structure/function relationship of amino acids and their charge, it does not agree with the conclusion reached by the opposition division that this general knowledge would have dissuaded the skilled person, faced with the technical problem, from a solution to that problem directly suggested by the document representing the closest prior art. In fact, the only consideration for designing synthetic peptides capable of interfering with the binding of ACT to Aβ set out in document D8 was that they should be "*sufficiently homologous with the sequence of the binding site of a serine protease or with the N-terminus of β- protein as shown in Figure 1*" (document D8, page 5, lines 17 to 20). This teaching would, in the board's opinion, have had a stronger influence on the skilled person than considerations based on general knowledge but not on the specific circumstances of the problem at hand.

14. In view of the above, the board concludes that the skilled person starting from document D8 and seeking an alternative agent for the treatment of Alzheimer's disease, would have considered the claimed $A\beta_{2-9}$ peptide as an obvious solution. Since the $A\beta_{2-9}$ peptide is the subject-matter of all requests submitted by appellant I, none of the requests meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The appeal of appellant I is dismissed.

2. The decision under appeal is set aside and the patent is revoked.

The Registrar: The Chairwoman:

A. Wolinski G. Alt

Decision electronically authenticated