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**Datasheet for the decision
of 10 October 2017**

Case Number: T 2500/12 - 3.3.04

Application Number: 06000288.8

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C07K14/47, A61P25/28

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Title of invention:
Beta-amyloid-analogue-T-cell epitope vaccine

Applicant:
H. Lundbeck A/S

Headword:
Beta-amyloid-analogue/LUNDBECK

Relevant legal provisions:
EPC Art. 83

Keyword:
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T 0609/02

Catchword:



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Case Number: T 2500/12 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 10 October 2017

Appellant: H. Lundbeck A/S
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted on 27 July 2012 refusing European patent application No. 06000288.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman G. Alt
Members: A. Chakravarty
M.-B. Tardo-Dino

Summary of Facts and Submissions

- I. An appeal against the decision of the examining division to refuse European patent application No. 06 000 288 entitled "*Beta-amyloid-analogue-T-cell epitope vaccine*" was filed by the patent applicant (appellant).
- II. The examining division considered a main and an auxiliary request. It held that the subject-matter of claim 1 of these requests lacked an inventive step.
- III. The appellant filed a statement of grounds of appeal together with sets of claims of a main request and of an auxiliary request, which were identical to the claim requests considered by the examining division.
- IV. Claim 1 of the main request reads:

"1. A pharmaceutical preparation containing an immunogen which induces production of antibodies against the animal's autologous APP or A β , wherein the immunogen incorporates

 - a) a polyamino acid which consists of a polyamino acid selected from the group consisting of:

- amino acid residues 1-12, which is a subsequence of residues 672-714 of SEQ ID NO:2, A β , followed by the amino acid residues of the tetanus toxoid P30 epitope followed by the amino acid residues of the tetanus toxoid P2 epitope, followed by amino acids 13-28, which is a subsequence of residues 672-714 of SEQ ID NO:2, A β ,

- amino acid residues 1-12, which is a subsequence of residues 672-714 of SEQ ID NO:2, A β , followed by the amino acid residues of the tetanus toxoid P30 epitope, followed by amino acid residues 1-12, which is a subsequence of residues 672-714 of SEQ ID NO:2, A β , followed by the amino acid residues of the tetanus toxoid P2 epitope, followed by amino acid residues 1-12, which is a subsequence of residues 672-714 of SEQ ID NO:2, A β ,

- amino acid residues 13-28, which is a subsequence of residues 672-714 of SEQ ID NO:2, A β , followed by the amino acid residues of the tetanus toxoid P30 epitope, followed by amino acid residues 13-28, which is a subsequence of residues 672-714 of SEQ ID NO:2, A β , followed by the amino acid residues of the tetanus toxoid P2 epitope, followed by amino acid residues 13-28, which is a subsequence of residues 672-714 of SEQ ID NO:2, A β ,

wherein all amino acid sequences are recited in the direction from the N- to the C-terminus, or

b) is a conjugate comprising a polyhydroxypolymer to which is separately coupled a polyamino acid as defined in a); or

c) is a nucleic acid that encodes the polyamino acid as defined in a); or

d) is a non-pathogenic microorganism or virus which is carrying a nucleic acid fragment which encodes and expresses the polyamino acid as defined in a),

for use in the treatment, prevention or amelioration in an animal of Alzheimer's disease or other diseases characterized by amyloid deposits."

Claim 1 of the auxiliary request differs from claim 1 of the main request in that the polyamino acid defined in part a) of the claim is limited to the second alternative of the three given in the main request.

- V. The board appointed oral proceedings and subsequently issued a communication pursuant to Article 15(1) RPBA in which it set out its preliminary appreciation of substantive and legal matters concerning the appeal and informed the appellant that, in relation to claim 1 of the main request, it was inclined to consider that the application as filed did not disclose the suitability of the claimed compositions for the claimed use and that therefore, the application did not meet the requirements of Article 83 EPC. It further informed the appellant that it was of the preliminary opinion that the subject-matter of claims 12 to 22 and 24 of the main request lacked an inventive step (Article 56 EPC).
- VI. Oral proceedings took place before the board. At the end of the oral proceedings, the chairman announced the decision of the board.

VII. The appellant's arguments relevant to the decision, made in writing and at oral proceedings, are summarised as follows:

Main request - claim 1

Article 83 EPC - Disclosure of the invention

The claimed invention was disclosed in the application in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. In particular, the claimed constructs were suitable for use in the treatment, prevention or amelioration in an animal of Alzheimer's disease or other diseases characterized by amyloid deposits.

