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Datasheet for the decision of 24 March 2014

Case Number: T 1770/10 - 3.3.08

Application Number: 04707166.7

Publication Number: 1594969

IPC: C12N15/85, C12N15/86, A61K39/00, A61K39/395, C07K5/00

Language of the proceedings: EN

Title of invention:
Active Immunization to Generate Antibodies to Soluble A-Beta

Applicant:
Janssen Alzheimer Immunotherapy
Wyeth LLC

Headword:
Soluble A-Beta/JANSSEN

Relevant legal provisions:
EPC Art. 56, 83
RPBA Art. 13(1)

Keyword:
Sufficiency of disclosure (yes)
Inventive step (yes)

Decisions cited:

Catchword:

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Case Number: T 1770/10 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 24 March 2014

Appellant: (Applicant 1)	Janssen Alzheimer Immunotherapy Little Island Industrial Estate Little Island, County Cork (IE)
Appellant: (Applicant 2)	Wyeth LLC Five Giralda Farms Madison, NJ 07940 (US)
Representative:	Kirsch, Susan Edith Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 16 February 2010 refusing European patent application No. 04707166.7 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman: M. Wieser
Members: T. J. H. Mennessier
D. Rogers

Summary of Facts and Submissions

I. The applicants (appellants) lodged an appeal against the decision of the examining division dated 16 February 2010, whereby the European patent application number 04707166.7 was refused. The application, entitled "*Active Immunization to Generate Antibodies to Soluble A-Beta*", originated from the international application published as WO 04/69182.

II. The decision was based on the main request filed with letter of 18 December 2008. The request was refused for lack of inventive step (Article 56 EPC).

III. Together with their statement setting out the grounds of appeal the appellants re-filed their previous main request and submitted three new auxiliary requests. Oral proceedings were requested.

IV. The board issued a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), which was sent together with the summons to oral proceedings and wherein the board expressed its provisional, non binding views. An objection for insufficient disclosure was raised.

V. In reply to the board's communication, the appellant filed a new main request and an amended description. Furthermore, all previous claim requests were withdrawn and the request for oral proceedings was made conditional.

VI. On 14 March 2014, the appellant filed a new main request to replace the previous one.

VII. The new main request consists of 32 claims of which claim 1 reads:

"1. A medicament comprising a fragment of Aβ consisting of Aβ16-23 (KLVFFAED) in the natural human amino acid form; wherein the fragment is linked to a carrier molecule to form a conjugate which helps elicit an immune response against the fragment;
for effecting treatment or prophylaxis of a disease associated with amyloid deposits of Aβ in the brain of a patient, whereby the induced antibodies specifically bind to soluble Aβ in the patient thereby inhibiting formation of amyloid deposits of Aβ in the brain from the soluble Aβ and thereby effecting treatment or prophylaxis of the disease."

Claims 2 to 32 are dependent on claim 1.

VIII. The board informed the appellants that the scheduled oral proceedings were cancelled.

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

(D1) WO 02/96937 (published on 5 December 2002)

(D2) M. M. Pallitto et al., Biochemistry, Vol. 38, 1999, pages 3570 to 3578

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

Admissibility of the main request

The main request was filed in direct response to the board's communication pursuant to Article 15(1) RPBA. It overcame all the objections, including the board's new objection under Article 83 EPC outlined in the communication.

Article 83 EPC

The claims have been limited to a medicament comprising a fragment of Aβ consisting of Aβ16-23 in the natural human amino acid form, linked to a carrier molecule.

Article 56 EPC

As stated in the decision under appeal, not document D2 which investigated the ability of short peptides to influence Aβ aggregation, but document D1 was to be considered as the closest prior art. It disclosed that immunisation with an Aβ peptide made up of residues 16-21 in the dextro form (D-isomers) resulted in clearance of soluble Aβ through the induction of antibodies. The technical problem to be solved was the provision of a medicament which generated a high immunogenic response and therefore elicited antibodies that were effective in treating a disease associated with amyloid deposits, but which did not elicit undesirable side-effects caused by a detrimental T-cell response.

The patent provided a clear scientific rationale for selecting Aβ16-23 in the natural human amino acid form. Due to its length it lacked an epitope that would generate a detrimental T-cell response to the fragment,

but it was long enough to generate a high immunogenic response.

The Aβ16-23 fragment was neither described nor suggested in the prior art, including document D1. It was not obvious that it was useful as a medicament to induce antibodies that bound to soluble Aβ and thereby inhibited formation of amyloid deposits of Aβ in the brain.

The absence of data demonstrating that the Aβ16-23 peptide had unexpected properties in the application was irrelevant.

XI. The appellants request that the decision under appeal be set aside and a patent be granted on the basis of claims 1 to 32 of the main request filed with letter of 14 March 2014.

Reasons for the Decision

Admissibility of the main request

1. The main request represents an amendment to the appellants' case which was made after they had filed their grounds of appeal and which, therefore, may be admitted into the proceedings and considered at the board's discretion (see Article 13(1) RPBA).

2. The main request is based on the previous third auxiliary request, which has been amended by deleting any reference to a polynucleotide from claims 1, 28, 29 and 30 This happened in response to the board's objection under Article 83 EPC newly raised in the

communication pursuant to Article 15(1) RPBA. In addition, former claims 19 and 29 have been deleted for reasons of redundancy in the light of claims 18 and 28, respectively.

3. The amendments are straightforward, they do not raise new issues, do not contribute to the complexity of the appeal case and, accordingly, do not lead to a delay of the proceedings. Therefore, exercising the discretion conferred to it by Article 13(1) RPBA, the board admits the main request into the proceedings.

Article 123(2) EPC

4. The international application WO 04/69182, the content of which is deemed to correspond to that of the application as filed, provides support for the medicament according to claim 1. The relevant parts of WO 04/69182 are the following:

4.1 Claims 6 and 53, which disclose the medical use of the Aβ16-23 fragment for effecting treatment (see claim 6) or prophylaxis (see claim 53) of a disease associated with amyloid deposits of Aβ in the brain of a patient, wherein the fragment induces antibodies which bind to soluble Aβ in the patient and thereby inhibit formation of amyloid deposits of Aβ in the brain from the soluble Aβ.

4.2 Paragraph [0017], which discloses the sequence of Aβ42, a natural human form of Aβ and from which it is unambiguously derivable that the Aβ16-23 fragment has the sequence KLVFFAED.

4.3 Paragraph [0038], which indicates precisely that, unless otherwise indicated, reference to Aβ fragments

includes fragments of the natural human amino acid sequences.

4.4 Paragraph [0046], which specifies that a peptide immunogen of the invention, such as the Aβ16-23 fragment, can be linked to a suitable carrier molecule to form a conjugate which helps to elicit an immune response.

5. The additional technical features of the medicaments to which the dependent claims are directed find support in the claims as filed (see WO 04/69182) as indicated below:

Claim 2: see claims 9 and 56 as filed.
Claim 3: see claims 10 and 57 as filed.
Claim 4: see claims 11 and 58 as filed.
Claim 5: see claims 12 and 59 as filed.
Claim 6: see claims 13 and 60 as filed.
Claim 7: see claims 14 to 16 and 61 to 63 as filed.
Claim 8: see claims 18 and 65 as filed.
Claim 9: see claims 19 and 66 as filed.
Claim 10: see claims 20 and 67 as filed.
Claim 11: see claims 21 and 68 as filed.
Claim 12: see claims 22 and 69 as filed.
Claim 13: see claims 23 and 70 as filed.
Claim 14: see claims 24 and 71 as filed.
Claim 15: see claims 25 and 72 as filed.
Claim 16: see claims 30 and 77 as filed.
Claim 17: see claims 31 and 78 as filed.
Claim 18: see claims 39 and 86 as filed.
Claim 19: see claims 27 and 74 as filed.
Claim 20: see claims 29 and 76 as filed.
Claim 21: see claims 33 and 80 as filed.
Claim 22: see claims 34 and 81 as filed.
Claim 23: see claims 35 and 82 as filed.

Claim 24: see claims 36 and 83 as filed.
Claim 25: see claims 37 and 84 as filed.
Claim 26: see claims 38 and 85 as filed.
Claim 27: see claims 39 and 86 as filed.
Claim 28: see claims 40 and 87 as filed.
Claim 29: see claims 41 and 88 as filed.
Claim 30: see claims 42 and 89 as filed.
Claim 31: see claims 43 to 46 and 90 to 93 as filed.
Claim 32: see claims 47 and 94 as filed.

6. Therefore, the main request meets the requirements of Article 123(2) EPC.

Article 84 EPC

7. The claims are clear, concise and supported by the description. Therefore, the main request meets the requirements of Article 84 EPC.

Article 83 EPC

8. As shown by (i) the disclosure in paragraph [0035] of the description indicating that fragment Aβ15-24 and subfragments of 7 to 9 contiguous amino acids thereof, including fragment Aβ16-23, induce a polyclonal mixture of antibodies that specifically bind to soluble Aβ, without binding to plaques of Aβ and (ii) the results presented in the experimental part of the description with fragment Aβ15-24 having the natural human amino acid form (L-amino acids)(see paragraph [0038], first sentence), it is evident that a therapeutic effect can be achieved with the fragment Aβ16-23 in the natural human amino acid form if linked to a carrier molecule to form a conjugate which helps to elicit an immune response against the fragment.

9. As the claims are restricted to the Aβ16-23 fragment the new main request meets the requirements of Article 83 EPC.

Article 54 EPC

10. The medicament according to claim 1 is not disclosed in any of the prior art documents on file and is therefore novel (Article 54 EPC).

Article 56 EPC

11. Document D1 has been considered by the examining division to represent the closest state of the art. In the appeal proceedings the appellant agreed that this was the case. The board sees no reason to depart from this choice.

12. Document D1 describes vaccines for preventing or treating Alzheimer's disease and other amyloid related diseases comprising an all-D immunogenic fragment of a fibril protein, such as beta amyloid (Aβ). The term "all-D" means that the fragments have at least 50% unnatural D-configuration amino acids (see page 37, lines 6 to 7). The vaccines are believed to elicit an immune response in a host resulting in the production of antibodies recognizing the naturally occurring target (see page 37, lines 1 to 10). Exemplary fragments are listed on page 58, not including an all-D Aβ16-23 fragment. These stereochemically based "non-self" antigen vaccines avoid the drawbacks generally associated with the use of "self" peptides, proteins or immunogens, which drawbacks include: a) possible development of autoimmune disease due to the generation of antibodies against "self-protein", b) difficulties in eliciting an immune response due to the failure of

the host immune system to break tolerance and c) possible development of an acute inflammatory response in the brain due to antibody-mediated phagocytosis by microglia cells and d) development of anti-idiotype antibodies (see.page 4, lines 1 to 10).

13. The objective technical problem underlying the patent in suit in the light of the disclosure in document D1 is defined as the provision of an alternative medicament which elicits antibodies that are effective in preventing or treating a disease associated with amyloid deposits. As a solution to this problem the patent application proposes the medicament according to claim 1, relying on the use of a fragment of Aβ consisting of Aβ16-23 (KLVFFAED) in the natural human amino acid form as its active ingredient. In view of the experiments reporting tests with the Aβ15-24 fragment (see paragraphs [0091] to [0095]), whose selection was based on the same rationale as the selection of the Aβ16-23 fragment, the technical problem is considered to be credibly solved. The experimental report, attached to the then applicants' letter of 3 August 2007, only confirms what is already evident from the application as filed, namely that Aβ16-23 (KLVFFAED) in the natural human amino acid form is effective at inducing antibodies to soluble Aβ without inducing a detrimental T-cell response, which marks it as a particularly promising candidate for the prevention and treatment of Alzheimer's disease.

14. It remains to be answered whether a skilled person, in the light of document D1, when combining it with document D2, would have arrived at the claimed solution in an obvious way, as was argued in the decision under appeal.

15. Document D1 is focused on the use of an immunogenic fragment of a fibril protein - Aβ being a preferred embodiment (see in particular page 9, lines 19 to 27)- having at least 50% of its amino acid residues in the dextro form (D-isomers). Its sole object was the provision of immunogenic fragments from any fibril protein, which were capable of overcoming the drawbacks associated with the use of "self" peptides, proteins or immunogens.

16. Document D2, which is not concerned with the selection of Aβ immunogens fragments, contributes to the improvement of the design of hybrid compounds capable of inhibiting Aβ toxicity and comprising a recognising element for Aβ linked to a disrupting element designed to interfere with Aβ aggregation (see the abstract on page 3570). Previous studies had revealed that a sequence encompassing the 15-25 domain of the human β-Amyloid peptide (in the natural amino acid form) could serve as an effective recognition element. In document D2, the authors explored the scope of the recognition element with two objectives: (1) to determine whether the recognition element alone could interfere with Aβ aggregation and (2) to ascertain the minimal sequence required for specific recognition (see page 3576, left hand column, first full paragraph). Shorter peptide segments within the 15-25 sequence of Aβ were examined for that purpose and their ability to inhibit Aβ toxicity was evaluated.

17. A skilled person would consequently not have found any incentive in document D2 to prepare a medicament containing, as its active ingredient, the Aβ16-23 fragment.

18. Therefore, the skilled person facing the objective technical problem to be solved (see point 13 above), when starting from the disclosure in document D1 and combining it with the disclosure in document D2 or in any other prior art document on file, would not have arrived at the solution provided in claim 1 in an obvious way.

19. The medicament according to claim 1 involves an inventive step. The same conclusion applies to the subject-matter of dependent claims 2 to 32. Consequently, the main request involves an inventive step and thereby meets 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 examining division with the order to grant a patent on the basis of claims 1 to 32 of the main request filed with letter of 14 March 2014 and a description to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated