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Datasheet for the decision of 19 March 2015

Case Number: T 2223/10 - 3.3.04

Application Number: 02755765.1

Publication Number: 1420032

IPC: C07K16/18, C12N5/16, C12N15/13, C12N15/85, C12P21/08, A61K39/395

Language of the proceedings: EN

Title of invention:
Antibody recognizing GM1 ganglioside-bound amyloid beta-protein and DNA encoding the antibody

Patent Proprietor:
Medical & Biological Laboratories Co., Ltd.
Japan as represented by The Director of Chubu National Hospital
Yanagisawa, Katsuhiko

Opponent:
Glaxo Group Limited

Headword:
Antibody binding GM1 ganglioside-bound amyloid beta-protein/ MEDICAL & BIOLOGICAL LABORATORIES

Relevant legal provisions:
EPC Art. 54, 56, 83
EPC R. 99(2)
RPBA Art. 12(1), 12(4)

Keyword:
Admissibility of appeal - (yes)
Late-filed evidence - admitted (yes)
Novelty - (yes)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

Decisions cited:
T 0015/01

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

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Case Number: T 2223/10 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 19 March 2015

Appellant: (Opponent)	Glaxo Group Limited Glaxo Wellcome House, Berkeley Avenue Greenford, Middlesex UB6 0NN (GB)
Representative:	Harrison, Anna GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Respondent: (Patent Proprietor 1)	Medical & Biological Laboratories Co., Ltd. Marunouchi Bldg. 5F, Sumitomo-shoji, 5-10, Marunouchi 3-chome, Naka-ku Nagoya-shi, Aichi 460-0002 (JP)
Respondent: (Patent Proprietor 2)	Japan as represented by The Director of Chubu National Hospital 36-3 Gengo, Marioka-cho Obu-shi, Aichi 474-0031 (JP)
Respondent: (Patent Proprietor 3)	Yanagisawa, Katsuhiko 36-3 Gengo, Marioka-cho Obu-shi, Aichi 474-0031 (JP)
Representative:	Steinecke, Peter Müller Fottner Steinecke Rechtsanwalts- und Patentanwaltspartnerschaft mbB Römerstrasse 16 b 52428 Jülich (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 14 September 2010 concerning maintenance of the European Patent No. 1420032 in amended form.**

Composition of the Board:

Chairwoman G. Alt
Members: M. Montrone
K. Garnett

Summary of Facts and Submissions

I. The appeal was lodged by the opponent (hereinafter "appellant") against the decision of the opposition division to maintain European patent No. 1 420 032 in amended form. The patent has the title "*Antibody recognizing GM1 ganglioside-bound amyloid beta-protein and DNA encoding the antibody*".

II. The patent was opposed under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and inventive step (Article 56 EPC), and under Articles 100(b) and (c) EPC.

III. In its decision the opposition division held that the subject-matter of the first auxiliary request - which is identical to the main request in the present appeal proceedings - complied with the requirements of the EPC.

IV. With its statement of grounds of appeal the appellant submitted two new documents, a declaration D28 and a scientific publication D29. It submitted arguments why the subject-matter of the claims maintained by the opposition division lacked novelty - referring mainly to documents D5 and D28, lacked an inventive step in view of document D29 as closest prior art and was not sufficiently disclosed (the respective documents are identified in section VIII, below).

V. The patent proprietors (hereafter "respondents") replied to the statement of grounds of appeal and requested that the appeal be dismissed.

Claim 1 of the main request reads as follows:

"1. An antibody having an activity of recognizing GM1 ganglioside-bound amyloid β-protein and inhibiting the formation of amyloid fibrils by amyloid β, the antibody being a recombinant IgG, Fab, Fab', $F(ab')_2$, scFv or dsFv comprising a heavy chain variable region and/or a light chain variable region, wherein

(i) the heavy chain variable region comprises at least one region of the regions described in a), b) and c):

a) a first region consisting of an amino acid sequence of SEQ ID NO: 1, or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 1;
b) a second region consisting of an amino acid sequence of SEQ ID NO: 2 or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 2; and
c) a third region consisting of an amino acid sequence of SEQ ID NO: 3 or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 3;

(ii) the light chain variable region comprises at least one region of the regions described in d), e) and f):

d) a fourth region consisting of an amino acid sequence of SEQ ID NO: 4, or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 4;
e) a fifth region consisting of an amino acid sequence of SEQ ID NO: 5, or the amino acid

sequence resulted from a partial alteration of SEQ ID NO: 5; and

f) a sixth region consisting of an amino acid sequence of SEQ ID NO: 6, or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 6;

(iii) the heavy chain variable region comprises complementarity determining regions (CDRs) described in g), h) and i), and the light chain variable region comprises CDRs described in j), k) and l);

g) CDR 1 consisting of an amino acid sequence of SEQ ID NO: 1, or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 1;

h) CDR 2 consisting of an amino acid sequence of SEQ ID NO: 2, or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 2;

i) CDR 3 consisting of an amino acid sequence of SEQ ID NO: 3, or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 3;

j) CDR 1 consisting of an amino acid sequence of SEQ ID NO: 4, or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 4;

k) CDR 2 consisting of an amino acid sequence of SEQ ID NO: 5, or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 5; and

l) CDR 3 consisting of an amino acid sequence of SEQ ID NO: 6, or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 6;

(iv) the heavy chain variable region comprises an amino acid sequence of SEQ ID NO: 7, or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 7;

(v) the light chain variable region comprises an amino acid sequence of SEQ ID NO: 8, or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 8; or

(vi) the heavy chain variable region comprises an amino acid sequence of SEQ ID NO: 7, or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 7; and the light chain variable region comprises an amino acid sequence of SEQ ID NO: 8, or the amino acid sequence resulted from a partial alteration of SEQ ID NO: 8."

VI. In response to the summons to attend oral proceedings the respondents filed auxiliary requests 1 to 3.

VII. Oral proceedings before the board took place on 19 March 2015 in the presence of both parties. During the oral proceedings the respondents raised an objection that the appeal should be held inadmissible and withdrew their auxiliary requests. At the end of the oral proceedings the chairwoman announced the decision of the board.

VIII. The following documents are cited in this decision:

D2: Yanagisawa et al., FEBS Letters 420: 43-46, (1997)

D5: WO 02/46237

D21: Declaration by Dr. Yanagisawa of 13 July 2006

D25: Declaration by Volker Germaschewski filed by the appellant with its letter of 15 April 2010

D26: Legleiter et al., JMB 335: 997-1006, (2004)

D27: Solomon et al., PNAS 93: 452-455, (1996)

D28: Declaration by Susannah Ford of 12 January 2011

D29: Kakio et al., JBC 276: 24985-24990, (2001)

IX. The appellant's arguments, insofar as far as they are relevant for the present decision, may be summarised as follows:

Admissibility of the appeal

The objection against the admissibility of the appellant's appeal was raised by the respondents for the first time during the oral proceedings. It was thus a new and procedurally late objection and should be rejected by the board as such. In any event, the statement of grounds of appeal provided sufficient arguments as to why the impugned decision was incorrect.

Non-admissibility of declaration D28 and document D29

The declaration D28 was essentially identical to the declaration D25 which had not been admitted into the proceedings by the opposition division. The reason for not admitting it was mainly that the 3D6 antibody of declaration D25 was not identical to the one of document D5. The murine 3D6 antibody of the declaration D28 overcame this deficiency because it was structurally identical to the murine 3D6 antibody of document D5 and thus suitable to establish that the murine 3D6 antibody possessed the functional properties of the antibody of claim 1. The declaration D28 was

thus highly relevant for the assessment of novelty and should be admitted.

The appellant wished to rely on document D29 not as representing the closest prior art but only in combination with document D2. It was not a new document since the patent in suit already referred to this document in the background art part. The respondent was thus familiar with its disclosure and it was *prima facie* relevant because it explicitly identified GM1 ganglioside-bound amyloid β-protein (GM1/Aβ) as a therapeutic target for the treatment of Alzheimer's disease (AD).

Novelty (Article 54 EPC)

The murine 3D6 antibody of document D5, a document of the state of the art according to Article 54(3) EPC, had all the functional properties of the antibody of claim 1, as established by the experimental data in the declaration D28 using the identical antibody. Moreover, the CDR H1 sequences of the 3D6 antibody and the antibody of claim 1 (see SEQ ID NO: 1) shared 40% sequence identity. The murine 3D6 antibody of document D5 was thus novelty destroying for the antibody of claim 1.

Sufficiency of disclosure (Articles 100(b) and 83 EPC)

The patent in suit lacked sufficient information to allow the skilled person to put all embodiments encompassed by claim 1 into practice over substantially the whole breadth of the claim. This was due to the broad functional and structural definitions in claim 1, in particular with regard to the terms "recognising" and "partial alteration" and the functional feature

"inhibiting the formation of amyloid fibrils". These features were also unclear as regards their meaning.

Inventive step (Article 56 EPC)

The anti-GM1/Aβ antibody of document D2 was considered to represent the closest prior art. The subject-matter of claim 1 differed therefrom by referring to an anti-GM1/Aβ antibody which inhibited the Aβ-dependent amyloid fibril formation. The technical problem to be solved was the provision of an anti-GM1/Aβ antibody effective in the treatment of AD.

Claim 1 lacked the feature "does not recognise soluble Aβ". The claim thus related to antibodies that bound to soluble Aβ, a form of Aβ that was not involved in fibril formation. These antibodies had therefore to be considered as not being effective in the treatment of AD. This view was supported by the fact that the patent disclosed only one effective antibody that did not bind to soluble Aβ. Hence, claim 1 encompassed a substantial number of embodiments that did not solve the problem identified above. Furthermore, the "non-binding to soluble Aβ" was considered to form an essential part of the superior properties of the specific antibody of the invention, as declared by the inventor (see declaration D21, points 6 and 10).

The subject-matter of claim 1 was obvious in the light of the disclosure of document D2 alone since this document already suggested GM1/Aβ as a target in the treatment of AD and thus provided a motivation for the skilled person to prepare anti-GM1/Aβ antibodies interfering with fibril formation.

The subject-matter of claim 1 was also obvious in view of the teaching of document D2 in combination with that of document D29 which explicitly identified GM1/Aβ as a seed in the polymerisation of amyloid fibrils.

Also, the combination of the teachings of document D2 and document D27 suggested the antibody of claim 1. In particular, the assays disclosed in document D27 allowed the screening and identification of antibodies inhibiting amyloid fibril formation.

X. The respondents' arguments, insofar as far as they are relevant for the present decision, may be summarised as follows:

Admissibility of the appeal

The appeal should be held inadmissible according to Article 108 EPC and Rule 99(2) EPC because the statement of grounds of appeal did not provide reasons why the conclusions of the opposition division with regard to any of the grounds of opposition were considered incorrect. In addition, it contained arguments against the decision based on documents submitted for the first time with the grounds of appeal. Thus lack of novelty over document D5 was alleged relying on newly filed declaration D28 and lack of inventive step was alleged taking newly filed document D29 as closest prior art. This amounted into a fresh case and these arguments could not be used to attack the correctness of the decision.

Non-admissibility of declaration D28 and document D29

The board should not admit the declaration D28 and the document D29 into the proceedings having regard to

Rule 76(2)(c) EPC.

The declaration D28 was *prima facie* not relevant since the murine 3D6 antibody used there had a different constant IgG2b region and was therefore not identical to the murine 3D6 antibody of document D5. The murine 3D6 antibody of document D5 also did not enjoy a valid priority, even if the two antibodies were identical.

The document D29 could have been filed during the first instance proceedings and should therefore not be admitted according to Article 12(4) RPBA. It was also *prima facie* not relevant since GM1/Aβ as a therapeutic target in the treatment of AD was already implicit from document D2.

Novelty (Article 54 EPC)

The document D5 neither disclosed that the murine 3D6 antibody bound GM1/Aβ nor that it inhibited the Aβ mediated formation of amyloid fibrils. These properties of the murine 3D6 were also not established by the experiments disclosed in the declaration D28 since the antibody used therein, although being denoted "3D6", was in fact structurally different from the murine 3D6 antibody of document D5. The two antibodies differed in their constant IgG2b regions and it could not be excluded that this had an influence on the functional properties of the antibody. Moreover, it was contested that the murine 3D6 antibody of document D5 enjoyed a valid priority.

Sufficiency of disclosure (Articles 100(b) and 83 EPC)

The features "recognising" and "inhibiting the formation of amyloid fibrils" and "partial alteration"

of claim 1 had a clear meaning in the art. The objection raised by the appellant was rather an objection of lack of clarity under Article 84 EPC which however was not a ground of opposition. The patent in suit disclosed sufficient information for the person skilled in the art to reproduce the invention claimed and the appellant had not submitted any evidence to the contrary.

Inventive step (Article 56 EPC)

The anti-GM1/Aβ antibody of document D2 represented the closest prior art. However, a therapeutic application for this antibody was not disclosed. There was also no further prior art document that suggested a therapeutic use of an antibody directed against GM1/Aβ. In fact the available prior art antibodies disclosed in document D27 as evidenced by the post-published document D26 were all directed against soluble Aβ for preventing Aβ-dependent fibril formation in the treatment of AD.

XI. The appellant requested that the decision under appeal be set aside and the patent be revoked.

The respondents requested that the appeal be held inadmissible, alternatively that it be dismissed.

Reasons for the Decision

Admissibility of the appeal

1. According to established jurisprudence of the Boards of Appeal, the admissibility of an appeal may be assessed *ex officio* at any stage of the appeal proceedings (cf. decision T 15/01, OJ EPO 2006, 153; Reasons, point 1), and accordingly also during oral proceedings. The

appellant's procedural objection against the late introduction of this point by the respondents cannot therefore be accepted.

2. The issue for the board is whether the statement setting out the grounds of appeal complies with Rule 99(2) EPC, which stipulates that in its statement the appellant shall indicate the reasons for setting aside the impugned decision and the facts and evidence on which the appeal is based. In line with established jurisprudence of the Boards of Appeal this is understood to mean that the arguments have to be clearly and concisely presented to enable the board and the respondent to understand immediately why the decision under appeal is alleged to be incorrect, and on what facts the appellant bases its arguments. In this respect it is enough if the appellant presents sufficient reasons for at least one ground why the decision under appeal should be set aside (Case Law of the Boards of Appeal, 7th edition 2013, section IV.E.2.6.3).

3. In the oral proceedings before the opposition division, the subject matter of the proprietor’s then main request was attacked under the headings of added subject matter (Article 123(2) EPC), lack of novelty (both Articles 54(2) and 54(3) EPC), lack of inventive step (Article 56 EPC) and insufficiency (Article 83 EPC).

The opposition division held that the subject matter satisfied the requirements of Article 123(2) EPC, was novel and inventive, but insufficiently disclosed. As regards the novelty attack, the opposition division *inter alia* held that the subject-matter was novel over the antibody 3D6 of document D5 mainly because there

was (a) no explicit disclosure in this document that 3D6 recognised specifically amyloid β-protein (Aβ) bound to GM1 ganglioside (GM1/Aβ) and inhibited amyloid fibril formation and (b) there was no other evidence available that unambiguously disclosed that the 3D6 antibody inherently possessed these two properties (see point 2.3 of the decision).

In this context, the opponent had filed declaration D25 in an attempt to prove that the 3D6 antibody did indeed inherently possess these two properties. However, it was not admitted into the proceedings because the opposition division held that the 3D6 antibody of declaration D25 was not identical to the one of document D5, and thus lacked *prima facie* relevance (see point 1.2.2 of the decision).

4. As regards the proprietor's first auxiliary request to maintain the patent in a more limited form, the only outstanding issue was then sufficiency, as to which the opposition division held that the requirements of Article 83 EPC were satisfied.

5. The appellant in its statement of grounds of appeal attacked the claims as maintained by the opposition division, arguing lack of novelty, lack of inventive step and insufficiency of disclosure. As regards lack of novelty, the attack was based on document D5, reliance now being partly placed on declaration D28 to establish that the 3D6 antibody of document D5 inherently had the properties of binding GM1/Aβ and inhibiting amyloid fibril formation.

It is readily apparent to the reader of the grounds of appeal that the declaration D28 was intended to overcome the problem with the declaration D25 (see the

passage bridging pages 13 and 14 of the grounds of appeal). This is indeed how the respondents understood the matter (see the passage bridging pages 1 and 2 of their reply, dated 12 May 2011). Both declarations D25 and D28 report on the murine antibody 3D6 of document D5 and aim at assessing the properties of this antibody to bind to GM1/Aβ and to inhibit amyloid fibril formation. The murine 3D6 antibody of declaration D28 is asserted to be identical to the murine 3D6 antibody of document D5. Although the grounds of appeal do not refer explicitly to the reasons for the opposition division's decision, the argument about novelty is apparent to the reader, and was also apparent to the respondents (see above).

It was essentially the same argument as that which it had made before the opposition division, bolstered now by what was alleged to be shown by declaration D28. The reader gathers from this part of the grounds of appeal that the appellant is arguing that the opposition division was wrong about this issue. The fact that the argument relies partly on a new piece of evidence is immaterial for the present purposes, since this point relates to the admissibility of the evidence (see below). In the board's view, therefore, the reasons and evidence presented by the appellant were a direct response to the reasoning in the part of the decision on lack of novelty, and challenged its correctness.

6. Since the grounds of appeal therefore give adequate reasons why at least one ground for the decision was said to be wrong, it is not necessary to say anything about the respondents' argument concerning the new inventive step attack in the grounds of appeal based on document D29.

7. The appeal is therefore admissible.

Non-admissibility of declaration D28 and document D29

8. The declaration D28 and document D29 were filed by the appellant for the first time with its statement of grounds of appeal. According to the Rules of Procedure of the Boards of Appeal they are therefore part of the appeal proceedings (see Articles 12(1) and (4) RPBA). The respondents requested that both documents be not admitted into the proceedings, relying on Rule 76(2)(c) EPC. However, Rule 76(2)(c) EPC is not an automatic bar to the filing of new documents by an opponent after the expiry of the 9-month opposition period. For present purposes what is relevant is Article 12(4) RPBA, which refers to the power of the Boards of Appeal to hold inadmissible, i.e., exclude, evidence filed for the first time with the statement of grounds of appeal and which could have been filed during the first instance proceedings.

9. The declaration D28 discloses a murine 3D6 antibody which is allegedly structurally identical to the murine 3D6 antibody of document D5 and seeks to overcome the objection against the declaration D25 upheld by the opposition division during the oral proceedings (see point 1.2.2 of the decision). The appellant could thus not reasonably have filed the declaration D28 earlier than with its statement of grounds of appeal.

10. The respondents also argued, first, that the declaration D28 should not be admitted because it was *prima facie* not relevant since the murine 3D6 antibody used there was not identical to the murine 3D6 antibody of document D5. Second, even if it was identical, the

murine 3D6 antibody of document D5 did not enjoy a valid priority. However, the declaration D28 seeks to establish that the murine 3D6 antibody of the document D5 inherently has the property to bind GM1/Aβ and to inhibit amyloid fibril formation, i.e. two functional properties which are referred to in claim 1, and is therefore *prima facie* relevant. Whether the respondents' two points are valid belongs to the discussion on the substantive appeal (see points 16 and 17, below), and not to the issue of admissibility.

11. Therefore the board decided not to exclude the declaration D28 from the proceedings pursuant to Article 12(4) RPBA.

12. The document D29 was cited for the first time in the grounds of appeal as part of a new inventive step attack, according to which it was said to represent the closest prior art. However, during the oral proceedings before the board the appellant stated that it no longer relied on this line of attack but rather that it would use the document D29 only in combination with document D2, D2 now being taken as the closest prior art. The document D2 had also been taken as the closest prior art by the opposition division in its decision. This change of case (from an attack based on document D29 as closest prior art to one based on document D2) was not as such objected to by the respondents.

13. The document D29, which was in fact cited in the patent as background art (see paragraph [0007]), is a scientific report of the inventor and disclosed for the first time that GM1/Aβ forms amyloid fibrils via a seeded polymerisation and that this "seed" could be a target for treating Alzheimer's disease (AD). The appellant's change of case and the reliance on document

D29 did not raise new issues which either the board or the respondents could not deal with without an adjournment of the oral proceedings. The document D29 is also technically *prima facie* relevant because of its explicit disclosure of GM1/Aβ as a therapeutic target in the treatment of AD (see page 24989, column 2, last paragraph). The board therefore decided not to exclude document D29 from the proceedings pursuant to Article 12(4) RPBA.

Novelty (Article 54 EPC)

14. Document D5 is a document according to Article 54(3) EPC disclosing the mouse monoclonal antibody 3D6. It neither discloses that the murine 3D6 antibody binds GM1/Aβ nor that this antibody inhibits the Aβ mediated formation of amyloid fibrils, i.e. the two functional properties recited in claim 1.

15. The declaration D28 is intended to establish that the 3D6 antibody disclosed in document D5 has these two properties. It reports that a mouse antibody denoted as "3D6" is a recombinant antibody having the variable light and heavy chains defined by SEQ ID NOs: 2 and 4 of document D5 and a constant region of the IgG2b isotype as disclosed in table 7 of document D5 (see page 2, point 7) which allegedly renders the antibody identical to the mouse 3D6 antibody of document D5.

The document D5, however, does not disclose the sequence information for the IgG2b constant region of the mouse 3D6 antibody and this information is likewise lacking from the declaration D28. Accordingly, the complete sequence of the mouse 3D6 antibody of document

D5 and that of the denoted "3D6" antibody of the declaration D28 is not disclosed by these documents.

16. It is therefore not apparent whether the mouse 3D6 antibody of document D5 and the denoted "3D6" antibody of the declaration D28 are identical. The experimental evidence of document D28 is thus not appropriate to establish that the murine 3D6 antibody of document D5 has the two functional properties recited in claim 1.

17. The board cannot therefore conclude that the 3D6 antibody of document D5 falls under the subject-matter of claim 1. As a consequence thereof the question about the validity of the priority of the murine 3D6 antibody of document D5 has no bearing for the assessment of novelty and the board therefore does not decide on this issue.

18. The subject-matter of claim 1 is thus novel and complies with the requirements of Article 54 EPC.

Sufficiency of disclosure (Articles 100(b) and 83 EPC)

19. Claim 1 refers to an antibody that recognizes GM1/Aβ, inhibits the formation of amyloid fibrils by Aβ and is further characterised by amino acid sequences, including partial alterations thereof.

20. The description of the patent in suit discloses in paragraphs [0006], [0016] and [0074] a reference to document D2 which informs the skilled person about the source for isolating GM1/Aβ and a suitable immunisation and hybridoma protocol for obtaining further anti-GM1/Aβ antibodies according to the invention (see document D2, page 43, column 2, points 2.2 and 2.3). The patent

also discloses screening assays to isolate antibodies binding to GM1/Aβ (see [0052] and [0053]) and assays assessing the isolated antibodies ability to prevent Aβ amyloid fibril formation (see [0057] to [0059]). The patent further discloses the protein and nucleic acid sequences of the antibody "4396c" having the functional properties and structural characteristics of the antibody of claim 1 (see figures 1, 2, 5 and 6).

In view of these passages, the board considers that the description of the patent in suit discloses sufficient information for the skilled person to obtain further anti-GM1/Aβ antibodies having the functional and structural characteristics of claim 1, in particular antibodies that "recognise" GM1/Aβ and "inhibit the formation of amyloid fibrils". The disclosure of the nucleic and amino acid sequence of the "4396c" antibody moreover enables the skilled person to alter its sequence by standard mutational processes.

21. The board therefore disagrees with the appellant's objection that the functional and structural features in present claim 1, namely "recognising", "inhibiting the formation of amyloid fibrils" and "partial alteration" are not sufficiently disclosed. They are also considered to be standard terms in the antibody field. The appellant's further objection that the terms are unclear since the skilled person cannot determine whether an antibody falls within the range of claim 1 is in reality an objection of lack of clarity Article 84 EPC. However, this lack of clarity does not arise out of an amendment made in claim 1 as granted (in which the objected features are already present) and is therefore not an allowable objection. It must therefore fail.

22. The subject-matter of claim 1 thus complies with the requirements of Article 83 EPC.

Inventive Step (Article 56 EPC)

Closest prior art

23. In assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the Boards of Appeal apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art.

The parties agree that the disclosure of document D2 represents the closest prior art and the board sees no reason to differ.

24. Document D2 reports on a study aimed at determining the immunoreactivity of Aβ bound to GM1 (GM1/Aβ) and soluble Aβ (see page 43, column 2, first paragraph). GM1/Aβ is isolated from the brain of AD patients and used as an antigen for the preparation of the antibody "4397". The antibody differentiates between bound and soluble Aβ which implies a structural transition of Aβ upon its binding to GM1 (see page 43, abstract and column 2, column 2, points 2.2 and 2.3). A structural change of Aβ in the process of binding GM1 was also detected by optical means (see page 46, column 1, lines 29 to 31). It is not known from document D2 whether the "4397" antibody inhibits Aβ-mediated amyloid fibril formation.

Technical problem and solution

25. Thus, the antibody of claim 1 differs from the "4397" antibody in that it prevents Aβ-mediated amyloid fibril formation. The deposition of amyloid fibrils in neurons is one of the features found in brains of AD patients (see paragraph [0003] of the patent). In view of the closest prior art antibody and in view of the effects achieved by the antibody of the present invention - the technical problem to be solved is formulated as the provision of an anti-GM1/Aβ antibody with therapeutic applicability.

26. The board is satisfied that this problem is solved by the antibody of claim 1, which binds to GM1/Aβ and prevents amyloid fibril formation by Aβ, in view of the experimental data of example 4 and figure 6A of the patent in suit.

27. The appellant argued that the antibody of claim 1 lacked the feature "does not recognise soluble Aβ". The antibody would therefore bind to soluble Aβ, which however, was not involved in amyloid fibril formation. Hence, a substantial number of embodiments of claim 1 were not suitable for the treatment of AD and therefore did not solve the technical problem defined in point 25 above.

28. The board notes that the appellant has not submitted any evidence for its assertion that the antibody of claim 1 lacking the feature "does not recognise soluble Aβ" is in fact unable to achieve the inhibition of amyloid fibril formation mediated by Aβ. There is also no evidence available to the board showing that soluble Aβ is not involved in amyloid fibril formation. On the

contrary, document D27 discloses that soluble Aβ forms amyloid fibrils (see figure 3).

Also the argument that the patent does not disclose a working example of an anti-GM1/Aβ antibody that inhibits amyloid fibril formation by binding to soluble Aβ does not support the appellant's case since there is no absolute requirement in the EPC for the presence of such an example.

The appellant further argued that the lacking feature constitutes an essential feature of claim 1 in the light of the declaration D21. However, the inventor refers in point 6 of the declaration to his understanding of the "*claims in the subject application*" involving "*recombinant anti-GM/Aβ-antibodies*" and their biological activity comprising, "*i.e. recognition of Aβ bound to lipid vesicles containing GM1 ganglioside but not soluble Aβ or GM1*". The board notes that none of the "claims of the application" in fact refer to anti-GM/Aβ-antibodies that do not bind soluble Aβ. The personal view of the inventor cannot therefore serve as a basis for concluding that claim 1 lacks an essential technical feature.

29. Consequently, in the absence of any convincing evidence that the inhibition of amyloid fibril formation cannot be achieved by the antibody of claim 1, the board has no doubt that the antibody has this property. Thus, the appellant's argument that the subject-matter of claim 1 encompasses a substantial number of non-working embodiments which do not solve the technical problem is not accepted by the board.

Obviousness

30. The question to be assessed is whether the skilled person, faced with the problem of providing an anti-GM1/Aβ antibody with a therapeutic applicability, would be motivated to do so when starting from the disclosure of document D2.

31. Document D2 discloses an anti-GM1/Aβ antibody that selectively binds to Aβ bound to GM1 but does not recognise soluble Aβ (see page 43, abstract). This antibody or antibodies with this property "*may be useful probes to gain new insight into the initial molecular mechanism of Aβ deposition, including the generation of GM1/Aβ, in the brains of subjects with AD*" (see document D2, page 46, column 1, lines 33 to 36). It further reports that "*GM1/Aβ accelerates the the rate of amyloid fibril formation*" (see page 46, column 1, lines 28 to 33). However, document D2 neither discloses that GM1/Aβ in fact triggers amyloid fibril formation by Aβ nor an anti-GM1/Aβ antibody that interferes with Aβ deposition or with the formation of Aβ-mediated amyloid fibrils, i.e. with any of the known molecular processes involved in the development of AD.

32. In the board's view, document D2 therefore contains no pointers for the skilled person to provide an anti-GM1/Aβ antibody with a therapeutic application. The subject-matter of claim 1 is therefore not obvious in the light of the teaching of document D2 alone.

33. Document D27 discloses that antibodies directed against aggregating epitopes of the soluble Aβ are able to inhibit the formation of Aβ amyloid fibrils (see abstract, figure 1 and page 454, column 1, last paragraph to column 2, second paragraph). However, it

neither discloses GM1/Aβ nor an antibody that recognises Aβ bound to GM1 or an antibody that is able to inhibit GM1/Aβ's seeding activity.

Moreover, Aβ bound to GM1 has a different secondary structure than soluble Aβ (see document D2, page 46, column 1, lines 29 to 31) and it is not known whether the processes resulting in amyloid fibril polymerisation starting from soluble Aβ are identical to the ones starting from GM1/Aβ.

34. Accordingly, in the board's view, the skilled person in view of the teaching of document D27 would be likely to turn to antibodies binding soluble Aβ rather than to antibodies directed against GM1/Aβ. The subject-matter of claim 1 is thus not obvious in the light of the teaching of document D27 in combination with document D2 as closest prior art either.

35. Document D29 is the only available prior art document that refers to GM1/Aβ as a "*seed*" in the accelerated polymerisation process of amyloid fibrils and thus identifies GM1/Aβ as a potential therapeutic target in the treatment of AD (see page 24985, abstract; page 24989, column 2, last paragraph). This document reports, however, primarily on a study wherein the role of cholesterol in cell membranes is analysed in enabling GM1 to form clusters or GM1-enriched microdomains that act as binding sites for native Aβ and the pathological implications of an altered cholesterol metabolism in the development of AD (see page 24985, column 2, second paragraph; page 24989, column 1, second paragraph to column 2, first paragraph).

The results presented in this document suggest that an increase in cholesterol in the cell membrane of neurons induces the formation of GM1/Aβ and that "*alterations in the content of cholesterol in neuronal membranes underlie the abnormal aggregation of Aβ in the AD brain*" (see page 24989, column 2, second paragraph).

The board takes further note that document D29 states, in its ultimate paragraph on page 24989, column 2: '*To generate a compound that specifically recognizes GM1/Aβ and inhibits its seeding ability, it will be necessary to clarify the molecular processes underlying alterations of the secondary structures of Aβ via binding to and accumulation in GM1 "clusters."*'.

This paragraph neither discloses nor suggests an antibody suitable for inhibiting GM1/Aβ's seeding ability. Hence, the skilled person would by the combination of the teaching of document D2 with D29 not automatically arrive at the subject-matter of claim 1. In the board's view, the skilled person would also in the light of the teaching of this paragraph not be motivated to provide a GM1/Aβ recognising antibody for a therapeutic application before the underlying processes of how Aβ binds to GM1 and how it accumulates in clusters were elucidated.

36. The appellant argued that the skilled person had a reasonable expectation of success in arriving at an antibody that specifically recognizes GM1/Aβ and interferes with its seeding activity in view of the teaching of documents D2 and D29.

37. According to the established jurisprudence of the Boards of Appeal the assessment of obviousness in the context of a reasonable expectation of success requires

that the skilled person would have followed an available teaching of the prior art which requires a scientific evaluation of the facts at hand to predict rationally the successful conclusion of such a project within acceptable time limits (see Case Law of the Boards of Appeal, 7th edition 2013, I.D.7.1).

38. In the case of a therapeutic agent interacting with a particular target this evaluation requires, according to the board's opinion, whether there are indications available in the prior art that an interference with the target has or will most probably have - since certainty is not required - a beneficial effect for the disease to be treated.

39. The board notes that the combined teaching of document D2 with that of D29 neither presents a model of how GM1/Aβ accelerates the process of amyloid fibril formation nor a concept providing the skilled person with an idea of how an antibody could interfere with GM1/Aβ to prevent the polymerisation process or Aβ's accumulation in GM1 cluster. Therefore document D29 does not provide facts concerning an antibody based GM1/Aβ interference. This document focuses on the importance of cholesterol in the "seeding" process, i.e. the initial binding of native Aβ to GM1 clusters (see point 34, above). In the board's view, the skilled person would therefore rather derive from document D29 that the control of cholesterol is a promising approach for the treatment of AD.

Hence, in the absence of any facts in document D29 regarding an anti-GM1/Aβ antibody and its effects on amyloid polymerisation, the skilled person is according to the board's view, unable to make a reasonable prediction about the outcome of a project focusing on

antibodies that specifically recognise GM1/Aβ to interfere with GM1/Aβ's seeding activity. Thus, the board cannot agree with the appellant that the skilled person would have had a reasonable expectation of success so as to arrive at the subject-matter of claim 1.

The subject-matter of claim 1 cannot therefore be considered obvious in the light of the combined teaching of documents D2 and D29.

40. Hence, the subject-matter of claim 1 involves an inventive step and complies with the requirements of Article 56 EPC. The same applies to the subject-matter of claims 2 to 16, which all depend on claim 1.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

D. Hampe G. Alt

Decision electronically authenticated