Although clinical trials carried out on a full length amyloid-beta ($A\beta$) construct, aggregated $A\beta$, AN1792 (see paragraph [0044]) had shown negative side effects (meningo-encephalitis due to uncontrolled autoimmunity), the claimed constructs contained only short subsequences of $A\beta$ which had a minimal number of T-cell epitopes and should therefore avoid such negative side effects. The application contained a clear statement that the claimed constructs were the preferred embodiments. Thus, while AN1792 might not have been suitable for therapeutic use, the claimed constructs differed from this in such a way that there was no reason to doubt their suitability.

The statement in the declaration of Dr Pedersen to the effect that "*whether an auto-vaccine within the CNS is being [sic] effective and safe is unpredictable*" was not to be taken as casting doubt on the therapeutic suitability of the claimed constructs because it related to the prior art and the person skilled in the

art reading it would have realised that the applicants had taken the earlier failed clinical trials into consideration and presented preferred constructs which overcame the previous problems. The Pedersen declaration contained evidence that the claimed immunogens unexpectedly induced a specific IgG response in comparison with prior art vaccine AN1792, which induced both an IgG and an IgM response, which further supported the thesis that the claimed constructs would not suffer from the same problems as AN1792.

Although the application contained no direct experimental evidence relating to the suitability of the claimed constructs for the intended therapeutic use, it was pointed out that there was no stipulation in the EPC requiring an example or even clinical evidence. The one and only threshold was plausibility. Notwithstanding the above, Example 2 of the application related to "*Immunisation of transgenic mice with A β and modified proteins*". It utilised a mouse model recognised in the art as relating to Alzheimer's disease. These mice expressed a mutated form of human APP (amyloid precursor protein) that resulted in a high concentration of A β -40 and A β -42 in the mouse brains. The human APP was therefore a "self" protein for such mice. The mice were immunised with either A β -42 or the hAB43+-34 variant (construct 34 in the table in Example 1, which contains three identical APP fragments separated by T-cell epitopes of the tetanus toxoid, P30 and P2 respectively). The experiment represented a valid test of the ability of constructs containing tetanus toxoid T-cell epitopes to break self tolerance and the results showed that this aim had been successfully achieved.

The fact that the examples related to experiments using a construct containing full length A β (construction 34) and not the constructs mentioned in the claim, would not have caused a skilled person to consider it implausible that the claimed constructs possessed the activity ascribed to them.

The application at paragraphs [0119] and [0120] disclosed that the danger that "*the adverse effect that the vaccinated individual's own protein will be able to function as an immunizing agent in its own right*" and establish an autoimmune condition, could be circumvented by avoiding the "*inclusion in the immunogen of peptide sequences that could serve as T_H-epitopes*".

Although the application stated that "*peptides shorter than about 9 amino acids cannot serve as T_H-epitopes*", the fact that the claimed constructs contained sequences longer than 9 amino acids would not have given the skilled person doubts about whether or not the aim of avoiding T-cell epitopes had been achieved, since the claimed constructs had been designated as particularly preferred.

In addition to the evidence provided in the application, the Pedersen declaration contained experimental evidence that "*construction 38*", an embodiment of the claimed invention, induced T-cell responses in APP/Tag-2576 mice, directed against the foreign determinant but not against self A β .

In summary, it was plausible to the skilled person that the claimed pharmaceutical preparations were suitable for the use mentioned in the claim and there was no

evidence on file to contradict this reasonable assumption.

- VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request or, alternatively, on the basis of the claims of auxiliary request 1, both filed together with the statement of grounds of appeal.

Reasons for the Decision

Main request - claim 1

Article 83 EPC - Disclosure of the invention

1. Article 83 EPC requires that the European patent application "*disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art*". In the case of a therapeutic use, it is established case law that the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application, unless this was already known to the skilled person at the priority date. In this respect, showing a pharmaceutical effect *in vitro* may be sufficient if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application, or, if there is a clear and accepted relationship between the shown physiological activities and the disease (see Case Law of the Boards of Appeal of the European Patent Office, 8th edition, II.C.6.2 and decision T 609/02, reasons 9).

2. In the case at hand, the question to be answered is whether or not either the application discloses that an immunogen containing the polyamino acid, defined in the

claim, would be suitable (i.e. would plausibly be considered to be useful) for the treatment, prevention or amelioration in an animal, for example a human, patient of Alzheimer's disease or other diseases characterized by amyloid deposits (i.e. for the therapeutic use defined in the claim), or if the skilled person at the priority date would have known this.

