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**Datasheet for the decision
of 24 November 2016**

Case Number: T 1825/12 - 3.3.04

Application Number: 06075479.3

Publication Number: 1679080

IPC: A61K39/00, A61K39/39, A61P25/28

Language of the proceedings: EN

Title of invention:
Prevention and treatment of amyloidogenic disease

Patent Proprietor:
Janssen Alzheimer Immunotherapy

Opponents:
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Esslinger, Dr., Alexander (opposition withdrawn)
Merck Sharp & Dohme Corp.
Chiesi Farmaceutici S.p.A. (opposition withdrawn)
Meier, Jürgen

Headword:
Active immunisation in treating amyloidogenic disease/JANSSEN

Relevant legal provisions:

EPC Art. 83, 100(b)

EPC R. 115(2)

RPBA Art. 15(3)

Keyword:

Sufficiency of disclosure - all claim requests (no)

Decisions cited:

T 0019/90, T 0063/06

Catchword:



Beschwerdekammern
Boards of Appeal
Chambres de recours

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Case Number: T 1825/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 24 November 2016

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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
5 June 2012 concerning maintenance of the
European Patent No. 1679080 in amended form.**

Composition of the Board:

Chairman B. Claes
Members: M. Montrone
M. Blasi

Summary of Facts and Submissions

I. Appeals were lodged by the patent proprietor (hereinafter "appellant I"), opponent 01 (hereinafter "appellant II") and by opponent 02 (hereinafter "appellant III") against the interlocutory decision of the opposition division concerning maintenance of the European patent No. 1 679 080 in amended form. The patent is based on a divisional application of the earlier European patent application No. 98 961 833.5 and has the title "*Prevention and treatment of amyloidogenic disease*".

Claim 1 of the patent as granted reads:

"1. A conjugate comprising an agent linked to a carrier protein for use in treatment or prevention of disease, wherein the agent is:

(i) A β ; or

(ii) an A β fragment that induces an immune response against A β ;

and wherein the carrier protein enhances the immune response against A β or the A β fragment."

II. The patent was opposed based on the grounds for opposition in Article 100(a) EPC (novelty and inventive step) and Articles 100(b) and 100(c) EPC.

III. In the impugned decision the opposition division held that the subject-matter of claim 1 of the patent as granted (main request) comprised added subject-matter (Articles 76(1) and 100(c) EPC), while auxiliary request 1 met the requirements of the EPC.

The subject-matter of claim 1 of auxiliary request 1 differed from that of the claim as granted (main request) in that the feature "A β " was deleted throughout the claim and replaced by the feature "(i) an A β fragment that induces an immune response against A β ;", *i.e.* feature (ii) of claim 1 as granted (main request).

- IV. With its reply to the statements of grounds of appeal of appellants II and III, appellant I submitted auxiliary requests 2 to 4.

The subject-matter of claim 1 of auxiliary request 2 differed from that of the main request in that the feature "disease" was replaced by "Alzheimer's disease".

The subject-matter of claim 1 of auxiliary request 3 differed from that of the main request in that the feature "A conjugate comprising an agent" was replaced by "An agent".

The subject-matter of claim 1 of auxiliary request 4 differed from that of the main request in that the feature "A β " was deleted throughout the claim and in that the feature "wherein said A β fragment is from the N-terminal half of A β " was added to the feature "an A β fragment that induces an immune response against A β ".

- V. The appeals of appellants II and III relied *inter alia* on the fact that the subject-matter of claims 1 of the main request and auxiliary request 1 was not disclosed in a manner sufficiently clear and complete for it to be carried out by the skilled person.

- VI. Appellant III withdrew its appeal and opposition.

VII. The board summoned the parties to oral proceedings. Subsequently, opponent 04 (hereinafter "respondent II") withdrew its opposition. Appellant I, opponents 03 (hereinafter "respondent I") and 05 (hereinafter "respondent III") announced that they would not be attending the oral proceedings.

VIII. Oral proceedings before the board were held on 24 November 2016. The duly summoned appellant I and respondents I and III were not present as announced. At the end of the oral proceedings the chairman announced the board's decision.

IX. Appellant I's arguments in relation to sufficiency of disclosure of the patent in suit for the invention as defined in claims 1 of the main and auxiliary requests 1 to 4 may be summarised as follows:

The invention was a ground-breaking since the patent disclosed for the first time an immunotherapy of amyloidogenic diseases.

Although the patent disclosed no experimental evidence for the efficacy of each of the conjugates encompassed by claim 1, their suitability for the claimed therapeutic application was nevertheless derivable for the skilled person from the experimental data in examples I, III, IV, and VII to IX. The immunisation of a mouse model for human Alzheimer's disease (AD) with A β 1-42, *i.e.* full-length A β , prevented either the formation or cleared already formed cerebral A β deposits, while the same mice without A β immunisation developed A β deposits. Further, the immunisation of these mice with conjugates of A β 1-5, A β 1-12 or A β 13-28 reduced the cerebral amyloid burden, although the

reduction obtained was significant for the A β 1-5 conjugate only (Figure 12 of the patent). Moreover, conjugates comprising A β 1-5, A β 1-12 or A β 13-28 induced moderate to very large titers of A β 1-42 specific antibodies which were detected in the brain of immunised mice, which however, did not correlate with the reduction of A β in the cortex.

The patent thus provided a detailed disclosure of the claimed invention, including extensive experimental data. Therefore a strong presumption existed that substantially all embodiments of the claimed invention were therapeutically suitable in view of the disclosure of the patent in suit (*cf.* decision T 63/06).

Appellant II had not submitted experimental evidence which raised serious doubts that the claimed invention could not be carried out over the whole ambit of the claim (*cf.* decision T 19/90).

- X. Appellant II's arguments in relation to sufficiency of disclosure of the patent in suit for the invention as defined in claims 1 of the main and auxiliary requests 1 to 4 may be summarised as follows:

The experimental evidence disclosed in example IV demonstrated that an N-terminal fragment, A β 1-5, conjugated to immunoglobulin G (IgG), when used for immunising mice prone to develop cortical amyloid deposits reduced significantly A β and the amyloid plaque burden in the brain. This effect was achieved, although the immunisation elicited only a low antibody titer against A β (paragraph [0141] of the patent). However, the conjugates of claim 1 were not restricted to this specific conjugate but encompassed as

embodiment all A β fragment-carrier conjugates which elicited an immune response against A β .

The experimental data disclosed in example IV showed that conjugates of A β 1-12, A β 13-28 and A β 33-42 with the same IgG, elicited all, either a high or a low antibody titer against A β (paragraph [0141]), but did not achieve a significant reduction of A β or of the amyloid burden in the cortex of the immunised mice.

Accordingly, the patent in suit disclosed evidence that the majority of embodiments of claim 1 were not suitable for the claimed therapeutic application.

Moreover, the patent did not inform the skilled person why conjugates comprising A β 1-5 were suitable for the claimed therapeutic application contrary to conjugates comprising either A β 1-12, A β 13-28 or A β 33-42. It only disclosed that the level of the elicited antibody titer against all A β fragment conjugates evaluated was no indication for their therapeutic efficacy, since conjugates which elicited a high antibody titer failed to achieve a significant therapeutic effect (A β 1-12), while others which elicited a low titer were either effective (A β 1-5) or not (A β 13-28 and A β 33-42) (paragraph [0141]). Therefore, the patent in suit provided no information to the skilled person how the claimed invention was to be carried out across the whole ambit of claim 1 without undue burden because it disclosed no guidance to find those embodiments which were suitable for the claimed therapeutic application since criteria for predicting their suitability were not provided.

XI. Appellant I requested in writing that the decision under appeal be set aside and the patent be upheld as granted (main request), or alternatively, that the

appeal of appellant II be dismissed, or further alternatively, that the decision under appeal be set aside and the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests 2 to 4 all filed with the letter dated 28 February 2013.

Appellant II requested that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

1. In the course of the appeal proceedings, appellant III withdrew its opposition and appeal, and opponent 04 its opposition. In view of these withdrawals, appellant III and opponent 04 ceased to be parties to the appeal proceedings as regards substantive issues. Other issues for which they would have remained parties to the proceedings did not arise in the present case. Appellants I and II's appeals against the interlocutory decision are not affected by these withdrawals.
2. Appellant I, opponents 03 and 05 were duly summoned to the oral proceedings before the board, but did not attend. In accordance with Rule 115(2) EPC and Article 15(3) RPBA the proceedings were continued in their absence and the absent parties were treated as relying on their written cases.

Introduction to the invention

3. Alzheimer's disease (AD) is characterised by the presence of amyloid deposits, also known as senile plaques, in the brain of AD patients. The β -amyloid

peptide (or "A β peptide") is the principal constituent of these amyloid deposits and is a natural proteolytic fragment of 39 to 43 amino acids in length of the amyloid precursor protein (APP). Several mutations within APP have been correlated with the presence of AD and are thought to increase the amount of pathogenic A β , in particular the long forms having a length of 42 or 43 amino acids. These long forms of A β are therefore thought to constitute a causative element in AD (see e.g. paragraph [0003] of the patent in suit).

4. The present invention concerns active immunisation in the "*treatment or prevention of disease*", for example, AD based on the administration of conjugates of A β or fragments thereof "*that induce an immune response against A β* ".

Main request

Sufficiency of disclosure

5. It is established case law of the boards of appeal that when assessing medical use claims attaining the claimed therapeutic effect is a functional technical feature of the claims. This applies to all claims relating to a therapeutic effect as a feature, *i.e.* purpose-limited product claims in accordance with Article 54(4) and 54(5) EPC or claims drafted in accordance with the "Swiss-type" format. As a consequence of Article 100(b) EPC, unless this is already known to the skilled person at the priority date, the patent in suit must disclose the suitability of the product for the claimed therapeutic application. Clinical trials are not required to establish suitability. It may suffice that *in vitro* or *in vivo* data directly and unambiguously

reflect the therapeutic effect on which the claimed therapeutic application relies or, alternatively, an established relationship between the physiologic activities of the compound under consideration and the claimed disease (see Case Law of the Boards of Appeal of the EPO, 8th edition 2016 (hereinafter "CLBA"), II.C.6.2, paragraphs 1 to 3 and 8).

6. Claim 1 is directed to conjugates comprising either (i) A β or (ii) A β fragments inducing an immune response against A β , both linked to a carrier protein for use in treatment or prevention of disease. Accordingly, the conjugates for use in the claimed therapeutic application comprise in feature (ii) of claim 1 as embodiment all A β fragments inducing an immune response against A β linked to a carrier protein.
7. It is uncontested that the prior art does not disclose experimental evidence that the administration of conjugates of A β fragments that induce an immune response against A β attain a therapeutic effect in the treatment or prevention of a disease such as AD. Accordingly, the question to be assessed in the context of Article 100(b) EPC in the present case is whether or not the patent in suit provides information such as evidence, which, having due regard of the common general knowledge, demonstrate the suitability of the embodiments of claim 1 for the claimed therapeutic application.
8. It is common ground between the parties that the patent in suit discloses explicit experimental evidence that the active immunisation of so-called "PDAPP" mice with conjugates comprising A β 1-5 linked to sheep anti-mouse IgG as carrier protein attain a therapeutic effect in the treatment of diseases characterised by amyloid

deposits in the brain, such as AD (see e.g. paragraph [0129], [0133], [0137] of the patent in suit).

9. The PDAPP mice used as animal model for the evaluation of the effectiveness of therapeutic agents in the patent in suit are transgenic for the human amyloid precursor protein (APP) gene, which carries a point mutation at position 717 of the protein sequence. Expression of this mutated gene inevitably causes the formation of A β amyloid deposits or plaques in mouse brains at an age of six months (see paragraph [0078]), which are an established characteristic of AD (see point 3 above).
10. Example III of the patent in suit discloses that the immunisation of PDAPP mice with human aggregated A β 1-42 reduces amyloid plaque deposits already established in the brain (see Figure 7), including a reduction of the total amount of detectable A β and A β 1-42 in certain regions of the brain (see Tables 2 and 3). An immunohistochemical analysis of the brains after immunisation with these antigens further indicates that activated phagocytic microglia and monocytes, *i.e.* cell-mediated processes, are involved in plaque removal (see paragraphs [0108] and [0112]).
11. The patent in suit further reports in example IV that a reduction of established amyloid plaques, including a reduction in total A β in the brain of PDAPP mice, is *inter alia* achieved by immunisation with a conjugated A β 1-5 fragment derived from the N-terminus of human A β linked to sheep anti-mouse IgG (see paragraphs [0129], [0133], [0134], [0137] and [0138]).
12. Example IV also discloses, however, that the immunisation of PDAPP mice with other conjugated human

A β fragments, *i.e.* A β 1-12, A β 13-28, A β 33-42 all likewise linked to sheep anti-mouse IgG as A β 1-5 (see paragraph [0129]), does not significantly reduce either the amount of established amyloid plaques or the total amount of A β in the brain of PDAPP mice (see paragraphs [0137] and [0138]). In this context, the board notes that the lack of a therapeutic effect upon immunisation with the three A β fragment conjugates cited appears not to be due to the absence of elicited anti-A β antibodies, since polyclonal antibodies binding to A β are detectable in the serum and on cerebral A β plaques (see paragraphs [0140], [0141]). Likewise the level of anti-A β antibody titer induced by the immunisation with all of the A β fragment conjugates cited in example IV is not an indicator for their therapeutic efficacy, since A β fragment conjugates, although eliciting a high antibody titer, fail to achieve a significant therapeutic effect (A β 1-12), while others which elicit only a low titer are either effective (A β 1-5) or not (A β 13-28 and A β 33-42) (see paragraph [0141]).

13. Accordingly, it can be derived from example IV of the patent in suit that upon immunisation, a specific A β fragment conjugate (A β 1-5) induces an anti-A β antibody response presumably combined with a cellular immune response which in turn prevents or reduces cerebral amyloid plaque formation, whereas other A β fragment conjugates (A β 1-12, A β 13-28, or A β 33-42) induce solely an anti-A β antibody response in PDAPP mice, which does not affect plaque formation. Therefore, the induction of an effective immune response is not correlated with the immunogenicity of the A β fragment in the conjugates *per se* since the level of the elicited antibody titer is not indicative of their therapeutic efficacy.

14. Furthermore, it can be derived from these two examples that a conjugate comprising an A β 1-5 fragment, *i.e.* the first five amino acids of the N-terminus of human A β , obviously comprises types of epitopes which elicit an effective antibody and presumably a cell-based immune response against A β in amyloid plaques. However, a conjugate comprising an A β 1-12 fragment, *i.e.* another human A β N-terminal derived peptide which is seven amino acids longer than A β 1-5, obviously lacks these beneficial epitopes since no effective immune response is induced. The same applies to A β fragment conjugates derived from the central (A β 13-28) or C-terminal region (A β 33-42) of human A β . Thus, also the location of the A β fragment within full-length A β appears to be no criterium to be relied on in designing conjugates which are effective in the claimed therapeutic application.

15. Appellant I has submitted that the patent in suit disclosed in Figure 12 that A β 1-12 and A β 13-28 conjugates induced a therapeutically effective immune response, although these effects "*did not reach statistical significance*".

16. The board notes that the data points disclosed in Figure 12 of the patent in suit relating to the cortical amyloid burden after immunisation with A β 1-12 or A β 13-28 conjugates are indistinguishable from those representing the control mice which have received only phosphate buffer. Moreover, also example IV, when analysing the results shown in Figure 12, distinguishes between results which are considered significant and those which are not (see paragraph [0138]). In the board's opinion it reflects an important component of proper scientific methodology to base conclusions on correlation of effects on statistical significance rather than on subjective observation. Accordingly, the

board judges that, independently of whether or not the contention of appellant I is correct with regard to Figure 12, results which are statistically non-significant fail to demonstrate a particular correlation. Consequently, appellant I's argument does not convince the board.

17. It follows from the above that the patent in suit - since there is no other more instructive disclosure than the examples - fails to provide the skilled person with a rationale, without trying each and every conjugate comprising a fragment individually, why A β fragments are either suitable to elicit a therapeutically beneficial immune response against A β or not.
18. It is however established case law of the boards of appeal (see CLBA, II.C.5.6.1) that, even though a reasonable amount of trial and error is permissible when it comes to sufficiency of disclosure, e.g. in an unexplored field or where there are many technical difficulties, the skilled person has to have at his disposal, either in the specification or on the basis of common general knowledge, adequate information leading necessarily and directly towards success through the evaluation of initial failures. Where the skilled person can only establish by trial and error whether or not his particular choice of numerous parameters will provide a satisfactory result, this amounts to an undue burden.
19. The board considers therefore that, in the present circumstances, the skilled person is in a trial and error situation and that carrying out the claimed invention across its whole ambit amounts to an undue burden.

20. Appellant I also submitted that according to e.g. decision T 63/06 of 24 June 2008 (see point 3.3 of the Reasons) in view of the detailed disclosure of the invention supported by abundant experimental evidence in the patent in suit a strong presumption existed that the patent as granted sufficiently disclosed the claimed invention. Moreover, appellant II had not submitted experimental evidence which raised serious doubts that the claimed invention could not be carried out over the whole ambit of the claim (*cf.* decision T 19/90 OJ EPO 1990, 476, point 3.3 of the Reasons).
21. While in general the board agrees with appellant I regarding the principles established in these two decisions, the situation in the present case is different since, as outlined in point 12 above, the patent in suit itself already discloses experimental evidence that conjugates comprising A β fragments from the N-terminal, central and C-terminal region of human A β , which induce an immune response against A β and are therefore encompassed as embodiments in claim 1, are not suitable for the claimed therapeutic application. In these circumstances, serious doubts that the invention could be carried out over the whole ambit of claim 1 are already reported in the patent in suit and no additional experimental evidence from appellant II is required, as it can rely on the evidence provided by the patent in suit itself. This shifts the burden of proof back to appellant I, whose argument must therefore fail.
22. Therefore, the board concludes that the subject-matter of claim 1, and therefore the main request as a whole, does not meet the requirements of Article 100(b) EPC.

Auxiliary requests 1 to 4

23. The subject-matter of claim 1 of auxiliary request 1 differs from that of the main request in that the feature "A β " was omitted throughout the claim and replaced by feature "(i) an A β fragment that induces an immune response against A β ;", *i.e.* feature (ii) of the main request. The subject-matter of claim 1 of auxiliary request 2 differs from that of the main request in that the feature "disease" was replaced by "Alzheimer's disease". Furthermore, The subject-matter of claim 1 of auxiliary request 3 differs from that of the main request in that the feature "A conjugate comprising an agent" was replaced by "An agent".
24. The board notes that the embodiment under consideration in claim 1 for the main request is identical to the subject-matter of claim 1 of auxiliary request 1 (see point 6 above). Furthermore, the amendments in claims 1 of auxiliary requests 2 and 3 do also not change the essence of the invention underlying claim 1 of the main request.
25. The subject-matter of claim 1 of auxiliary request 4 differs from that of the main request in that the feature "A β " was omitted throughout the claim and in that the feature "wherein said A β fragment is from the N-terminal half of A β " was added to the feature "an A β fragment that induces an immune response against A β ".
26. As set out above (see point 12), the patent in suit discloses in example IV that conjugates comprising A β 1-12 and therefore a fragment from the N-terminal half of A β , are not suitable for the claimed therapeutic application. Accordingly, the reasons given

in points 13 to 19 above also apply to the subject-matter of claim 1 of auxiliary request 4.

27. The board, in view of these considerations, therefore concludes that the auxiliary requests 1 to 4 do not meet the requirements of Article 83 EPC.

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:



P. Cremona

B. Claes

Decision electronically authenticated