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Datasheet for the decision of 22 November 2010

Case Number: T 0386/08 - 3.3.04

Application Number: 01913081.4

Publication Number: 1257584

IPC: C07K 16/18

Language of the proceedings: EN

Title of invention:
Humanized antibodies that sequester amyloid beta peptide

Patentees:
Washington University St. Louis, et al.

Opponent:
Neuralab Ltd.

Headword:
Humanized antibodies to the amyloid beta peptide/WASHINGTON UNIVERSITY

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 114(2), 123(2)

Keyword:
"Main request - added matter (yes);
Auxiliary requst I - clarity (no);
Auxiliary request II - added matter, extension of scope (no); clarity, enablement, novelty, inventive step (yes)"

Decisions cited:
G 0001/03, T 0409/91, T 0435/91, T 0792/00, T 0397/02, T 1023/02, T 0601/05

Catchword:
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Case Number: T 0386/08 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 22 November 2010

Appellants I: (Patent Proprietors)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 20 December 2007 concerning maintenance of European patent No. 1257584 in amended form.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: G. Alt
R. Gramaglia

Summary of facts and submissions

I. Two appeals were lodged, one by the joint patent proprietors and one by the two joint opponents, against the decision of the opposition division by which it held that the European patent No. 1 257 584 could be maintained in amended form on the basis of the third auxiliary request.

II. The opposition division was of the opinion that the main request was not allowable since its claim 1, corresponding to claim 1 as granted, did not comply with the requirements of Article 100(c) EPC.

III. The claim 1 referred to above read:

"1. A humanized antibody, or fragment thereof, comprising:

a. a light chain comprising three light chain complementarity determining regions (CDRs) having the following amino acid sequences:

light chain CDR1:
[*sequence omitted*](SEQ ID NO:1); or
[*sequence omitted*](SEQ ID NO:15)

light chain CDR2:
[*sequence omitted*](SEQ ID NO:2)

and, light chain CDR3:
[*sequence omitted*](SEQ ID NO:3)

and a light chain framework sequence from a humanized immunoglobulin light chain; and

b. a heavy chain comprising three heavy chain CDRs having the following amino acid sequences:

heavy chain CDR1:
[*sequence omitted*](SEQ ID NO: 4)

heavy chain CDR2:
[*sequence omitted*](SEQ ID NO: 5); or
[*sequence omitted*](SEQ ID NO: 16)

and, heavy chain CDR3:
[*sequence omitted*](SEQ ID NO: 6)

and a heavy chain framework sequence from a humanized immunoglobulin heavy chain."

IV. The opposition division reasoned that none of the following features/subject-matter was derivable from the application as filed: (i) the sequences recited in claim 1 denoted as SEQ ID Nos. 15 and 16; (ii) the definition in claim 1 of the light/ heavy chain framework region as being "from a humanized immunoglobulin" heavy or light chain; (iii) humanized antibodies which were not characterized as specifically binding to an epitope contained within positions 13 to 28 of the Aβ polypeptide. The Aβ polypeptide is the peptide involved in conditions such as Alzheimer's disease or Down's syndrome.

V. The opposition division did not admit auxiliary requests 1 and 2, both filed during the oral

proceedings, into the proceedings because they were filed late, not filed in response to new objections from the opponents and not prima facie allowable due to a lack of clarity of the term "substantially homologous" to a native heavy/light chain framework.

VI. Claim 1 of the third auxiliary request, i.e. the request on which the opposition division eventually intended to maintain the patent, differed from claim 1 of the claims as granted and thus that of the main request dealt with by the opposition division in that (i) the term "humanized" in the definition of the framework sequences read "human", (ii) references to SEQ ID Nos. 15 and 16 were absent, and (iii) the feature "wherein the antibody or fragment specifically binds an epitope contained within position 13-28 of Aβ" was present.

VII. With their statement of the grounds of appeal the patent proprietors (hereinafter "the appellant-patentees") filed a new main request which differed from the third auxiliary request dealt with in the decision under appeal in that (i) the term "human" in the definition of the framework sequences read "humanized" and (ii) references to SEQ ID Nos. 15 and 16 were present. Furthermore, first and second auxiliary requests were filed which were the same as those filed, but not admitted, during the oral proceedings before the opposition division. A reference to SEQ ID Nos. 15 and 16 was absent from claim 1 of both of these requests.

VIII. With their reply to the opponents' statement of grounds of appeal, the appellant-patentees made further

requests: as a third auxiliary request that the opponents' appeal be dismissed and as fourth and fifth auxiliary requests that the patent be maintained on the basis of amended claims.

IX. The board informed the parties in a communication inter alia about its preliminary view that the sequences denoted as SEQ ID Nos. 15 and 16 were derivable from the application as filed.

X. With a letter dated 19 November 2010 the appellant-opponent I withdrew its opposition (opponent II will be referred to as the "appellant-opponent" hereinafter).

XI. Oral proceedings in appeal proceedings were held on 22 November 2010 at which the appellant-patentee and the appellant-opponent were represented.

XII. In reply to a question by the appellant-patentees and after hearing the parties' arguments thereon, the board announced that it considered that the sequences of the alternative complementary determining regions (CDRs) sequences in claim 1 of the main request having SEQ ID Nos. 15 and 16 were disclosed in the application as filed.

XIII. As a consequence the appellant-patentees withdrew their previously filed first and second auxiliary requests and filed new first and second auxiliary requests.

XIV. Claim 1 of the main and the new first and second auxiliary requests (hereinafter referred to as "Auxiliary requests I and II") read as follows:

Main request

"1. A humanized antibody, or fragment thereof, comprising:

a. a light chain comprising three light chain complementarity determining regions (CDRs) having the following amino acid sequences:

light chain CDR1:
[*sequence omitted*](SEQ ID NO:1); or
[*sequence omitted*](SEQ ID NO:15)

light chain CDR2:
[*sequence omitted*](SEQ ID NO:2)

and, light chain CDR3:
[*sequence omitted*](SEQ ID NO:3)

and a light chain framework sequence from a humanized immunoglobulin light chain; and

b. a heavy chain comprising three heavy chain CDRs having the following amino acid sequences:

heavy chain CDR1:
[*sequence omitted*](SEQ ID NO: 4)

heavy chain CDR2:
[*sequence omitted*](SEQ ID NO: 5); or
[*sequence omitted*](SEQ ID NO: 16)

and, heavy chain CDR3:
[*sequence omitted*](SEQ ID NO: 6)

and a heavy chain framework sequence from a humanized immunoglobulin heavy chain,

wherein the antibody or fragment specifically binds an epitope contained within positions 13-28 of Aβ."

Auxiliary request I differed from the main request in that in claim 1 the definition of the framework, i.e. the sentences after "(SEQ ID NO:3)" and "(SEQ ID NO:6)" read, respectively:

"and a light chain framework sequence substantially identical to a native human light chain framework";

"and a heavy chain framework sequence substantially identical to a native human heavy chain framework".

Auxiliary request II differed from the main request in that in claim 1 the light and heavy chain framework sequences are defined as being "from a human immunoglobulin" light or heavy chain.

XV. During the oral proceedings both parties explicitly referred to their written submissions in the context of the issues of novelty and inventive step.

XVI. The appellant-patentees finally requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request filed with the statement of grounds of appeal or one of auxiliary requests I and II filed at the oral proceedings, or one of the third or fourth auxiliary

requests, originally filed during the appeal proceedings as fourth and fifth auxiliary requests.

XVII. The appellant-opponent requested that the decision under appeal be set aside and that the patent be revoked.

XVIII. At the end of the oral proceedings the chairman announced the board's decision.

XIX. The following documents are cited in the present decision:

D5 Proceedings of the Natural Academy of Science USA, vol. 86, 1989, pages 10029-10033, Queen C. et al.

D7 Proceedings of the Natural Academy of Science USA, vol. 89, 1992, pages 4285-4289, Carter, P. et al.

D8 Cell, vol. 22, 1980, pages 197-207, Hieter, P.A. et al.

D9 The Journal of Biological Chemistry, vol. 257, no. 3, 1982, pages 1516-1522, Hieter, P.A. et al.

D11 The Journal of Experimental Medicine, vol. 188, no. 11, 1998, Matsuda, F. et al.

D18 Declaration of Dr. D. Gill dated 8 August 2007

D18B Methods, vol. 36, 2005, pages 69-83, Tsurushita, N. et al.

D19 Declaration of Dr. Tsurushita dated 6 September 2007

D21 The Journal of Immunology, vol. 166, 2001, pages 1748-1754, Landolfi, N. F. et al.

D27 Declaration of Dr. Barbour dated 12 November 2008

D31 Declaration of Dr. Demattos dated 8 May 2009

XX. The appellant-patentees' arguments in writing and during the oral proceedings, insofar as they were relevant to the present decision, may be summarized as follows:

Main request

Article 123(2) EPC

The skilled person would derive the sequences denoted as SEQ ID Nos. 15 and 16 from the disclosure on pages 8 and 9 of the application as filed.

In view of the application as filed the skilled person would not interpret the expressions in claim 1 "from a humanized immunoglobulin light chain" and "from a humanized immunoglobulin heavy chain" when used in the context of the definition of "a light chain framework sequence from a humanized immunoglobulin light chain" and "a heavy chain framework sequence from a humanized immunoglobulin heavy chain" as meaning that the light and heavy chain framework sequences of the claimed humanized antibody originated from a different "pre-humanized" antibody. Rather, in view of the disclosure

in the application as filed, the skilled person would understand that the definition simply meant that the light and heavy chain framework of the claimed humanized antibody **were** humanized. Hence, claim 1 did not contravene the requirements of Article 123(2) EPC.

Auxiliary request I

Article 84 EPC

The skilled person knew that in the context of the definition of the light or heavy chain framework sequence as being "substantially identical" to a native human light or heavy chain framework, the term "identical" referred to the identity of amino acids between the native human and the subsequent humanized framework sequence. Moreover, paragraph [0035] of the description helped to interpret the term "substantially". Thus, the expression "substantially identical" in claim 1 was clear and therefore the requirements of Article 84 EPC were fulfilled.

Auxiliary request II

Article 84 EPC

It was clear that in the context of the patent the definition of the light and heavy chain framework as being "from a human immunoglobulin light chain" and "from a human immunoglobulin heavy chain" had to be interpreted such that the framework sequence of the claimed humanized antibody "came from" or "originated from" a human immunoglobulin light or heavy chain. This interpretation also meant that the framework sequences

could be native, i.e. unmodified human framework sequences. This interpretation was in line with the definition of a humanized antibody given in paragraph [0034] of the patent.

Article 83 EPC

Case Law
Burden of proof

The patent disclosed a specific humanized version, Hu266, of the mouse antibody Mu266 and also many specific alternatives thereof. Therefore, the case was not comparable to cases underlying decisions T 792/00 and T 397/02 where not a single specific example of the claimed subject-matter was disclosed. Therefore also, it was the appellant-opponent who had the burden of proving that the invention could not be carried out.

Queen's technology

As stated by Dr Turushita in declaration D19, the sequence of the murine antibody Mu266 was not necessary for making antibodies with framework regions which were different from, i.e. which were not derived from, those of the specifically disclosed antibody Hu266.

Since the basic framework structure of the variable regions of antibodies was conserved among species, there was no reason why humanized antibodies could not be used as a template for making additional humanized antibodies according to Queen's technology.

Binding affinity and specificity

Based on the experiments set forth in Examples 15 and 17 of the patent there was no doubt that the engineered humanized antibody Hu266 and the original murine antibody had the same affinity to Aβ. Thus, there could be no concerns about loss of affinity/specificity that might occur when making a variant humanized antibody on the basis of the humanized antibody Hu266 disclosed in the patent.

Therefore, since it had good binding properties, the humanized antibody Hu266 could be used to search for other homologous human germ-line sequences that could be used as framework sequences. Doing so, the skilled person would have found, for example, the known VH3-07, VH3-74 and the VH3-23 human germ line sequences (for example disclosed in document D11) which, when coupled with the also known JH4 fragment, provided framework sequences that had greater than 90% sequence identity to the humanized antibody sequence of Hu266 and could therefore certainly be used to make additional functional humanized antibodies.

Backmutation

The patent disclosed the framework residues critical for the three-dimensional structure of the complementarity determining regions (CDRs) and how they were back-mutated. This knowledge could also be used in the context of framework regions different from that disclosed in the patent.

Site directed mutagenesis

Since the murine and the disclosed humanized antibody had the same binding affinity, the humanized antibody could also serve as a guide in preparing variants by site-directed mutagenesis. On the basis of common general knowledge the skilled person knew which parts of the framework of an antibody might or might not be important for antigen binding. Thus, there was not so much variation possible as suggested by the appellant-opponent.

Direct CDR-grafting

Antibodies with alternative frameworks could be made by grafting the claimed CDRs directly, i.e. without sequence identity-based pre-selection, onto other known human frameworks, the grafting technology being that practised for a long time by Winter and colleagues and referred to, for example, in document D5.

Articles 54 and 56 EPC

In contrast to the appellant-opponent's view, claim 1 could not be interpreted as relating to fragments of humanized antibodies lacking the expressly recited CDR sequences, in particular it could not be interpreted to relate to fragments derived from only the constant region of human antibodies. Therefore, none of the disclosures in documents D8 or D9 destroyed the novelty of the subject-matter of claim 1.

Since the appellant-opponent's interpretation of claim 1 was wrong, an argument as to lack of inventive step based on this interpretation could not succeed. Therefore, all embodiments of claim 1 had to be considered as solving the problem underlying the invention, i.e. they were capable of binding and sequestering the soluble Aβ polypeptide.

The disclosure in document D21 of two antibodies with a lack of correlation between affinity and biological function could not imply that such a correlation was also lacking in the case of the Mu266 - Hu266 antibody pair. Moreover, document D31 demonstrated that both Hu266 (called LA300A in that document) and Mu266 increased plasma Aβ levels with essentially equal potency, i.e. Hu266 had the same biological properties as Mu266. Thus, it had to be concluded that the problem underlying claims 25 to 27 was solved.

XXI. The appellant-opponent's arguments in writing and during the oral proceedings, insofar as they were relevant to the present decision, may be summarized as follows:

Main request

Article 123(2) EPC

The sequences denoted as SEQ ID Nos. 15 and 16 were not as such disclosed in the application as filed. Therefore, claim 1 was not in conformity with the requirements of Article 123(2) EPC.

The application as filed described the normal humanization process according to Queen's procedure and thus, that the framework regions of the claimed humanized antibody were selected from a set of **human** sequences and thus were either native human framework regions or variants thereof adapted to the specific CDRs according to Queen's rules. However, according to the definition in claim 1 the light or heavy chain framework could be selected from any **humanized** immunoglobulin light or heavy chain. Thus, the claimed antibodies could have framework sequence which were either native human, humanized with regard to the donor antibody, or humanized with regard to the acceptor antibody. Consequently, the definition in claim 1 encompassed a much broader range of framework regions than that described in the application as filed. Also for that reason, the subject-matter of claim 1 extended the content of the application as filed, contrary to the requirements of Article 123(2) EPC.

Auxiliary request I

Article 84 EPC

The degree of variation between the framework sequences of the native human heavy or light chains and the humanized heavy and light chains was not clearly conveyed by the expression "substantially identical" because the term "substantially" did not have a well-defined meaning.

Auxiliary request II

Article 84 EPC

The expressions "from a human immunoglobulin light chain" and "from a human immunoglobulin heavy chain" did not clearly convey whether the light and heavy chain framework sequences of the claimed humanized antibody could also be native, unmodified human framework sequences. Therefore, claim 1 was not clear, contrary to the requirements of Article 84 EPC.

Article 83 EPC

Claim 1 related to humanized antibodies binding to an epitope contained within positions 13-28 of Aβ. While the CDRs of the humanized antibody were defined by their sequence in claim 1, the framework regions were not. Thus, claim 1 related to humanized antibodies comprising the specifically indicated CDRs in combination with any framework sequence suitable to position the CDRs such that the binding specificity indicated in the claim was achieved.

The patent disclosed specifically one specific humanized antibody, Hu266, having a particular combination of framework regions.

With the exception of the CDRs, the patent did not disclose any sequence information of the mouse CDR donor antibody Mu266.

Thus, the only available sequence for preparing antibodies with a combination of framework regions **different** from the exemplified one - and this was a type of variants encompassed by claim 1 - was that of the specifically disclosed humanized antibody Hu266.

However, with only this sequence information available, this type of variants (hereinafter "variants at issue") could not be prepared, or only prepared with undue burden for the reasons derivable inter alia from Dr. Gill's declaration D18.

No disclosure

Neither the patent nor the prior art disclosed a method for preparing a humanized antibody on the basis of a "pre-humanized" antibody.

Queen's technology

Screening for framework regions with the highest identity to the framework region of the non-human donor antibody was a first step in the method for the humanization of antibodies specifically disclosed in the patent, i.e. the technology developed by Queen and colleagues.

However, selecting alternative human framework sequences on the basis of identity to the sequence of the "pre-humanized" Hu266 antibody would result in the selection of a group of sequences **different** to those that would be selected if that selection was made by identity to sequences of the Mu266 antibody. Moreover, framework regions would be found having an identity that was **lower** in relation to the original mouse antibody framework sequence than if screening was made with the parent antibody Mu266. Using such framework sequences in combination with claimed CDRs would result

in obtaining an antibody with no, or at least grossly reduced, affinity.

Binding affinity

There was a serious doubt, see for example declaration D27, that the specifically disclosed humanized antibody Hu266 and the parent mouse antibody Mu266 even had the same affinity, aggravating the danger of a gross loss of affinity, if sequences were used that were the result of screening with the humanized antibody Hu266.

Binding specificity

Moreover, there was no evidence in the patent that the humanized antibody Hu266 had retained the binding specificity of the original Mu266 antibody at all. A shift in epitope specificity was often observed as a result of the process of humanization – see for example document D21. In this document the humanized versions of antibody AF2 and antibody p185HER2 were mentioned as examples of this effect. Thus, even if it was assumed that the antibody Hu266 had retained the level of binding affinity of Mu266, this was not tantamount to retaining biological activity. Selecting an alternative framework with an antibody from which it was not sure that it had the required binding specificity, entailed the danger that the newly constructed humanized antibody did not have it either.

Backmutation

A further mandatory step according to Queen's method was the determination of residues in the non-human

donor antibody which were in contact with the CDRs and thus responsible for ensuring their three-dimensional structure. According to the teachings of Queen the residues in the human framework at these critical positions should be backmutated to those of the non-human donor-antibody residues. Thus, even if an alternative framework had been selected on the basis of the disclosed Hu266 antibody, the skilled person could not determine which of its residues had to be backmutated and how.

Thus, in summary, the Queen technology could not be used for obtaining humanized antibodies with alternative framework regions.

Site-directed mutagenesis

"Random" mutagenesis in order to arrive at an antibody with suitable affinity and the required binding specificity required a burdensome amount of experimentation. There were over 150 amino acid positions in the light and heavy chains that could be randomly mutagenized with 20 amino acids. The number of permutations was astronomic. The probability that this would result in the same humanized antibody as would be obtained when starting with the mouse Mu266 antibody was negligibly small.

Case Law

The present case was reminiscent of the case in decision T 792/00 where it was stated that if, for an invention which went against prevailing technical opinion the patentee had failed to give even a single

reproducible example, sufficiency of disclosure could not be acknowledged.

Reference might also be made to decision T 397/02 which stated that, on the basis of the common general knowledge, the skilled person might be expected to carry out modifications of a routine kind in the context of an already well-tried method. It was beyond the skilled person's ability however to carry out modifications with the mere hope that they would enable a method for which there is no suggestion that it would work. Thus, the board in this decision concluded that if, for an invention that was conceptually different from earlier approaches in the prior art, the patentee failed to give even a single example, sufficiency of disclosure could not be acknowledged.

Burden of proof

The factual situation in the present case was such that it was not the appellant-opponent who had the burden of showing that the variants at issue could not be made. Rather here it was the appellant-patentees who had to show that they could be made.

In summary, the claimed invention could not be carried out by the skilled person over the whole scope of the claim without undue burden and thus the requirements of Article 83 EPC were not fulfilled.

Articles 54 and 56 EPC

The subject-matter of claim 1 was either anticipated or rendered obvious by the disclosure in documents D8 and

D9. This was so because it was not specified that the fragments referred to in claim 1 had to comprise the three light chain and the three heavy chain CDRs referred to in the claim. Thus, the claim encompassed, for example, fragments that would not have any CDRs at all, or fragments of the constant region, or fragments containing just a few randomly picked amino acids of an antibody according to claim 1.

Since claim 1 encompassed fragments without CDRs, it encompassed embodiments which were not capable of binding and sequestering the soluble Aβ protein and which thus did not solve the problem that the patent purported to solve.

Therefore, this effect, i.e. binding and sequestering the soluble Aβ protein, could not be taken into account when formulating the problem which, as a consequence, had to be reformulated and consequently be defined as the mere provision of further fragments of an antibody having no particular function at all.

The solution according to claim 1, fragments of the antibody of claim 1 with no particular function, were merely an arbitrary solution to this problem which did not therefore involve an inventive step.

Moreover, the subject-matter of the second medical use-claims 25 to 27 did not involve an inventive step because evidence in the application was lacking that the problem underlying these claims - the provision of means for the treatment of Alzheimer's disease, Down's syndrome and other Aβ polypeptide related conditions - was solved. There were only data in the application

that mouse antibodies Mu266 and 4G8 binding to an epitope contained in positions 13-28 of Aβ sequestered Aβ protein. There were no corresponding data for the humanized antibody Hu266.

However, it was known from document D21 that there was no strict correlation between binding affinity and specificity. Thus, even if it was assumed that the binding affinities of the mouse Mu266 and the humanized antibody Hu266 were the same (which was anyhow doubtful), this did not necessarily mean that they had the same biological function. Consequently, the Mu266 antibody could not establish that the humanized antibody Hu266 solved the problem underlying claims 25 to 27. Therefore, document D31 could not make good the lack of evidence in the patent. Thus, for the same reason, auxiliary request II lacked an inventive step.

Reasons for the decision

General remarks on antibodies, "humanized" antibodies and the Aβ polypeptide

1. Any antibody is composed of two identical heavy and two identical light chains. Both heavy and light chains comprise, at the carboxy terminus regions with sequences relatively conserved among different immunoglobulins in a single species, so-called constant regions and, at the amino terminus regions with sequences more variable among different immunoglobulins in a single species, the so-called variable regions.

The antigen-recognition site is situated at the amino-terminal end of the variable region and is composed of three hypervariable regions, the so-called complementarity determining regions (CDRs) which are held in place by four "framework" regions which, compared to the CDRs, have sequences which are relatively conserved among different immunoglobulins in a single species. The CDRs are exposed on the surface of the antibody and are mostly responsible for antigen-binding.

2. Monoclonal antibodies are produced by the hybridoma technology originally established by Köhler and Milstein. The utility of monoclonal antibodies as therapeutics was recognized soon after the introduction of the Köhler and Milstein method. The use of monoclonal antibodies as human therapeutics was hampered by the problem that the non-human, mostly rodent, antibodies produced by the hybridoma technology were immunogenic in humans. It was recognized that unwanted immune responses could be prevented by avoiding non-human amino acid sequences i.e. by "humanizing" the non-human antibody.

3. At the priority date of the patent the method developed by Queen and colleagues was one known technique for the humanization of antibodies. This is also the method specifically referred to in the patent. It essentially comprises the following steps:

(i) sequencing the non-human donor antibody variable regions;

(ii) selection of a suitable human framework region based on sequence homology with the donor antibody framework;
(iii) determination by three dimensional modelling and sequence analyses of the non-human donor antibody of a set of framework residues in the donor antibody potentially important for maintaining the structure of the CDRs;
(iv) transfer of the identified donor antibody framework residues and the CDRs to the selected human antibody;
(v) expression of the humanized antibodies.

4. Conditions such as Alzheimer's disease or Down's syndrome are associated with neuritic and cerebrovascular plaques in the brain containing the amyloid beta peptide (Aβ). These peptides circulate in the blood and in the cerebrospinal fluid. The Aβ peptide in circulating form is composed of 39 to 43 (mostly 40 or 42 amino acids) resulting from cleavage of the amyloid precursor protein, often designated as "APP". Aβ can be transported back and forth between the brain and the blood. In plaques it is in an equilibrium with soluble Aβ in brain and blood (see the patent paragraphs [0002] and [0003]).

Main request

Article 123(2) EPC

5. Claim 1 relates to humanized antibodies or fragments thereof. One of the features by which they are characterised, i.e. the framework sequences of the heavy and light chain, are defined in claim 1 as "a

light chain framework sequence from a humanized immunoglobulin light chain" and "a heavy chain framework sequence from a humanized immunoglobulin heavy chain".

6. The appellant-opponent submits that the above-cited definition means that the framework sequences are "derived from" a set of "pre-humanized" framework sequences. This option was however not disclosed in the application as filed. The appellant-patentees submit that the skilled person, interpreting claim 1 in a technically meaningful way, would exclude the meaning suggested by the appellant-opponent, since he/she knows that, according to common methods for the humanization of antibodies like the one disclosed in the patent, the framework regions are not selected from a set of **humanized**, but from a collection of **human** framework regions. The skilled person would therefore understand that the feature at issue simply means that the framework sequences of the humanized antibody **are** humanized.

7. In the board's view, on a linguistic basis, the skilled person would interpret the term "from" in the expressions "a light chain framework sequence from a humanized immunoglobulin light chain" and "a heavy chain framework sequence from a humanized immunoglobulin heavy chain" as meaning "derived from" or "coming from". This meaning would make sense in the present context since the skilled person knows that the process of humanization involves the selection of appropriate framework sequences "from" a collection of known framework sequences.

8. A patent document may be its own dictionary. However, in the present case any explicit statement of what "from" in the definition "a light chain framework sequence from a humanized immunoglobulin light chain and "a heavy chain framework sequence from a humanized immunoglobulin heavy chain" is intended to mean, i.e. in particular that it means, as suggested by the appellant-opponent "which is", is not present in the patent.

9. The skilled person might perceive the linguistically obvious meaning as expressing a technically unusual fact, because he/she knows that, normally, the process of humanization involves the selection of appropriate framework sequences among a collection of **human**, and not **humanized** framework sequences and this is also the process disclosed in the present patent specification.

10. However, from a technical point of view, it is not impossible to derive framework sequences from a pool of **humanized** framework sequences. Therefore, and also because the skilled person is here faced with the interpretation of a patent claim which he/she knows may by its very nature relate to unknown or unexpected subject-matter, the skilled person would not have doubts that the literal interpretation is correct.

11. The boards have often stated that the skilled person is supposed to rule out claim interpretations that do not make technical sense or are technically illogical. However, this standard is not reached in the present case in which, as observed above, the skilled person would regard correct interpretation as technically "unusual", but not technically "impossible".

12. Thus, in summary, the skilled person would interpret the expressions "a light chain framework sequence from a humanized immunoglobulin light chain" and "a heavy chain framework sequence from a humanized immunoglobulin heavy chain" in claim 1 as meaning that the light and heavy chain framework regions of the humanized antibody are derived from humanized immunoglobulin chains.

13. Both parties agree that such a definition of framework sequences is not disclosed in the application as filed.

14. However, Article 123(2) EPC requires that the European patent may not be amended in such a way that it contains **subject-matter** which extends the content of the application as filed.

Therefore, it has to be determined whether or not the subject-matter defined by the words of claim 1 is disclosed in the application as filed.

15. The board has observed above that the "normal" process of humanization of an antibody comprises the selection of framework sequences from a collection of known human framework regions and, if necessary, the modification of the selected framework sequence to adapt them to the specific CDRs.

16. Consequently, claim 1 of the main request, where the framework is - according to the interpretation above - derived from a set of "humanized" framework sequences, is to be considered as encompassing humanized

antibodies with one of the following types of frameworks:

(a) unmodified, i.e. native human framework sequences (if the framework in the humanized antibody was the native human framework); or
(b) modified human framework sequences which are adapted to CDRs different from those recited in claim 1 (if the framework in the humanized antibody was an adapted native human framework); or
(c) modified human framework sequences which are native human framework sequences according to a) modified for adaptation to the CDRs recited in claim 1; or
(d) modified humanized framework sequences which are humanized framework sequences according to b) further modified for adaptation to the CDRs recited in claim 1.

17. The application as filed discloses the "normal" humanization process. Thus, the humanized antibodies disclosed in the application as filed only have framework regions of types (a) and (c) above.

18. Consequently, present claim 1 defines a class of antibodies which is broader compared to the class disclosed in the application as filed.

19. Thus, the board comes to the conclusion that claim 1 relates to subject-matter extending the content of the application as filed and consequently does not fulfil the requirements of Article 123(2) EPC. The main request is not allowable.

Auxiliary requests I and II

Admissibility

20. When announcing its decision at the oral proceedings with regard to the main request, the board also informed the parties that it considered one of the appellant-opponent's further objections raised pursuant to Article 123(2) EPC against claim 1 of the main request was not well-founded, i.e. it considered that the alternative CDR sequences mentioned in claim 1 of the main request having SEQ ID Nos. 15 and 16 were disclosed in the application as filed.

The appellant-patentees reacted by withdrawing their previously filed first and second auxiliary requests - neither of which contained references to these sequences in claim 1 - and by filing new auxiliary requests I and II which did contain references to these sequences.

Whether or not to admit these late-filed requests is a matter for the board's discretion (Article 114(2) EPC).

On the one hand the appellant-patentees could certainly have filed these requests at an earlier stage, not least because the board in its communication had informed the parties about its positive preliminary opinion in this respect (see section IX above).

On the other hand, not only have claims reciting the SEQ ID Nos. 15 and 16 feature been in issue during the whole proceedings, but also only with respect to their acceptability under Article 123(2) EPC (see for example sections II to IV and VII above).

Thus, no substantive objections could be expected with regard to such claims, and the appellant-opponent could not be surprised by having to argue about such claims. Hence, since neither procedural efficiency nor the appellant-opponent's right to be heard were affected, the board decided to admit auxiliary requests I and II into the proceedings.

Auxiliary request I

Article 84 EPC

21. Since Article 84 EPC is not a ground of opposition, the examination of compliance with this requirement is confined to amendments made over the claims as granted (see for example decision point 24 of decision T 1023/02 of 19 May 2006).

22. The expressions in claim 1 "a light chain framework sequence substantially identical to a native human light chain framework" and "a heavy chain framework sequence substantially identical to a native human heavy chain framework" were not as such present in the claims as granted and are therefore to be examined for their compliance with the requirements of Article 84 EPC.

23. According to Article 84 EPC the claims shall define the subject-matter for which protection is sought in a clear manner.

24. Whether or not a claim or terms in a claim are clear is determined from the point of view of the skilled person reading the claim with his/her background knowledge.

25. In the present case it is in dispute whether or not the term "substantially identical" has a clear meaning. Within the feature "a light/heavy chain framework sequence substantially identical to a native human light/heavy chain framework", the term "substantially identical" defines the extent of variation in the amino acid sequence between the humanized framework and the native human framework sequence.

26. It is without doubt that the term "identical" per se has a precise meaning i.e. it means "the same". This is not so however with regard to the term "substantially" per se. However, terms which are per se ambiguous may nevertheless be clear in a given context.

27. However, in the present case, even when the two terms are read together, the board considers that they do not convey a precise definition for the extent of variation between the native human and the humanized framework sequence. This is so because, first, the skilled person knows that the framework sequences of a humanized antibody may be completely identical to the native human framework sequences. However, this technical understanding would be in contrast to the skilled person's linguistic understanding of the term "substantially", namely that it would normally not be

perceived to mean "completely". Therefore, prima facie the skilled person would have doubts whether or not the expression "substantially identical" also encompasses the meaning "completely identical", or in other words, whether the variation between the native human and the humanized framework sequences may be "zero".

28. In the board's view, the meaning of the term "substantially identical" can also not be clarified when considering it in the context of claim 1. This is so because, when humanizing an antibody, the positions of amino acid residues to be changed are determined based on, in particular, the contact points of the donor antibody framework with the donor antibody CDRs. Consequently, the ultimate number of changes, i.e. the extent of variation, can only be determined with the knowledge of the sequence of the framework of the non-human donor antibody and that of the human acceptor antibody. Claim 1 however only recites the sequence of the CDRs.

29. The appellant-patentees submit that the term "substantially identical" was clear in the light of the description.

30. On the one hand it is accepted case law that the skilled person is supposed to interpret a claim by taking account of the whole content of the patent specification, i.e. also the description (see Case Law of the Boards of Appeal of the EPO, 6th edition 2010, for example section II.B.5.3.1). On the other hand the Boards of Appeal have also ruled that a claim has to be unambiguously understandable in itself without the need to refer to description of the patent (see Case Law of

the Boards of Appeal of the EPO, 6th edition 2010, for example section II.B.5.3.5, paragraph 5 et seq.).

31. Which of these approaches is appropriate in the present case needs not to be decided since, even if the description was taken into account, the passage in paragraph [0035] referred to by the appellant-patentees (or any other passage) would not help to clarify the meaning of "substantially identical".

32. The passage referred to reads:

"A humanized antibody again refers to an antibody comprising a human framework, at least one CDR from a non-human antibody, and in which any constant region present is substantially identical to a human immunoglobulin constant region, i.e. at least about 85-90%, preferably at least 95% identical. Hence all parts of a humanized antibody except possibly the CDRs, are substantially identical to the corresponding parts of one or more native human immunoglobulin sequences. For example, a humanized immunogloblin would typically not encompass a chimeric mouse variable region/human constant region antibody."

33. The appellant-patentees interpret this passage such that the sentence "[h]ence all parts of a humanized antibody except possibly the CDRs, are substantially identical to the corresponding parts of one or more native human immunoglobulin sequence" relates only to the sentence before the quoted sentence and thus infers that the definition of "substantially identical" in that sentence with regard to the constant region, i.e. "at least about 85-90%, preferably at least 95%

identical" also applies to the identity of the parts of the humanized antibody with corresponding parts of the native human antibody to other parts of the antibody mentioned in the quoted sentence. Thus, in the appellant-patentees' view the passage in paragraph [0035] makes it clear that "substantially identical" in relation to the framework region meant an identity of 85-90%, preferably 95%.

34. However, in the board's view, when considering that passage in its proper context the skilled person would not arrive at the appellant-patentees' suggested interpretation.

35. In the immediately preceding paragraph [0034], the meaning of the expression "humanized antibody" is explained, namely that it is an antibody that is "composed partially or fully of amino acid sequences derived from a human antibody germline by altering the sequence of an antibody having non-human complementarity determining regions (CDR)". It is further explained that the simplest alteration consists in substituting the constant region, but that it is preferable that the variable regions are also altered. It is stated that when choosing this latter possibility "the framework regions of the variable regions are substituted by the corresponding human framework regions, leaving the non-human CDR substantially intact, or even replacing the CDR sequence with sequences derived from a human genome". Finally it is mentioned in paragraph [0034] that fully human - in contrast to humanized - antibodies may be made in mice which have an immune system corresponding to the human one and

that also immunologically relevant fragments of the antibodies may be used.

36. Paragraph [0035] continues with the definition of the meaning of "humanized antibody". The first sentence gives a short summary of the information from paragraph [0034] - see the word "again" - and also adds further information about parts of the humanized antibody, namely about the constant region: "A humanized antibody again refers to an antibody comprising a human framework, at least one CDR from a non-human antibody, and in which any constant region present..." (for the complete text, see point 32 above).

37. Thus, in paragraph [0034] the nature of the framework region and CDRs and in paragraph [0035] that of the constant region is explained. The board considers that due to this structure of the text, the sentence "[h]ence all parts of a humanized antibody except possibly the CDRs, are substantially identical to the corresponding parts of one or more native human immunoglobulin sequences" can only be understood as summarizing in terms of sequence identity what has been said in both paragraphs [0034] and [0035] in relation to the individual parts of the antibody. i.e. the sentence at issue is not only related to the directly preceding sentence. Thus, the information conveyed in relation to the sequence identity of the framework region is that disclosed in paragraph [0034], i.e. that the framework regions of the non-human antibody "are substituted by the corresponding human framework regions". Thus, no specific percentage or range of percentages of identity capable of clarifying the

expression "substantially identical" is derivable from the description.

38. Thus, in conclusion, the term "substantially identical" does not have a clear meaning in the context of claim 1. Therefore, claim 1 does not fulfil the requirements of Article 84 EPC. Consequently, auxiliary request I is not allowable.

Auxiliary request II

Articles 123(2)(3) EPC

39. The claims of auxiliary request II differ from the claims as granted in that in claim 1 the light and heavy chain frameworks are defined as being "from a human" immunoglobulin light or heavy chain and in that in claim 1 the antibody or fragment is defined in that it "specifically binds an epitope contained within position 13-28 of Aβ".

The appellant-opponent did not raise any objections pursuant to Articles 123(2)(3) EPC. Also the board has no objections.

Article 84 EPC

40. The board considers in contrast to the appellant-opponent's view that for the reasons given in point 7 above the skilled person would also in the context of the present claim 1 clearly understand that the term "from" in the expressions "a light chain framework sequence from a human immunoglobulin light chain" and "a heavy chain framework sequence from a human

immunoglobulin heavy chain" means "derived from", i.e. that the light and heavy chain framework sequences are derived from a collection of human light and heavy chain immunoglobulin sequences.

41. The skilled person would also understand that the mere indication of the origin of the framework sequences, does not restrict the framework sequences used in the "final" humanized antibodies to exactly the selected ones. In other words, in the present context the skilled person would not interpret "derived from" as "is". Thus, claim 1 relates to humanized antibodies with either native human framework sequences or modified native human framework sequences.

42. Thus, claim 1 is clear. The requirements of Article 84 EPC are fulfilled.

Article 83 EPC

43. The patent discloses in SEQ ID Nos. 11 and 12 (describing sequences of the variable and constant regions for the heavy and light chain of the humanized antibody) the sequence of a specific humanized antibody having CDR sequences as recited in claim 1 and modified human framework sequences. In particular, the framework sequences of the heavy chain variable region framework according to SEQ ID No. 12 are derived from the human germline VH segment DP53 and J segment JH4 with amino acid substitutions according to the Queen procedure (see paragraph [0040] of the patent). The light chain variable chain framework according to SEQ ID No. 11 originates from the human germline Vkappa segments DPK18 and J segment Jkappa1 with amino acid

substitutions according to the Queen procedure (see paragraph [0041] of the patent). This exemplified humanized antibody is the one denoted as "Hu266" (see paragraph [0112] of the patent).

44. The patent moreover discloses in SEQ ID Nos. 7 and 8 (recited for example in claim 3 of the present request) positions labelled as "XAA" which denote potential sites of variation of the sequence of the specifically disclosed Hu266 antibody. More precisely, ten and eight sites, respectively, for modification in the light and heavy chain variable regions are listed in SEQ ID Nos. 7 and 8 with two to three and two to four, respectively, possible amino acid substitutions at each of those sites.

45. Thus, the patent discloses not only one, but many examples. The appellant-opponent does not contest that the skilled person is able to obtain Hu266 and its disclosed derivatives.

46. The appellant-opponent's argument however is that, because the framework sequences are defined in claim 1 as framework sequences **from** a human immunoglobulin light or heavy chain, this claim does not only encompass the specifically disclosed antibody Hu266 and its disclosed derivatives, but also humanized antibodies with framework sequences **unrelated** to the exemplified one.

47. According to the appellant-opponent these variants (in the following "variants at issue") cannot be obtained when following the disclosure in the patent. The reason is in the appellant-opponent's view that the only

method for the preparation of humanized antibodies disclosed in the patent is that developed by Queen et al. This method requires knowledge of the sequence of the non-human donor antibody from which the CDRs are derived. However, the sequence of, in the present case, the mouse donor antibody Mu266, is not disclosed in the patent (nor in the prior art) and there is no disclosure either in the patent or in the prior art of how humanized antibodies could be obtained without knowledge of the sequence of non-human donor antibody. Thus, the appellant-opponent concludes that the disclosure in the patent, even when taking into account common general knowledge, does not enable the skilled person to carry out the invention over its whole claimed scope and therefore, the requirements of Article 83 EPC are not fulfilled.

Burden of proof

48. The appellant-opponent has suggested that in a case such as the present where neither the patent nor the prior art expressly disclose how to obtain particular embodiment of the claim, it should not be for the opponent to prove that the variants at issue cannot be obtained, but rather the burden should be on the patentee to prove that the variants at issue can be obtained. To support its view the appellant-opponent refers to decisions T 792/00 of 2 July 2002 and T 397/02 of 10 October 2003 and argues that the appellant-patentees have not provided evidence that the invention is enabled with respect to the variants at issue.

49. The board in point 9 of the reasons of decision T 792/00 alludes to the general rule that "he who asserts something positive has the burden of proof" and concludes thus that "if a patentee asserts that an example in a patent works as stated, and an opponent denies this, it is up to the patentee to provide proof. However, if the example contains a complete experimental protocol and the patentee affirms that the results reported have been obtained, a Board is likely to accept that the patentee has done enough to shift the burden of proof to the opponent to provide a repeat of the experiment to show that it does not, in fact, work as stated. Finally, however, the board must be satisfied, considering all the evidence, that the example works as stated."

50. The board in decision T 792/00 considered that the burden of proof was on the patentee because (i) the claimed invention went against a prevailing technical opinion and (ii) the patent contained only an example which was expressly labelled as a hypothetical experimental protocol.

51. In the case underlying decision T 397/02 the board emphasized that the invention did not consist in adapting an already known method to make it simpler or more efficient, but the claimed method was conceptually different from the approach taught in the prior art (see point 12 of the reasons). There was one example, but it was not suited to show that the claimed subject-matter was enabled (see point 7 of the reasons), i.e. an example was in principle absent. As is apparent from points 13 to 16 of the decision, the board in that case considered that these were circumstances where the

proprietor had to demonstrate that the claimed invention worked because, since it was not convinced of the patentee's arguments that the invention worked, it denied sufficiency of disclosure.

52. The circumstances of the present case are different from those dealt with in decisions T 792/00 and T 397/02 insofar as the concept of and methods for humanization are known and can, from a technical point of view, be applied to each antibody donor-acceptor pair, i.e. also to a humanized donor-human acceptor pair (see point 10 above). The appellant-opponent's submission that there is no disclosure that any-one has applied the known method to this particular situation does not necessarily establish that there was a prevailing opinion that this could not be done. In addition, the appellant-patentees submit that there was no obstacle.

53. In the present board's view, the situation in the case at issue here rather coincides with the situation mentioned by the board in point 10 of decision T 792/00 - a situation which was considered not to be present in case T 792/00: "[I]n the special situation where an opponent accepts that the invention can be carried out as stated in the examples, but alleges that there are other circumstances where something falling under the claim cannot be carried out, then Boards of Appeal would normally expect the opponent to provide concrete evidence of this (cf. Latin legal tag "Qui excipit, probare debet, quod excipitur" : he who raises an objection should prove it)".

54. In conclusion, in the board's view, in the present case it is the appellant-opponent who should prove that the variants at issue cannot be made.

Enablement

55. It is established case law that the disclosure of a European patent is only considered as sufficient in the sense of Article 83 EPC if the skilled person is able to obtain substantially all embodiments falling in the ambit of the claim (for example, decisions T 409/91 of 18 March 1993 and T 435/91 of 9 March 1994).

56. Yet, the concept of "sufficiency of disclosure over the whole scope of the claim" does not mean that, for a disclosure to be considered as sufficient, it has to be demonstrated that each and every conceivable embodiment of a claim can be obtained.

57. This is explicitly acknowledged in decision G 1/03 of 8 April 2004. The Enlarged Board of Appeal states in point 2.5.2 of the reasons that if a claim comprises "non-working" embodiments this may have different consequences with regard to the fulfilment of the requirements of Article 83 EPC, depending on the circumstances. There may be situations where the specification contains sufficient information on the relevant criteria for finding appropriate alternatives ("variants") over the claimed range with reasonable effort. Under these circumstances the non-availability of certain variants encompassed by the claim at the priority date is considered immaterial for the sufficiency of disclosure.

58. An example where this was not so is the case underlying decision T 601/05 of 2 December 2009. In that case the board found that a whole class of compounds falling under the terms of a claim - antibodies binding with a high affinity to TNF alpha - could not be produced on the basis of the teaching in the patent and/or the common general knowledge and that the class concerned was the very class which was particularly aimed at by the scientific community. Moreover, also the single example disclosed in the patent was an antibody which did not have high affinity (see points 24 to 44 of this decision).

59. The present situation differs however from that in case T 601/05 in that the present patent describes quite a number of appropriate alternatives and in that the allegedly non-obtainable variants are "hypothetical" variants.

60. Taking into account the above mentioned case law and in view of the number of examples given the patent, the board comes to the conclusion that the requirements of Article 83 EPC are fulfilled.

61. Since most of the parties' arguments in relation to sufficiency of disclosure dealt with the question of whether or not the variants at issue, humanized antibodies with framework sequences unrelated to the exemplified one, could be made, the board has nevertheless considered the situation that the present case was one where the requirements of Article 83 EPC could be considered as fulfilled only if there was evidence that the variants at issue could be made. Starting from this assumption, the board agrees with

the appellant-opponent that these variants cannot be obtained by following the "classical" Queen-procedure disclosed in the patent, because this procedure requires knowledge of the non-human donor sequence.

62. However, this finding would be irrelevant for sufficiency of disclosure as long as the skilled person knows other ways of making the variants at issue. It is established case law that the skilled person may use his/her common general knowledge when it comes to carrying out an invention.

63. Thus, the question is whether or not there is any other way available to the skilled person by which the variants at issue could be made. The board can only come to the conclusion that the requirements of Article 83 EPC are not fulfilled, if it is convinced that there is not a single method for obtaining the variants at issue.

64. The appellant-opponent argues that the variants at issue cannot be made by, for example, a) a modified Queen procedure, i.e. by applying the Queen-technology to humanized antibody Hu266 as the donor antibody or b) by random site-directed mutagenesis or c) by reconstruction of the mouse sequence and subsequent application of the Queen method.

65. It is established case law that an objection of lack of sufficiency of disclosure only succeeds, if there are serious doubts that claimed subject-matter is enabled, and these doubts are supported by verifiable facts.

66. As for example to method a) above, the appellant-opponent submits that screening the database of human germline immunoglobulin sequences for sequences with highest identity - this is a central step of the Queen procedure - with the sequence of the humanized Hu266 would result in the provision of sequences with an identity that was much lower than that which would result if the database was screened with the sequence of the mouse parent antibody. It appears that the appellant-opponent's implicit conclusion is that the identity is in fact so low that the framework would not be suitable to properly support the specific CDRs from the mouse parent antibody Mu266 and that therefore an antibody constructed with these low-identity frameworks would not have a useful affinity and may even have lost the binding specificity.

67. The appellant-opponent - who has the burden of proof, see points 48 to 57 above - has not provided, for example, tangible evidence that homology-screening with the humanized antibody Hu266 would result in finding only framework regions with a sequence identity that was lower in relation to the original mouse antibody framework sequence than the identity of sequences that would be found if screening was made with the parent antibody Mu266. Even if this was assumed to be so, there is also no evidence that the retrieved sequence, even if it had a lower identity, would not properly three-dimensionally position the specific CDRs of the Mu266 antibody.

68. It appears that there have been cases where the grafting of CDRs to framework sequences which were not selected on the basis of sequence identity resulted in

functional humanized antibodies. It is reported in, for example, document D7 on page 4285, in the middle of the second column and document D18B page 70, in the middle of the first column, that simple transplantation of CDRs without changes to framework residues resulted in antibodies with the expected specificity and affinity: "In some cases, transplanting hypervariable loops from rodent antibodies into human frameworks is sufficient to transfer high antigen binding affinity (16, 18) whereas in other cases it has been necessary to also replace one (17) or several (20) framework region (FR) residues."; "[a]lthough CDR grafting was successful in some cases [10,11], [...]".

69. Evidence allowing the verification of alleged facts may vary in nature according to each case, i.e. experimental data are certainly not always necessary as a means of proof. However, in the present case, as in particular shown by the observations in point 67 above, without such experimental data the board cannot verify the facts alleged by the appellant-opponent.

70. Thus, the board is not convinced that the variants at issue cannot be obtained by a "modified" Queen procedure or the procedures referred to in documents D7 or D8.

71. The appellant-opponent has relied on decisions T 792/00 and T 397/02 to support its case. However, in both cases sufficiency of disclosure was denied because not a single embodiment could be obtained on the basis of the disclosure in the patent and even less on the disclosure in the prior art. Thus, these cases do not

help in the present situation where the question of the obtainability of a particular embodiment is at stake.

72. Thus, even assuming that the present case was one where the requirements of Article 83 EPC could be considered as fulfilled only if there was evidence that the variants at issue could be made, the board would come to the conclusion that no case of lack of sufficiency of disclosure has been made.

73. The requirements of Article 83 EPC are fulfilled.

Article 54 EPC

74. Claim 1 relates to a humanized antibody, or fragment thereof, which is inter alia defined in that the antibody or fragment specifically binds an epitope contained within position 13-28 of the Aβ polypeptide.

75. Thus, the antibody fragments according to claim 1 are characterized by their binding property. The appellant-opponent's interpretation of the term "fragment" as relating to fragments that would not encompass any CDRs at all and fragments containing just a few randomly picked amino acids of an antibody according to claim 1 or fragments of the constant region is therefore not tenable in relation to the present claim 1.

76. Document D8 discloses cloned human and mouse kappa immunoglobulin constant and J region genes and that they conserve homology in functional segments. Document D9 deals with the evolution of human immunoglobulin kappa J region genes. There is no disclosure in either of documents D8 or D9 that any of the immunoglobulin

fragments disclosed therein binds an epitope contained within position 13-28 of Aβ.

77. Thus, the appellant-opponent's novelty objection fails.

78. The requirements of Article 54 EPC are fulfilled.

Article 56 EPC

79. The appellant-opponent attacks the claims of the present request by two lines of argumentation.

(i) Claim 1 encompasses fragments that would not comprise any CDRs at all or fragments of the constant region of an antibody and fragments containing just a few randomly selected amino acids of an antibody. These fragments do not solve the problem, therefore the problem has to be reformulated to a less ambitious one the solution of which is obvious.

(ii) There is no evidence in the patent that the problem underlying claims 25 to 27 is solved because functional data are only shown for the mouse antibody Mu266, but not for the humanized version Hu266. This is detrimental because, as demonstrated in document D21, affinity and biological function do not always correlate.

80. The problem underlying the present invention is to provide means for the treatment of Alzheimer's disease, Down's syndrome and other conditions related to the Aβ polypeptide (see the patent, for example paragraph [0020].

81. As to the appellant-opponent's first line of argument, in view of its wording claim 1 only encompasses humanized antibodies and fragments of humanized antibodies binding to an epitope contained within positions 13-28. According to paragraph [0012] of the patent these binding properties confer the capability of sequestering soluble forms of Aβ from their bound, circulating forms in the blood and result in rapid efflux of relatively large quantities of Aβ peptide from the central nervous system into the plasma.

82. Thus, the property of the antibodies and fragments of binding to an epitope contained within positions 13-28 of Aβ are the basis for the treatment of Aβ-related disorders. Consequently, in view of their characterization by these specific binding properties, claim 1 has to be considered to relate only to those antibodies and fragments that solve the problem. Thus, the appellant-opponent's first argument fails.

83. As to the second argument, there is a disclosure in document D21 on page 1752, second column that in the case of two antibodies, i.e. humanized versions of the antibodies AF2 and p185HER2, binding affinity and specificity did not correlate. This is no proof however, that this is always so, and in particular with regard to the Mu266-Hu266 antibody pair of the present patent. In these evidential circumstances, in the board's view, the mouse antibody can be considered as evidence to establish that the invention as set out in claims 25 to 27 is a genuine solution to the above formulated problem.

84. Thus, the appellant-opponent's second argument also fails.

85. The requirements of Article 56 EPC are fulfilled.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent on the basis of the Second Auxiliary Request filed at the oral proceedings on 22 November 2010, and a description and drawings to be adapted thereto.

The Registrar: The Chairman:

P. Cremona C. Rennie-Smith