3. The appellant presented two main lines of argument in response to the above question.
 - 3.1 Firstly, it was widely accepted in the art that Alzheimer's disease or other diseases characterized by amyloid deposits could be treated by generating an immune response to A β . It was therefore sufficient that the application made it plausible that such an immune response was generated. The application did this by showing, in a mouse model, that A β constructs including tetanus toxoid epitopes P2 and P30 were able to break self-tolerance and generate a suitable immune response.
 - 3.2 Secondly, concerns about unsuitability based on potential negative side effects, such as those seen in clinical trials of AN1792, had been addressed by designing the claimed constructs to omit native T-cell epitopes. Data presented in the Pedersen declaration supported the thesis that the claimed constructs elicited a different immune response from that generated by vaccine AN1792. The former unexpectedly induced a specific IgG response while the latter induced an IgG and an IgM response.
4. As to the first line of argumentation, Example 2 of the application, relied upon by the appellant, concerns the immunogenicity of a construct, the so-called

"*construction 34*", that contains three identical A β -43 fragments separated by tetanus toxoid epitopes P30 and P2 and shows that this construct can elicit an immune response in a mice transgenic for human APP, i.e. it is able to break self tolerance. However, this construct is not an embodiment of claim 1. It differs from the claimed constructs in that it contains full-length A β -43 rather than shorter sub-sections of said peptide. The application does not contain any evidence that the claimed constructs will behave in the same way as "*construction 34*" in the mouse model.

5. Even if it were accepted that it is at least plausible that the claimed constructs can elicit an immune response to A β , the board has seen no evidence in the application, that at the effective date, a direct and unambiguous link, for example, by means of an animal or *in vitro* model, had been established between the observed effect of eliciting anti-A β antibodies and the effective treatment of disease.
6. Thus, the application on its own does not disclose the suitability of the claimed constructs for the claimed therapeutic purpose. It remains to be assessed whether this suitability was already known to the skilled person at the relevant date of the application, for example because of a known clear and accepted relationship between the physiological activities shown in the application and the disease.
7. In this context, the appellant argued that the fact that the AN1792 vaccine had been tested in clinical trials illustrated that an A β based immunotherapy was commonly regarded as effective by the skilled person at the effective date of the patent, i.e. it was a widely accepted concept.

8. However, while these trials do illustrate that A β directed immunotherapy was widely regarded as attractive, the board has seen no evidence showing that these trials were regarded in the art as experimental proof of concept for the above mentioned type of therapy. Thus, the board is not satisfied that the clinical trials of the AN1792 vaccine show that ability to elicit an A β specific immune response was generally accepted in the art as proof that there was a known, clear and accepted relationship between A β based immunotherapy and the successful treatment, prevention or amelioration in an animal of Alzheimer's disease or other diseases characterized by amyloid deposits.
9. The data contained in the Pedersen declaration is not evidence for this either, as none of the reported experiments relate to treatment of clinical disease or models thereof. In fact, like example 2 of the application, the experiments described in said declaration relate to the ability to generate A β specific immunogenicity.
10. Thus, in the present case, the board is not satisfied that evidence of the ability to elicit an A β specific immune response is also evidence of the ability to successfully treat, prevent or ameliorate in an animal, Alzheimer's disease or other diseases characterized by amyloid deposits.
11. The line of argument relating to concerns about potential unsuitability of the claimed constructs in view of potential negative side effects is moot in view of the above considerations.
12. Thus, the board concludes that the suitability of the immunogen containing a polyamino acid defined in the

claim for the treatment, prevention or amelioration in an animal of Alzheimer's disease or other diseases characterized by amyloid deposits (i.e. for the therapeutic use defined in the claim) is not shown by either the application or the prior art. The application therefore does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

Auxiliary request

13. The above reasoning holds equally for immunogens containing each of the three alternative constructs set out in claim 1 (a) of the main request and thus for claim 1 of auxiliary request 1, which differs from claim 1 of the main request in that two of the three constructs are deleted.

Article 56 EPC - Inventive step

14. During the oral proceedings, the board announced its decision that the subject-matter of claim 1 of the main and auxiliary request also lacked an inventive step. In view of the above decision on disclosure of the application, there is no need for this decision to include the detailed reasons for this finding.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated