Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 9 June 2020

Case Number: T 2127/16 - 3.3.04

Application Number: 05820737.4

Publication Number: 1812062

IPC: C07K16/18, G01N33/50, G01N33/68

Language of the proceedings: EN

Title of invention:
Anti-ADDL antibodies and uses thereof

Applicants:
Merck Sharp & Dohme Corp.
Northwestern University

Headword:
Anti-ADDL antibodies/MERCK

Relevant legal provisions:
RPBA Art. 12(4)
EPC Art. 123(2), 84, 87, 54, 56, 83

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

Decisions cited:
T 0609/02

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2127/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 9 June 2020

Appellant: (Applicant 1)	Merck Sharp & Dohme Corp. 126 East Lincoln Avenue Rahway, NJ 07065-0907 (US)
Appellant: (Applicant 2)	Northwestern University 633 Clark Street Evanston, IL 60208 (US)
Representative:	FRKelly 27 Clyde Road Dublin D04 F838 (IE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 11 April 2016 refusing European patent application No. 05820737.4 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	B. Rutz
	R. Romandini

Summary of Facts and Submissions

I. The appeal of the applicants ("appellants") lies from the decision of the examining division refusing European patent application No. 05 820 737.4 entitled "*Anti-ADDL antibodies and uses thereof*".

II. In the decision under appeal the examining division held *inter alia* that claims 1 and 5 of the main request were unclear due to a lack of proper definition of the term "fragment" and thus not in accordance with Article 84 EPC. Claim 13 of the main request was found unclear because the disease to be treated was not identified. Further terms were objected to in claims 6 to 8, 10 and 11 of the main request for lack of clarity. As regards inventive step the decision stated that the subject-matter of the sets of claims of the main request and auxiliary requests 1 and 2 failed to meet the requirements of Article 56 EPC citing documents D11 or D3 as closest prior art.

III. With the statement setting out the grounds of appeal the appellants submitted a set of eight claims as their sole amended main request. Claims 1 and 5 of this request differ from the claims on which the decision under appeal was based in that they further define the term "fragment" as "binding". Former claims 6 to 8, 10 and 11 were deleted and former claim 13 was amended to relate to "preventing or treating Alzheimer's disease".

Independent claims 1 and 8 of the main request read:

"1. An isolated anti-Aβ-derived diffusible ligand (ADDL) antibody, or binding fragment thereof, wherein
(A) a light chain CDR1 has the sequence Arg-Ser-Ser-Gln-Ser-Ile-Val-His-Ser-Asn-Gly-Asn-Thr-Tyr-Leu-Glu (SEQ ID NO: 49);
(B) a light chain CDR2 has the sequence Lys-Ala-Ser-Asn-Arg-Phe-Ser (SEQ ID NO: 56);
(C) a light chain CDR3 has the sequence Phe-Gln-Gly-Ser-His-Val-Pro-Pro-Thr (SEQ ID NO: 64);
(D) a heavy chain CDR1 has the sequence Ser-Phe-Gly-Met-His (SEQ ID NO:28);
(E) a heavy chain CDR2 has the sequence Tyr-Ile-Ser-Arg-Gly-Ser-Ser-Thr-Ile-Tyr-Tyr-Ala-Asp-Thr-Val-Lys-Gly (SEQ ID NO: 36); and
(F) a heavy chain CDR3 has the sequence Gly-Ile-Thr-Thr-Ala-Leu-Asp-Tyr (SEQ ID NO:48).

8. The anti-ADDL antibody of claim 1 for use for preventing or treating Alzheimer's disease."

IV. In a communication pursuant to Article 15(1) RPBA, the board expressed *inter alia* its opinion that document D1 appeared a good starting point for assessing inventive step using the problem-solution approach.

V. The appellants replied by providing further arguments and additional experimental data.

VI. The board cancelled the oral proceedings originally summoned for 10 December 2019 and indicated that the proceedings would be continued in writing.

VII. In reply to a further communication from the board the appellants clarified their requests.

VIII. The following documents are cited in this decision:

D1 WO 2003/104437

D3 WO 2005/011599

D11 R. V. Ward et al., "Fractionation and characterization of oligomeric, protofibrillar and fibrillar forms of β-amyloidpeptide", Biochemical Journal 248, 2000, 137-144.

D14 W. L. Klein et al., "Targeting small Aβ oligomers: The solution to an Alzheimer's disease conundrum?", Trends in Neurosciences 24(4), 2001, 219-224.

D23 First declaration of Dr Goure dated 17 December 2015

IX. The appellants' arguments submitted in writing may be summarised as follows:

Main (sole) request

Clarity (Article 84 EPC)

In relation to "fragment thereof" the term "binding" was introduced into claims 1 and 5. The disease to be treated according to claim 8 (former claim 13) was restricted to the "use for preventing or treating Alzheimer's disease". The further claims which were held to lack clarity in the decision under appeal were deleted. Hence the main request fulfilled the requirements of Article 84 EPC.

Inventive step (Article 56 EPC)

Neither document D3 nor document D11 could represent the closest prior art since they both constituted non-enabling disclosures for the monoclonal antibodies described in these, MOAB-1/7A2 and WO2, respectively. Moreover, document D3 did not disclose the Aβ oligomer preparation used as an antigen to prepare monoclonal antibodies capable of differentially recognising Aβ-derived diffusible ligands (ADDLs).

The assay format of Example 14 of the application did not permit, as the examining division had done, a side-by-side comparison of the binding affinities of both antibodies to the same amyloid beta peptide preparation. All that could be learned from Example 14 was that each of WO-2 and 3B3 showed about 10- to 11-fold higher affinity for ADDL over monomer.

The objective technical problem should be formulated as "*to provide a selective monoclonal antibody against Aβ peptide species that are most relevant to the development of Alzheimer's therapeutics and diagnostics, **soluble oligomeric Aβ peptides**, compared to non-toxic Aβ species such as APP or monomeric Aβ that are always present to a greater extent in Alzheimer's patients*".

Aβ existed in three main forms: (i) as monomeric Aβ peptides; (ii) as soluble oligomeric Aβ peptides; and (iii) as insoluble fibrillic aggregates of Aβ peptides.

While general methods for preparing and developing antibodies with selective affinity for discrete antigens were well known to skilled scientists, because of the complex heterogeneity of the various Aβ peptide

species and challenges associated with preparing and characterising physiologically relevant preparations of Aβ peptides, the discovery and development of monoclonal antibodies with selective affinity for various soluble Aβ oligomers over monomeric Aβ forms was not obvious or routine when the application was filed.

Antibody 3B3 furthermore showed differential efficacy in inhibiting the binding of ADDLs to primary hippocampal neurons compared to other oligomer selective antibodies: see figures 3 and 4 and table 3 in the application. This was unexpected.

X. The appellants requested that the decision under appeal be set aside and the case be remitted to the examining division with the order to grant a patent on the basis of the main request filed with the statement of grounds of appeal and a description and figures adapted thereto.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is therefore admissible.

Introduction

2. The present invention relates to antibodies that differentially recognise multi-dimensional conformations of Aβ-derived diffusible ligands (ADDLs). These soluble oligomers of amyloid β 1-42 peptides ($A\beta_{1-42}$) have been found in brain tissue, and their levels are elevated in Alzheimer's disease patients and animal models of Alzheimer's disease.

$A\beta_{1-42}$, also called amyloid β protein or Aβ peptide, is a 42-amino acid amphipathic peptide derived proteolytically from the transmembrane amyloid precursor protein (APP).

There are three main distinct classes of Aβ peptide species: 1. monomeric Aβ peptides; 2. soluble oligomeric Aβ peptides; and 3. insoluble fibrillic aggregates of Aβ peptides.

Main (sole) request

Admission (Article 12(4) RPBA)

3. The amendment of claims 1 and 5 of the main request can be seen as a direct reaction to the objection of lack of clarity raised for the first time in the decision under appeal (see point 14.3.1). The same applies to the deletion of claims 6 to 8, 10 and 11 (see points 14.3.2 to 14.3.4 and 14.3.6). Also, the limitation of claim 8 (former claim 13) to "use for preventing or treating Alzheimer's disease" can be considered a reaction to an objection raised for the first time in the decision under appeal (see point 14.3.5). Since the applicants did not attend the oral proceedings before the examining division they did not have an opportunity to react earlier to these clarity objections.

4. Thus, the board sees no reason to hold the new main request inadmissible.

Amendments (Article 123(2) EPC)

5. The decision under appeal did not deal with the issue of added subject-matter. The board considers that the claims of the main request find basis throughout the application as filed (see e.g. original claim 1 for antibody fragments "capable of differentially recognizing a multi-dimensional conformation of one or more Aβ-derived diffusible ligands" as well as page 18, line 23 to page 19, line 6 for "fragments of an isolated antibody" and page 8, lines 16 to 20 for "Alzheimer's disease").

Clarity (Article 84 EPC)

6. The amendments carried out (see point 3 above) overcome all objections raised in relation to the issue of clarity in the decision under appeal. The claimed subject-matter is considered clear.

Priority (Article 87 EPC)

7. The board considers that the finding of the examining division in point 14.5 of the decision under appeal applies to the present claims, i.e. the subject-matter enjoys priority from the second priority document (14 February 2005) because the sequences defining the claimed antibody are not disclosed in the first priority document.

8. Document D3, which was published on 10 February 2005, is therefore state of the art pursuant to Article 54(2) EPC.

Novelty (Article 54 EPC)

9. The decision under appeal did not deal with the issue of novelty. However, from the discussion of the relevant state of the art with regard to inventive step it is evident that none of the cited documents were considered novelty destroying (see also point 18 below). This also applies to the presently claimed subject-matter.

Inventive step (Article 56 EPC)

Closest prior art

10. In accordance with established jurisprudence the closest prior art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (see Case Law of the Boards of Appeal of the European Patent Office, 9th edn., 2019, section I.D.3.1).

11. The purpose of the present invention is the provision of antibodies that differentially recognise a multi-dimensional conformation of one or more Aβ-derived diffusible ligands, also known as ADDLs or soluble oligomeric Aβ peptides (see page 3, lines 12 to 15 of the application; see point 2 above).

12. In the decision under appeal the examining division assessed inventive step starting from either document D11 or document D3 as the closest prior art document.

13. Document D11 deals with the "*Fractionation and characterization of oligomeric, protofibrillar and fibrillar forms of β-amyloidpeptide*" (see title). It makes reference to monoclonal antibody WO-2. Document D11, however, is silent about the capacity of this antibody to differentially recognise different Aβ isoforms and/or oligomers. This characteristic was only reported in the present application, which used antibody WO-2 for comparison (see Table 3). Document D11 concludes by saying that "*Further fractionation studies will be required to determine conclusively whether Aβ 1-42 polymerizes through identical, toxic, protofibrillar intermediates to those observed for the shorter Aβ 1-40 form*" (page 143, right column).

14. Hence, the purpose of document D11 is to improve fractionation methods to detect different polymeric forms of Aβ peptide. This purpose is different from the one underlying the present invention. Thus, document D11 is not suited as the closest prior art.

15. Document D3 is concerned with providing "*monoclonal antibodies that specifically bind to soluble, non-fibrillar oligomeric amyloid β protein assemblies proteolytically derived from the transmembrane amyloid precursor protein (APP) while not reacting with fibrillar amyloid β protein assemblies*" (see document D3, page 1, lines 12 to 14). It reports that "*oligomer-specific antibody (7A2) shows little recognition of fibrils by antigen/antibody blotting (FIG. 1) and ELISA (FIG. 2). By Western analysis of SDS-PAGE, 7A2 detects primarily dimer and trimer but no amyloid β protein monomers in unaggregated or oligomeric samples, and little immunoreactivity is detected in the fibril samples (FIG. 3)*" (see page 35, lines 21 to 25). Monoclonal antibody 7A2 (or MOAB-1) is neither

characterised by its CDR sequences nor was the respective hybridoma deposited.

16. The argument by the appellants that the antibody reported in document D3 was not publicly available and thus was not disclosed in an enabling manner is considered irrelevant in the context of establishing the closest prior art. Even if the specific antibody 7A2 was not available, document D3 provides a general teaching on how to obtain anti-ADDL antibodies. The further argument by the appellants that the antigenic preparation was not sufficiently described also cannot be agreed with because document D3 provides a detailed method for the generation of oligomeric immunogens for immunisation of mice (see document D3, Example 1, page 33) which is in fact very similar to the method used in the present application (see application, Example 1, pages 35 to 36).

17. In conclusion, document D3 is considered to represent the closest prior art because, as the present application, it provides monoclonal antibodies that differentially recognise soluble, non-fibrillar oligomeric amyloid β protein, i.e. ADDLs.

Difference and effect

18. The difference between the claimed antibodies and the antibodies generated according to the method of document D3 resides in the specific sequences of the CDRs as defined by SEQ ID NOs 49, 56, 64, 28, 36 and 48. These CDR sequences belong to a monoclonal antibody denoted "3B3".

19. In addition to its differential binding to ADDLs, monoclonal antibody 3B3 was shown in the application to

inhibit binding of ADDLs to primary hippocampal neurons (see Figure 1). In view of the common general knowledge that the six CDRs define the binding specificity of an antibody to its antigen, the board considers it plausible that antibodies carrying the CDRs as defined in the claims show, as antibody 3B3, the effect of inhibition of binding of ADDLs to primary hippocampal neurons.

20. It remains to be established whether this effect is an effect resulting from the structural difference between the claimed antibodies and the antibodies obtainable by the methods disclosed in the closest prior art document D3 or whether it might also have been achieved with those antibodies.

21. This question arises for the following reason.

21.1 As already observed in point 16 above, document D3 demonstrates how to obtain anti-ADDL antibodies. The comparison of binding of monoclonal antibody MOAB-1/7A2 to unaggregated, oligomeric, and fibrillar preparations of amyloid β proteins (see Figures 6 and 7: Aβ11-42 unaggregated, Aβ11-42 oligomers and Aβ11-42 fibrils) shows that the antibody binds preferentially to oligomers (see Example 7). However, the document does not provide any data in respect of the inhibition of binding of ADDLs to neurons.

21.2 In the decision under appeal the examining division came to the conclusion that inhibiting the binding of ADDLs to neurons was an inherent property of the antibodies of document D3 on the basis of the following reasoning. The examining division compared the ADDL-affinity data for antibodies 3B3 and WO-2 in Table 3 of the application and drew the conclusion that antibody

WO-2 - which was considered identical to the antibody of the same name used in document D11 - was even more discriminatory (i.e. had a higher affinity) for ADDL than antibody 3B3 (points 14.4.4 to 14.4.6 of the decision). This led the examining division to state that "*in the absence of evidence to the contrary this functional feature* [inhibition of ADDL binding to neurons] *is considered to represent an inherent feature of monoclonal antibody WO-2*" (point 14.4.6). The examining division then went on to find that "*mutatis mutandis*" this also applied to the antibodies disclosed in document D3 (point 14.5.1).

22. The board finds this reasoning of the examining division to be flawed for several reasons.

22.1 Firstly, as rightly observed by the appellants, the data in Table 3 of the application does not allow a direct comparison of the antibody affinities because each antibody was tested at a different antibody concentration.

22.2 Secondly, as evidenced by the present application, antibodies that differentiate between oligomeric and monomeric Aβ do not necessarily inhibit the binding of ADDLs to primary neurons. This is apparent from a comparison of Table 3 and Figure 1. While Table 3 shows that most antibodies analysed show differential binding (see e.g. K_D for antibody 3B3, 20C2, 2A10, 2B4, 2D6, 5F10, 4E2 comparing ADDL and Aβ1-40), Figure 1 reveals that only few of those differentially binding antibodies also inhibit binding of ADDLs to hippocampal neurons (e.g. 3B3, 20C2). Some antibodies which show differential binding do not inhibit binding of ADDLs to neurons (e.g. 4E2, 2B4, 2D6, 5F10).

22.3 Thirdly, none of the antibodies disclosed in document D11 or document D3 have been structurally characterised, i.e. it is not known whether the antibodies have a similar or even identical structure. Therefore, even if it was accepted for the sake of argument that the antibody WO-2 had the ability to inhibit the binding of ADDLs to primary neurons, it is not possible to predict on the basis of structure whether the antibodies of document D3 also have this characteristic.

23. Hence, on the evidence before it, the board finds the conclusion of the examining division, that antibodies obtainable by the methods disclosed in document D3 have the inherent property of inhibiting the binding of ADDLs to neurons, not correct. In fact, in the board's view, to determine whether an antibody inhibits binding of ADDLs to primary hippocampal neurons a dedicated assay is required.

24. Consequently, the inhibition of ADDL-binding to hippocampal neurons is an effect resulting from the structural difference of the claimed antibodies to the antibodies obtainable by the method disclosed in document D3.

Technical problem and its solution

25. The objective technical problem can be formulated as the provision of anti-ADDL antibodies which inhibit the binding of ADDLs to primary hippocampal neurons.

26. The problem can be considered as solved by providing the antibodies according to claim 1 (see also point 19 above).

Obviousness

27. The examining division reasoned that the skilled person wishing to provide alternative antibodies to those already disclosed, for example the antibody WO-2, would have done so by "*routine experimentation*" (see point 14.4.9 of the decision). The board does not agree with this conclusion for the following reasons.

28. The closest prior art document D3 is silent about an inhibitory effect of the produced antibodies on the binding of ADDLs to neurons and also does not provide any method to obtain antibodies showing such effect. Therefore, the skilled person would not arrive at the antibodies as claimed from the disclosure of document D3 alone.

29. The skilled person might have turned to document D1 for further teaching because the polyclonal antibodies reported in this were shown to differentiate between Aβ monomers and soluble oligomers (ADDLs) (see Figures 19 and 20) and to have some effect on ADDL toxicity (see Figure 24).

30. Document D1 discloses polyclonal antibodies (M93 and M94) which were obtained by immunisation of rabbits with pre-formed synthetic ADDLs. Polyclonal antibody M94 reduced toxicity of ADDLs toward PC12 cells in an reduction assay of the dye MTT (see Example 22, pages 77 to 78 and Figure 24). This assay, however, measures toxicity (see Example 77 and 78 and Figure 24), but not binding of ADDLs, and uses a different cell type (PC12 neuron-like cells) to the present application (hippocampal neurons).

31. Document D1 states that: "*ADDLs act through a particular cell surface receptor, and that early events mediated by the ADDLs (i.e., events prior to cell killing) can be advantageously controlled (e.g., for treatment or research) by compounds that block formation and activity (e.g., including receptor binding) of the ADDLs.*" (see page 25, lines 26 to 30).

32. This statement might have indicated to the skilled person that blocking receptor binding of ADDLs might be advantageous for treatment. However, in view of the limited information from the MTT reduction assay the skilled person would neither have derived from the disclosure in document D1 that the disclosed polyclonal antibodies were indeed able to inhibit ADDL-binding to neurons nor that providing such polyclonal antibodies would be possible at all.

33. This was even more so with respect to monoclonal antibodies as none of those tested in document D1 were able to discriminate between monomers and oligomers in the first place (see page 15, lines 2 to 4): "*These commercial monoclonals also recognized epitopes common to several states of Aβ assembly, including monomers and dimers, which were not detected by anti-ADDL antibodies.*"

34. In conclusion, none of the documents cited by the examining division disclose the inhibition of ADDL binding to neurons generally or as a feature of the disclosed antibodies, nor do they disclose methods for arriving at monoclonal antibodies inhibiting ADDL binding to neurons.

35. Thus, in summary, the skilled person would not have arrived at antibodies capable of inhibiting binding of

ADDLs to primary hippocampal neurons, in particular not by routine experimentation (see points 27 to 29 above). Consequently, the subject-matter of claim 1 involves an inventive step.

36. As the remaining claims 2 to 8 refer to and thus contain the subject-matter of claim 1, they also involve an inventive step.

Sufficiency of disclosure (Article 83 EPC)

37. The decision under appeal did not deal with the issue of sufficiency of disclosure.

38. Claim 1 is directed to a product, namely an antibody defined by its six CDRs. The board considers that the skilled person at the date of filing was able to produce antibodies carrying the six CDRs as defined in the claim without undue burden on the basis of the disclosure in the application and common general knowledge.

39. Claim 8 is a claim to a second medical use in the format according to Article 54(5) EPC. With regard to this category of claim 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, 9th edn., 2019, section II.C.7.2 and decision T 609/02, reasons 9).

40. In the case at hand, the question to be answered is whether or not either the application discloses that anti-ADDL antibodies as defined in the claims would be suitable for the treatment or prevention of Alzheimer's disease (i.e. for the therapeutic use defined in the claim), or the skilled person at the priority date would have known this.

41. The present application discloses several *in vitro* studies to characterise monoclonal antibody 3B3. The experiments show in particular that antibody 3B3 binds preferentially to ADDL while having little specificity for Aβ monomers (see Table 3). This is relevant because in the brains of Alzheimer's patients monomer Aβ peptides constitute a high background level that might prevent therapeutic use. Furthermore, the application shows that antibody 3B3 is capable of abating the binding of ADDLs to hippocampal neurons which are critical for learning and memory.

42. Several years before the filing of the present application the review article D14 indicated that "*oligomers correlate better than fibrils with neurodegeneration*" (page 221, last heading) based on findings that "*AD brains contain oligomeric Aβ*" (page 222, sentence bridging left and right columns) and that "*complex mixtures of water-soluble oligomers, detectable in normal brain, were 12-fold elevated in individuals with AD*" (page 222, right column, first paragraph). The same article also considered "*that Aβ*

antibodies could be therapeutic" (page 222, right column, end of first paragraph) and "*therapeutic antibodies designed to target oligomers could ultimately intervene early in AD*" (page 223, last sentence).

43. The board considers that the common general knowledge at the time of filing (see document D14) and the experiments in the patent application demonstrate the suitability of the antibody 3B3 - and the further antibodies encompassed by claim 1 (see point 19 above) - to prevent or treat Alzheimer's disease.

44. For the sake of information only, the board observes that the appellants provided post-published evidence to support a preventive or therapeutic effect of the antibodies referred to in claim 8. Declaration D23 contains as an annex copies of three posters shown at the Society for Neuroscience 2014 Annual Meeting. The board considers that the posters show results that support *in vivo* effects of the antibody 3B3 in mice.

45. The disclosure of the invention fulfils the requirements of Article 83 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 8 of the main request, filed with the statement of grounds of appeal, and a description to be adapted thereto.

The Registrar: The Chair:

I. Aperribay G. Alt

Decision electronically authenticated