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Datasheet for the decision of 4 May 2011

Case Number: T 0418/07 - 3.3.04

Application Number: 97906572.9

Publication Number: 0929578

IPC: C07K 16/24

Language of the proceedings: EN

Title of invention:
Human antibodies that bind human TNFalpha

Patentee:
Abbott Biotechnology Ltd.

Opponent:
Hepworth, John Malcolm

Headword:
Human anti-TNFα antibodies/ABBOTT

Relevant legal provisions:
EPC Art. 56, 69, 83, 113(1)
EPC R. 4
RPBA Art. 13(1)

Keyword:
"Main request: Sufficiency of disclosure, inventive step (yes)"
"Copying services for multiple representatives (no)"
"Provision of translation in oral proceedings (no)"
"Requests for decision prior to oral proceedings (no)"
"Admissibility of late filed documents (no)"

Decisions cited:
T 0951/91, T 0923/92, T 1002/92, T 0296/93, R 0011/08

Catchword:
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Case Number: T 0418/07 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 4 May 2011

Appellant: (Opponent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 29 December 2006 rejecting the opposition filed against European patent No. 0929578 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: C. Rennie-Smith
Members: B. Claes
R. Gramaglia

Summary of Facts and Submissions

I. This is an appeal by the opponent (hereinafter "appellant") against the decision of the opposition division of 29 December 2006 to reject the opposition against European patent No. 0 929 578 having the title "*Human antibodies that bind human TNF-alpha*".

II. The independent claims of the patent read:

"1. An isolated human antibody, or antigen-binding portion thereof, with the following characteristics:

a) dissociates from human TNFα with a K_{off} rate constant of 1 x $10^{-3}s^{-1}$ or less, as determined by surface plasmon resonance;

b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:3, or modified from SEQ ID NO:3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at position 1, 3, 4, 6, 7, 8, and/or 9;

c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO:4, or modified from SEQ ID NO:4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

13. An isolated human antibody, or an antigen binding portion thereof, with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID

NO:1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO:2.

19. A recombinant human antibody, or antigen-binding portion thereof, that neutralizes the activity of human TNFα but not human TNFß and has the identifying characteristics of an antibody as defined in anyone of claims 1 to 18.

27. An isolated nucleic acid encoding the heavy chain of an antibody of claim 1 wherein the CDR3 domain comprises the amino acid sequence of SEQ ID NO:4, or modified from SEQ ID NO:4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11, or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

31. An isolated nucleic acid encoding the light or heavy chain of the antibody of claim 1 wherein the CDR3 domain comprises an amino acid sequence selected from the group consisting of:
a) Light chain: SEQ ID NO:3, SEQ ID NOs:11—26;
b) Heavy chain SEQ ID NO:4, SEQ ID NOs:27-34.

32. An isolated nucleic acid encoding an antibody light chain variable region comprising the amino acid sequence of SEQ ID NO:1.

35. An isolated nucleic acid encoding an antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO:2.

40. A recombinant expression vector encoding:

a) an antibody light chain having a variable region comprising the amino sequence of SEQ ID NO:1; and
b) an antibody heavy chain having a variable region comprising the amino acid sequence of SEQ ID NO:2.

41. A host cell into which the recombinant expression vector of claim 40 has been introduced.

42. A method of synthesizing a human antibody that binds human TNFα, comprising culturing the host cell of claim 41 in a culture medium until a human antibody that binds human TNFα is synthesized by the cell.

43. A pharmaceutical composition comprising the antibody, or antigen-binding portion thereof, of any of claim 1 — 22, an [*sic*] pharmaceutically acceptable carrier.

45. A method for inhibiting human TNFα activity in vitro comprising contacting human TNFα with the antibody, or an antigen-binding portion thereof, of any of claim 1—22 such that human TNFα activity is inhibited.

46. The antibody, or antigen-binding portion thereof, of any of claim 1—22 for use in inhibiting human TNFα activity in a human subject suffering from a disorder in which TNFα activity is detrimental.

47. The use of the antibody, or antigen-binding portion thereof, of any of claims 1-22 in the manufacture of a medicament for the treatment of a disorder in which TNFα activity is detrimental.

61. The antibody, of antigen-binding portion thereof, of any of claims 1-22 for use in therapy.

62. The antibody, or antigen-binding portion thereof, of any of claims 1-22 in combination with at least additional therapeutic agent for use in treating a disorder in which TNFα activity is detrimental."

III. The patent was opposed pursuant to Article 100(a) EPC on the ground of lack of inventive step (Article 56 EPC), Article 100(b) EPC and Article 100(c) EPC.

IV. The appellant filed a notice of appeal dated and faxed on 7 March 2007. The statement of grounds of appeal was filed by fax on 8 May 2007 together with annexes 1 to 3 and three new documents (D38) to (D40). On 16 June 2008 the respondent (patent proprietor) filed its reply in which it requested that annexes 2 and 3 and documents (D38) to (D40) be held inadmissible. Both parties requested oral proceedings.

V. The appellant filed further written submissions in a letter dated 21 December 2010, with which was enclosed seven new documents, i.e. documents (D44), a declaration with four annexes and four referenced documents, and documents (D45) to (D51). In a further letter dated 1 April 2011, the appellant announced he would not attend the oral proceedings which the board had appointed for 4 May 2011.

VI. In two letters from a new representative dated and filed on 4 April 2011, the respondent informed the board that it had appointed a co-representative and asked that all further communications be sent to both

the original and new representatives and requested the board to indicate whether the oral proceedings remained necessary. The respondent furthermore requested that the documents filed by the respondent on 21 December 2010 be held inadmissible and requested the board to inform the respondent as soon as possible whether or not it intended to admit those documents and those filed with the statement of grounds of appeal into the proceedings. The respondent also announced it would use German at the oral proceedings, although its representatives might use English if that was helpful and requested translation from German to English. Subsequent inquiry by the board's registrar established that the respondent's reason for requesting such translation was for the benefit of the appellant and of an employee of the respondent who would attend and who did not speak German.

VII. In a communication to the parties dated 12 April 2011, the board answered several of the matters raised in the respondent's letters.

VIII. In a letter dated 13 April 2011 in reply to the communication, the appellant withdrew his request for oral proceedings.

IX. With a letter dated 14 April 2011, the respondent filed a sub-authorisation for its new representative and again requested the board to send all correspondence to both the original and new representatives. In a further letter dated 21 April 2011, the respondent announced it requested oral proceedings only if its main request, i.e. that the appeal be dismissed, was not granted.

X. Oral proceedings were duly held on 4 May 2011.

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

D1: EP-A-0 614 984

D3: WO92/16553

D5: Griffiths *et al.* (1993), EMBO J., Vol. 12(2), pages 725-734.

D7: US 5231024

D8: Jespers *et al.* (1994), Bio/Technology, Vol. 12, pages 899-903.

D16: Marks *et al.* (1992), Bio/Technology, Vol. 10, pages 779-783.

XII. The appellant's arguments submitted in writing and as far as they are relevant to the present decision may be summarised as follows:

Admissibility of his written submissions and documents filed in the appeal proceedings

– The appellant presented no arguments on any issue of admissibility.

Construction of the subject-matter of claim 1

– Claim 1 could be interpreted so that the "antigen-binding portions" were being limited by all of the

features a), b) and c) or alternatively that the "antigen-binding portions" were being derived from an antibody which antibody itself was limited by all the features a), b) and c).

– Paragraph [0031] of the patent in suit stated that an isolated variable domain, a domain antibody (dAb) and even an isolated CDR, fell within the term "antigen binding portion.

– The claims should be interpreted on the basis of what the claim language meant to the person skilled in the art at the priority date, having regard to the description and the drawings and in the light of Article 69 EPC.

Sufficiency of disclosure - Article 83 EPC

– In accordance with paragraph [0031] of the patent in suit an isolated CDR fell clearly and unambiguously within the term "antigen-binding portion". In so far as antigen-binding portions were not required to have any of the features a), b) and c) of claim 1, the patent failed to comply with Article 83 EPC.

– The patent in suit was furthermore completely silent on how an isolated CDR which has a 12 amino acid heavy chain CDR3 peptide somehow coupled to a 9 amino acid light chain CDR3 should be manufactured which had all the features of claim 1. A CDR having a heavy chain CDR3 related to SEQ ID NO 4 and a light chain CDR3 related to SEQ ID NO 3 failed to comply with Article 83 EPC because no

guidance was provided in the patent in suit and the skilled person was forced to make such structural changes that would result in the product no longer being recognisable as an isolated CDR.

– The patent in suit did not disclose any antibodies which had conservative substitutions apart from the single example of VH1-D2.N/LOE7.T. This antibody had only one conservative mutation as opposed to the five per chain which claim 1 allowed for. The skilled person, seeking to work the invention across the scope of the claim had to manufacture these variants himself and test them in order to determine whether or not they possess the requirements of claim 1 with respect to K_{off}, TNFα binding and neutralisation. This constituted an undue burden on the skilled person to determine which variants would provide a satisfactory result.

Inventive step - Article 56 EPC

– Document (D8) disclosed guided selection as a tool for producing a human anti-hTNFα antibody (P3A2) using monoclonal antibody-derived rodent VL and VH chains as templates (MAb32). Guided selection conveyed the superior properties of murine antibodies to a human context so that the inferior properties disappeared.

– Substituting mouse monoclonal antibody MAK-195 disclosed in document (D7) for the MAb32 rodent monoclonal antibody used in the guided selection of document (D8) would have been a particularly

natural choice for providing such an alternative solution. The person skilled in the art would have had a reasonable expectation that a human anti-hTNFα could be produced without any process operational difficulties and that the antibody so produced would have increased affinity relative to chimeric, humanized and known recombinant hTNFα, antibodies, have an affinity comparable to MAb32 disclosed in document (D8) and have satisfactory properties in other respects, for example the ability to "neutralise" the hTNFα cytokine. Using MAK-195 instead of MAb32 would inevitably produce an anti-hTNFα antibody with functional properties similar to D2E7, thereby solving the objective problem.

– Since the ability to neutralise was related to the epitope, the choice of the murine template antibody in the initial step of guided selection was important. Guided selection was generally expected to "guide" the selection of human antibodies which bind to the same epitope (see document (D8), page 899, left column, second paragraph and document (D11), page 76, left column, third paragraph) and was therefore also known by the synonym "epitope" imprinting.

– The skilled person would have expected some degree of alteration in the kinetic properties between the mouse template antibody and the human antibodies obtained from the guided selection step. In view of statements in document (D8) under the discussion section, certain alterations could be expected in the antigen/antibody contacts which

could lead to observable alterations in the functional properties of the human antibody compared to the rodent template. Therefore, a reduction in the kinetic properties of the selected human antibodies would not have been unexpected, and indeed might have been predicted by the skilled person.

– However, even if human antibodies were selected from the initial guided selection screen which did not display the desired kinetics and potency, the skilled person would not have been dissuaded from continuing. In fact, it was well known in the prior art that the kinetic properties of an antibody could be improved by the known and routine techniques of chain shuffling, random mutagenesis and backmutation/"germlining" (see paragraphs [0084] to [0088] of the patent).

– It was in fact known to combine guided selection with optimisation of the kinetic properties of the human antibody obtained by guided selection. Document (D11), which was also concerned with guided selection, stated in the second paragraph of the introduction that: "*Furthermore, with phage display, the antigen binding site can be diversified further by random point mutation ... and by chain shuffling allowing the isolation of antibodies with higher affinities...*". Therefore, it would have been obvious to perform random point mutagenesis and chain shuffling in order to optimise the kinetic properties (e.g. K_{off}) of an antibody which had already been identified by guided selection starting from MAK195. Similarly,

also document (D5) stated that: "*For therapeutic application, the binding affinities of such antibodies could be improved in vitro by mutation and selection for slower dissociation kinetics*. Document (D5) taught the principle that for therapeutic purposes a potential technique for improving the kinetic properties a human anti-TNFα antibody was by mutagenesis and chain shuffling" (see Discussion, last paragraph).

– The most important and primary feature to be obtained in any human antibodies obtained directly from the guided selection step was that they recognise a particular epitope (i.e. the same epitope as is recognised by the mouse template antibody). The skilled person, knowing he could improve these at a later stage by routine techniques, would regard the exact kinetic properties of an antibody obtained directly from the guided selection step as being of secondary importance at that stage.

– The activities employed to arrive at the final D2E7 antibody therapeutic in the patent in suit were analogous to those activities which are commonly employed by research teams in industrial drug discovery and development programmes to arrive at conventional chemical compound therapeutics, i.e. an initial step of "high throughput screen" (i.e. the guided selection step) to select candidate "lead compounds", followed by lead optimisation (i.e. improvements in the kinetic properties of the antibody) to obtain

antibodies which recognise the desired epitope and which have optimal kinetics.

– There was thus a reasonable expectation that guided selection would allow, in principle, the conversion of a murine neutralising anti-TNFα antibody to a human neutralising anti-TNFα antibody, even if the human antibody obtained directly from the guided selection step had poor kinetic properties at that stage, seeing that there would have been a reasonable expectation that the kinetic properties of that antibody could have been further optimised.

– The goal of obtaining fully human neutralising anti-human TNFα antibodies was known. The process of guided selection was known. The starting mouse template antibody MAK-195 was known. The skilled person would expect that the antibodies obtained from the guided selection step would have reduced functional properties in comparison with the starting template. The steps for optimising the antibody (chain shuffling, back mutation and random mutations of CDR3 sequences) were all known (see paragraphs [0084] to [0088]).

XIII. The respondents arguments in writing and at the oral proceedings, so far as relevant to the present decision, can be summarised as follows:

Admissibility of the appellant's written submissions and documents filed in the appeal proceedings

– There was no reason why the new documents filed with the statement of grounds of appeal, i.e. documents (D38) to (D40) as well as the experimental data summarized in annexes 2 and 3, should be admitted into the appeal proceedings. The respondent had no objection to annex 1 because it corresponded to table 6 of the opposed patent.

– Based on documents (D38) and (D39) the appellant tried to open a completely new line of argument that the respondent had ignored the importance of framework residues for the functionality of an antibody. However those documents related to "humanized" antibodies whereas the present invention was directed to "fully human" antibodies, the definition of which excluded humanized antibodies (cf. paragraph [0033] of the patent in suit) from the scope of the claims, so documents (D38) and (D39) were *prima facie* irrelevant.

– Document (D40) was published almost ten years after the priority dates of the patent. It was not prior art and there was no reason why it should be considered as *prima facie* more relevant than the numerous pre-published prior art documents cited by the appellant during the opposition proceedings.

– The experimental evidence in annex 2 should not be admitted into the proceedings for several reasons. It was late filed, over three years after the end of the opposition period. Although the patent had been maintained as granted, the appellant had not explained why such experiments were only filed with the appeal. There were also doubts about the

credibility of the data in annex 2 for several reasons. The appellant had not explained how the variant antibodies had been obtained and had not provided any data about the biochemical characterization of the tested antibodies. Furthermore, the appellant had not provided all the data: for example, his numbering of variants from HUMOOl to HUMO23 indicated that twenty-three variants had been made yet only eight were disclosed in the annex. The appellant had thus selected a subset of the data to make his argument rather than present the complete story. Further, it was not known who had actually performed the alleged experiments. This had certainly not been the appellant himself, a patent attorney acting as straw man for an unknown third party.

– Annex 3 corresponded to experiments filed in the opposition proceedings but not admitted because related to subject matter not covered by the present main claim (see point 3.2 of the decision under appeal). Since claim 1 of the main request was identical to that maintained by the opposition division, the same reason for non-admissibility should apply.

– As regards the appellant's submissions of 21 December 2010, these should not be admitted at all. The appellant should have filed his complete case with his statement of grounds of appeal as required by Article 12(2) RPBA and the criteria in Article 13(1) RPBA for later amendment to a party's case all pointed to non-admissibility. The appellant had offered no reasons for the late

filing of the further submissions six years and ten months after the opposition period. In decision T 951/91 (OJ 1995, 202, see Reasons, point 6) nearly five years after filing of the notice of opposition and some twenty months after filing the statement of grounds of appeal had been held to be too late. None of the late filed documents was *prima facie* relevant (see decision T 1002/92 OJ 1995, 605, second headnote) and the huge amount of additional papers (more than 1000 pages) caused an enormous and unnecessary workload for both the board and the respondent.

– The function of appeal proceedings is to examine whether the decision of the first instance was correct and not to make a fresh case. It was thus for the appellant to provide the board with arguments why the reasoning of the opposition division was wrong. However, the appellant had attempted to make a new case and misused the legal framework of an appeal. None of the submissions objected to should be admitted into the proceedings.

Construction of the subject-matter of claim 1

– Claim 1 could only be understood to mean that the "antigenic-binding portions" of the isolated human antibodies had to have all three characteristics a), b) and c). They therefore had to show an off-rate of $10^{-3}s^{-1}$ or less, and had to comprise a light and heavy chain sequence each of which comprises a characteristic CDR3 sequence. Isolated CDR molecules and individual heavy or light chains

were therefore not covered by the claim. Suitable types of "antigen-binding portions" were Fab, $F(ab')_2$ and F_v disclosed in paragraph [0031].

Sufficiency of disclosure - Article 83 EPC

- The skilled person did not have to carry out trial and error experiments in order to provide further embodiments of the claimed invention. Claim 1 identified specific positions within the explicitly mentioned CDR sequences for modification.

- Insufficiency objections could be raised only in case of serious doubts, substantiated by verifiable facts. In opposition proceedings the burden of proof lies with the opponent. The opponent had not shown either that the skilled person would encounter experimental uncertainties, the patent lacked a complete guidance due to the presentation of wrong references or, that scientific research was necessary to carry out the invention.

- The skilled person was provided in the patent with a detailed teaching allowing the repetition of the invention by starting from antibodies/antigen binding portions exhibiting the motifs claimed and exemplified in the present examples of the present invention. It was just a matter of routine to the person skilled to repeat the modifications already exercised in the examples and the provision of so far not exemplified variants by just introducing conservative amino acid substitution, this being

the decisive teaching to the skilled person. The so-obtained variants could be easily tested for their binding properties by conducting the same tests as the present inventors did when determining the K_{off} rate constant. Upon conducting this experiment, the skilled person was well in a position to determine, whether an antibody falls within the definition of the claims or lies outside the scope of the present claims. The appellant could not and had not shown otherwise.

Inventive step - Article 56 EPC

- For the first time in history, an isolated fully human antibody to human TNFα was provided exhibiting the features required for therapeutic potency, i.e. sufficient binding strength and structural CDR3 motifs.

- In the cited prior art, so far only low affinity antibodies with fast K_{off} rates had been described (i.e. with a K rate in the range of $10^{-2}s^{-1}$ or higher; see patent in suit paragraph [0005]: "*Because of their relatively fast dissociation kinetics these antibodies might not be suitable for therapeutic use*"). On the other hand the antibodies provided by the present patent exhibited a considerably slower K_{off} rate constant than those in the prior art, overcoming a noted drawback of the prior art and were the first fully human antibodies exhibiting therapeutic potency. In addition, the CDR3 domains mentioned in claim 1 were characterised by key positions (amino acid positions) identified by the present inventors

while conducting the binding analysis of examples 2 and 3. It was known in the art that CDR3 domains played the important role in the binding specificity and affinity of an antibody for an antigen (see e.g. document (D16), page 781, discussion, paragraph 1). Overall, the combination of all features of granted claim 1 reflected the essential characteristics of the new class of antibodies provided by the presently claimed invention.

– There was no hint in the prior art to the existence of fully human antibodies with binding characteristics necessary to qualify as therapeutically useful candidates. No neutralising, fully human anti-hTNFα antibody with a K_{off} value of 1 x $10^{-3}s^{-1}$ or less existed at the priority date of the invention, while potent neutralizing murine anti-hTNFα antibodies (like MAK195, see document (D7)) had already been disclosed many years before reflecting the actual difficulties which a skilled person encountered trying to obtain a human antibody having similar properties. The selection of MAK195 as tool was a lucky snatch by the present inventors and was part of the present invention.

– Others had been unsuccessful in providing fully human anti-hTNFα antibodies with said binding characteristics, e.g. documents (D3) and (D8) disclosed a specific anti-human TNFα antibody denominated P3A2 (derived from the murine template Mab32), which, however was a low-affinity, non-

neutralising and consequently therapeutically ineffective antibody.

– The means employed in the prior art to obtain a fully human antibody of the desired binding characteristics were insufficient. For example a guided selection step as disclosed in document (D8) alone, failed to provide a fully human antibody equivalent to the potent murine anti-hTNFα.

– The new class of antibodies defined by the present claims were the result of a new and ingenious research program. They exhibited new CDR3 regions unrelated to antibodies known in the prior art. In addition, the present inventors established that a plurality of variants do meet the desired binding characteristics which were identified by conducting experiments; including single alanine mutagenesis (see example 2) as well as experiments identifying the key positions within these CDR3s (example 3), thereby providing a teaching with regard to further conservative substitution variants.

– The antibodies identified by the present invention are superior to the known human anti-human TNFa antibodies (see documents (Dl), (D3), (D5) and (D8)) and to the murine high affinity antibodies such as MAK195 (see document (D7)).

XIV. The appellant requested in writing that the board base its decision on its written submissions and revoke the patent. The board inferred accordingly that the

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

The respondent requested that the appeal be dismissed or that the decision under appeal be set aside and the patent be maintained on the basis of one of its auxiliary requests 1 to 11 filed on 4 April 2011. The respondent also requested that all the documents filed during the appeal proceedings by the appellant (other than annex 1 to the statement of grounds of appeal) be held inadmissible.

Reasons for the Decision

1. The appeal is admissible.

Procedural matters

Multiple representatives

2. On 4 April 2011, shortly before the oral proceedings on 4 May 2011, the respondent appointed a second firm of representatives as joint representatives in addition to the firm already acting and asked the board to send copies of all correspondence to both firms (see section VI, above). After the board gave a negative answer to that request in its communication of 12 April 2011, the respondent repeated the request in a subsequent letter of 14 April 2011 (see section IX, above).

3. While it is open to a party to appoint as many representatives as it may wish, the board is not aware of any requirement on it or on other parties to send

correspondence to more than one representative of one party. If a party wants to retain multiple representatives, it must make its own arrangements for copying correspondence to them all. Parties cannot expect the board to provide copying services for their convenience.

Provision of translation in oral proceedings

4. The respondent announced in its letter of 4 April 2011 that it would use German at the oral proceedings and requested the board to provide translation from German into English for the benefit of the appellant and of one of its own employees who would attend the oral proceedings and who does not speak German (see section VI above).

5. It is a right of any party to use any one of the three official languages in EPO proceedings, but the right to translation from either of the two other languages is circumscribed by Rule 4 EPC. It is clear from Rule 4(1) and (5) EPC that a party who gives at least one month's prior notice is free to use an official language other than the language of the proceedings and that interpretation must then be provided by the EPO.

6. However, such interpretation is quite manifestly only for the benefit of other parties not using the same language who would otherwise be at a disadvantage. In the present case that might have included the appellant had it not decided not to attend the oral proceedings but then it would clearly have been he, and not the respondent, who was responsible for requesting free translation at least one month before the date of the

oral proceedings (see Rule 4(1) EPC). In the board's view it is equally clear that a party which elects to use a language which is not understood by one of its own representatives or employees cannot for that reason request a free translation. The board cannot provide translation merely to suit the convenience of a party.

Requests for decisions in advance of oral proceedings

7. The respondent made several attempts to obtain a decision or partial decision from the board before the date of the oral proceedings. In one of its letters of 4 April 2011 it requested the board to indicate whether or not the oral proceedings were necessary and also requested the board to inform it whether or not it intended to admit the documents whose admissibility the respondent had challenged (see section VI, above). This would have required the board to decide those admissibility issues before the oral proceedings. In its letter of 21 April 2011, it limited its request for oral proceedings so as only to be effective if its main request was not granted. Again this would have required the board to decide the main request before the oral proceedings.

8. The respondent's objective seems to have been the quite understandable one of avoiding or reducing the costs of attending the oral proceedings. However, even if only one party makes or maintains a request for oral proceedings, the board cannot make any decision before the oral proceedings. The purpose of oral proceedings being to hear the parties before making a decision, any decision or part-decision in advance of the oral proceedings could deny a party the right to be heard,

assist one party to the prejudice of another, and compromise the board's duty of impartiality (see Article 113(1) EPC and decision R 11/08 of 6 April 2009, Reasons, point 14). If avoidable costs are a concern to a party, its remedy is to request not a premature decision but an apportionment of costs.

Admissibility of the appellant's written submissions and documents filed in the appeal proceedings

9. With the exception of annex 1, which was stated to correspond to table 6 on page 24 of the patent in suit and to which the respondent for that reason did not object, the board finds that all the evidence filed by the appellant with its statement of grounds of appeal, i.e. documents (D38) to (D40) and the experimental evidence in annexes 2 and 3, is inadmissible.

10. The appellant has provided no reason why any of this evidence was not filed in the first instance proceedings and no such reason is otherwise apparent, as might be the case if the decision under appeal had produced a substantially different case from that facing the appellant when he filed his opposition. Additionally, the experimental evidence in annex 3 was held inadmissible by the opposition division and, since the board agrees with the opposition division on the interpretation of claim 1 of the patent (see point 15, below), there is no basis for reversing the opposition division's decision not to admit that evidence.

11. While that is enough to dispose of the matter, the board also agrees with the respondent that the case presented in the statement of grounds of appeal was

very largely a new case and was only to a small extent a reasoned challenge to the first instance decision (see for example page 26 of the statement which contains the first reference therein to the decision under appeal). At the oral proceedings, the respondent suggested that the appeal as a whole was inadmissible but the limited reference to the first instance decision just avoids that result. However, the fact that the new evidence filed in the appeal almost entirely relates to the fresh case is a further reason (if such were needed) why it is inadmissible.

12. Turning to the appellant's written submissions of 21 December 2010 and the accompanying documents, no reason was provided why these were filed more than three years after the statement of grounds of appeal or why they were not filed with that statement. They clearly demonstrate that the appellant did not file its complete case in its statement of grounds of appeal. Equally clearly, they constitute an amendment to the appellant's case, both as to substance, i.e. the submissions run to thirty pages of additional argument, and as to volume, i.e. the documents comprise more than 1,200 pages.

13. Accordingly, the board has no hesitation in exercising its discretion to refuse to admit them under Article 13(1) RPBA.

Scope of the appeal

14. During the appeal proceedings the appellant has not objected to the claims under Article 100(c) EPC. The

board therefore needs to decide on compliance with Articles 56 and 83 EPC.

Construction of the subject-matter of claim 1

15. The opposition division considered in the appealed decision the construction of claim 1 (see point 3.2) and decided that the scope of the claim did not encompass dAbs or isolated CDRs.

15.1 The appellant has reiterated this point during the appeal proceedings in the context of its submissions under Article 83 EPC. It stated in particular that claim 1 could be interpreted so that the "antigen-binding portions" of the isolated human antibody were limited by all of the features a), b) and c) or alternatively that the "antigen binding portions" were derived from an antibody which antibody itself was limited by all the features a), b) and c). Paragraph [0031] of the patent in suit stated that an isolated variable domain, a domain antibody (dAb) and even an isolated CDR, fell within the term "antigen-binding portion".

15.2 Paragraph [0031] of the patent in suit defines the term "antigen-binding portion" of an antibody in general to refer to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., hTNFα) and lists examples of binding fragments which are encompassed within the term "antigen-binding portion" of an antibody including indeed "a dAb fragment which consists of a VH domain" (page 5, line 32) and "an isolated complementarity determining region (CDR)" (page 5 line 32 to 33). The board notes

however that the definition of the term given in paragraph [0031] of the patent in suit constitutes the common understanding of the skilled person at the relevant date. The appellant has not denied this fact. Furthermore, the paragraph as such defines merely a term used in the claims but not the subject-matter of the claims as such. For construing the latter the whole wording of the claim ought to be taken into account.

15.3 Claim 1 pertains to "an isolated human antibody, or antigen-binding portion thereof, with the following characteristics: a)..., b) ... and c)... .". The wording "*with the following characteristics*" unambiguously requires the subject-matter of the claim as such, conventionally, to conform to these characteristics. The board considers therefore that a proper construction of claim 1 rules out that the subject-matter also reads on "antigen binding portions" derived from an antibody itself characterised by all the features a), b) and c) and which themselves as such, as the appellant has argued, are *not* necessarily characterised by all the features a), b) and c).

15.4 Indeed, in accordance with established case law of the boards of appeal (see Case Law of the Boards of Appeal of the EPO, 6th Edition, 2010, II.B.5), a skilled person when considering a claim should rule out interpretations which are illogical or which do not make sense. He should try to arrive at an interpretation of the claim which is technically sensible and takes into account the whole disclosure of the patent. The patent must be construed by a mind willing to understand, not a mind desirous of misunderstanding. In the present case the board

considers that the appellant's interpretation of the claim goes beyond any logical and sensible interpretation of the subject-matter of claim 1.

16. The appellant has also argued that the subject-matter of claim 1 is not defined as to require the claimed antibodies to be capable of neutralising hTNFα. The board cannot agree with this contention.

17. The claims relate to a fully human antibody reactive against human TNFα and exhibiting features relating to particular structural CDR3 motifs and a minimum binding strength. The board considers these features sufficient for a therapeutic potency of the claimed antibody based on hTNFα neutralisation.

17.1 In particular, the binding strength is defined by the kinetic rate constant K_{off} which has been tested in the patent in suit as a measurement of sufficient binding strength (see examples 1-3). A borderline value for K_{off} rate limit $10^{-3}s^{-1}$ was chosen in examples 2 and 3 to delimit antibodies with desired binding strength from those without desired binding strength.

17.2 Furthermore, the CDR3 motives of the claimed antibody relate to the epitope recognised by the antibody. SEQ ID NO: 3 and SEQ ID NO: 4 represent the CDR3 domains of the variable light and heavy chain regions, respectively, of the antibody D2E7, i.e. the preferred embodiment of the claimed invention with a high therapeutic applicability concerning hTNFα neutralisation.

17.3 These sequences SEQ ID NO: 3 and SEQ ID NO: 4 were also identified in other antibodies disclosed in the patent in suit, such as e.g. LOE5 and LOE7 for SEQ ID NO:3 (see figure lb) and VH1-D2 as well as VHI-D2Y as regards SEQ ID NO:4 (see figure 2b). The impact of alanine mutations within SEQ ID NOs: 3 and 4 was tested by performing an alanine scanning mutagenesis of CDR3 domains (example 2). The binding characteristics as determined by K_{off} rate constant values in this experiment demonstrated that a single alanine mutation does not significantly affect the binding characteristics of D2E7 (see table 5, in which alanine mutations were performed at positions 2, 3, 4, 5, 6, 8, 9, 10 and 11 of SEQ ID NO:4 for the antibodies denominated HD2E7*.A1-A9 and alanine mutations at positions 1, 3, 4, 5, 7 and 8 were performed in the light chain with the antibody chains denominated LD2E7*.A1, A3, A4, A5, A7 and A8). The positions 2, 3, 4, 5, 6, 8, 9, 10 and 11 of the heavy chain (SEQ ID NO: 4) as well as 1, 3, 4, 5, 7 and 8 of SEQ ID NO: 3 (light chain) show a K_{off} rate constant of 1 x $10^{-3}s^{-1}$ or less. The results are summarised in paragraph [0131] of the patent in suit. Further modifications of SEQ ID NO: 3 and 4 are taught in example 3, in which further D2E7 related antibodies are identified with a binding strength of K_{off} rate constant 1 x $10^{-3}s^{-1}$ or less. The positions 2 and 5 within SEQ ID NO: 3 as well as positions 1 and 7 within SEQ ID NO: 4 are indicated as being critical (see paragraphs [0134] and [0135]). Claim 1 does not allow modifications at these critical positions within SEQ ID NOs: 3 and 4, respectively, but allows for one to five conservative substitutions at the other positions.

17.4 In view of the above considerations the board is satisfied that the independent claims relate to antibodies which are capable of neutralising hTNFα and that, although the claims do not explicitly state the neutralisation, this functional feature is to be read into the meaning of the claims by virtue of features a), b) and c).

Sufficiency of disclosure - Article 83 EPC

18. The board considers that a proper construction of claim 1 rules out that the subject-matter also reads on "antigen binding portions" which are not characterised by all the features a), b) and c) (see point 15, above). Accordingly, the appellant's argument that in so far as such antigen-binding portions were concerned, the patent fails to comply with Article 83 EPC, is moot and needs not to be dealt with further by the board.

19. The appellant has argued during the appeal proceedings that the patent in suit did not disclose any antibodies which have conservative substitutions as indicated in claim 1 apart from the single example of VH1-D2.N/LOE7.T. The skilled person therefore had to manufacture and test, by trial and error, these variants himself in order to determine whether or not they posses the requirements of claim 1 with respect to K_{off} rate constant, TNFα binding and neutralisation. This constituted an *undue burden* on the skilled person.

20. The appellant's argument is specifically directed to the manufacturing and testing of antibodies which have conservative substitutions as indicated in features b) and c) of claim 1. The patent in suit, inter alia in

paragraph [0050], defines a "conservative amino acid substitution" and example 1 discloses a particular antibody, D2E7, which is characterised by the sequence of its VL and VH regions depicted in Figures 1A and 1B and Figures 2A and 2B, respectively. Claim 1 indicates in characteristics b) and c) specific positions in SEQ IDs NO 3 and 4, the CDR3s, respectively, in which the conservative mutations may be generated. As the appellant has confirmed, the patent in suit discloses, in addition to the originally identified D2E7 antibody, an example of an antibody which has conservative substitutions as indicated in features b) and c) of claim 1 and which has the K_{off} rate constant as required in feature a) of claim 1, i.e. VH1-D2.N/LOE7.T (see example 3).

21. The board concurs with the respondent that the description and claim 1 suggest specific positions within the explicitly mentioned CDR sequences of features b) and c). Guided by this teaching, the skilled person routinely preparing mutations of amino acid sequences does not have to perform extensive trial and error experiments in order to find further embodiments of the invention.

22. The board therefore comes to the conclusion that no case has been made that the invention can only be carried out with undue burden since the skilled person had to test each and every conservative substitution variant whether or not they posses the requirements of claim 1.

23. Thus, on the evidence before it, the board considers that the patent in suit, in particular the examples,

sufficiently discloses the claimed invention across its whole scope.

24. In view of the above considerations the patent in suit is considered to disclose the invention in accordance with Article 83 EPC.

Inventive step - Article 56 EPC

25. In its decision the opposition division has argued in essence that the problem to be solved was the provision of high affinity and slow dissociating hTNFα neutralising human antibodies. The solution was the D2E7 antibody provided in the examples. Document (D7) was regarded as the closest prior art as it related to a mouse antibody that binds hTNFα with the desired properties (i.e. MAK195 used as the starting point in the patent examples, aka AM19S disclosed in document (D7)). The murine antibody would however cause a HAMA (human antibody against a mouse antibody) reaction if used in human patients for a protracted period. The opposition division considered that one way in which a human equivalent might be obtained was by using the method shown in document (D8). The opposition division considered that the skilled person seeking to solve the technical problem would turn to document (D8) as providing a solution despite the final sentence of the discussion for an attempt to produce a human antibody to TNFα. From the patent in suit it was however clear that guided selection (as shown in document (D8)) did not provide the desired antibody and several other techniques were additionally necessary.

The opposition division considered further that the specific sequence data provided in parts b) and c) of claim 1 provided a specific requirement which had to be arrived at. Bearing in mind the structural differences that mark out a mouse antibody from a human one (to the immune system), a direct one to one replacement of amino acids in the CDRs could not be made. Consequently, the sequences as recited in the claims were critical and could not simply be regarded as unimportant in assessing the inventive step of the claims. Therefore it had to be shown in document (D8) that the sequences of claim 1 could be arrived at. A skilled person could therefore not arrive at the exact antibody disclosed in claim 1, following the method of document (D8), without undue burden, but only with the need to use some other inventive ingredient.

The closest prior art

26. The claims of the patent in suit relate to a fully human and isolated antibody reactive against human TNFα and exhibiting features relating to particular structural CDR3 motifs and a minimum binding strength expressed as a specific dissociation rate constant of 1 x $10^{-3}s^{-1}$. The latter features provide the antibodies with the capability to neutralise hTNFα efficiently thereby rendering it applicable in therapy. It is noted, and the appellant has not argued differently, that the prior art does not disclose any isolated human antibody reactive against human TNFα having the capability to neutralise hTNFα activity efficiently.

27. For 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. In accordance with the established case law of the boards of appeal, the closest prior art is a teaching in a document conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications to arrive at the claimed invention.

28. On various occasions, during both the opposition and appeal proceedings, the appellant has argued that document (D8) represented the closest prior art.

29. Document (D8) discloses the so-called "guided selection" method as a tool for producing a human anti-hTNFα antibody, i.e. P3A2, using monoclonal antibody-derived rodent VL and VH chains as templates, i.e. MAb32. The appellant argued that document (D8) addressed the general core problem of providing anti—hTNFα antibodies which avoid the known difficulties of the murine antibodies which had been used in the art, such as human anti-mouse antibody response (HAMA) when administered.

30. The board notes however that it is clear from the disclosure in document (D3), a patent document relating to the same experiments as disclosed in document (D8), i.e. from the sentence bridging pages 36 and 37, that MAb32, being the mouse anti—hTNFα antibody being used for isolating a human equivalent, does not inhibit the cytolytic effect of TNF.

31. Document (D7) on the other hand discloses a mouse antibody that binds hTNFα with the desired properties (i.e. MAK195, also called AM19S) and which was used in the examples of the patent in suit as the starting point to isolate D2E7 antibody which was provided in the examples of the patent in suit. Document (D7) therefore discloses an antibody which complies with the functional requirements as set for the claimed antibodies and which is capable of neutralising hTNFα. The board therefore agrees with the opposition division that, rather than document (D8), document (D7) represents the closest prior art, in particular one of the four antibodies disclosed therein, i.e. MAK195.

The objective problem to be solved

32. The opposition division has formulated the problem to be solved, based on the disclosure in document (D7) representing the closest prior art, as the provision of high affinity and slow dissociating hTNFα neutralising human antibodies. The appellant has not challenged this problem as defined by the opposition division in its decision, in particular not in any submissions on inventive step in the statement of grounds of appeal. Also the board can agree with the formulation of the problem to be solved by the opposition division especially in view of paragraphs [0004] and [0006] of the patent in suit which define the problem to be solved as: "*A preferred hTNFα inhibitory agent to murine mAbs or derivatives thereof (e.g., chimeric or humanized antibodies) would be an entirely human anti-hTNFα antibody, since such an agent should not elicit the HAMA reaction, even if used for prolonged periods*." and "*Accordingly, human antibodies, such as recombinant*

human antibodies, that bind soluble hTNFα with high affinity and slow dissociation kinetics and that have the capacity to neutralize hTNFα activity, including hTNFα-induced cytotoxicity (in vitro and in vivo) and hTNFα-induced cell activation, are still needed."

33. The board is also satisfied that the said problem is solved by the claimed invention in view of the results obtained in the examples of the patent in suit.

Obviousness

34. The relevant question to be answered in the context of the assessment of inventive step is whether the skilled person, having possession and knowledge of the murine MAK195 antibody and its specific properties, would find sufficient guidance in the prior art to have the comfort of a reasonable expectation that the identification of a human antibody falling within the scope of the independent claims would be successful.

35. The appellant has referred to the disclosure of document (D8) as to give the skilled person such guidance. Document (D8), entitled "*Guiding the Selection of Human Antibodies from Phage Display Repertoires to a Single Epitope of an Antigen*", reports on a screening strategy for guiding the selection of human antibody fragments from phage display repertoires to a single epitope of an antigen using rodent monoclonal antibodies fragments as templates. It is clear from the patent in suit that a similar screening method, i.e. guided selection, as disclosed in document (D8) has also been used in the process of the

identification of the D2E7 antibody of the present invention.

36. The appellant has argued that there was overall a reasonable expectation that guided selection as disclosed in document (D8) would allow the conversion of a murine neutralising anti-TNFα antibody, i.e. MAK195 as disclosed in document (D7), to a human neutralising anti-TNFα antibody falling within the claimed scope.

37. During the appeal proceedings, the appellant has noted that the skilled person would have expected some degree of alteration in the kinetic properties between the mouse template antibody and the human antibodies obtained from the guided selection steps. In this context the appellant referred to document (D8), for instance under the discussion section, where it was stated that: "*It would therefore be expected that the antibody ... has the same "footprint" on the antigen ... and the relative orientations of heavy and light chains are similar. However, the molecular contacts of the antibody to the antigen are likely to be different. … in guided selection, the antigen binding site and specificity are most likely to differ, the epitope is retained, but the antibodies are entirely human*." The appellant acknowledged that any alterations in the antigen/antibody contacts could indeed lead to observable alterations in the functional properties of the human antibody compared to the rodent template. Therefore, a reduction in the kinetic properties of the selected human antibodies would not have been unexpected to the skilled person, and indeed might have been predicted.

38. The board notes in this context therefore that by these statements the appellant rather confirms that the skilled person, combining the teaching of documents (D7) and (D8), as such, would seem not to have had a reasonable expectation that an eventually isolated human antibody resulting directly from a screen based on the murine MAK195 antibody would fall within the scope of the claims.

39. The appellant has however further argued that, nevertheless, even if the human antibody obtained directly from the guided selection step had poor kinetic properties at that stage, the skilled person had a reasonable expectation that the kinetic properties of this antibody could have been further optimised successfully for therapeutic purposes. It was well known in the art that the kinetic properties of an antibody could be improved by the known and routine techniques of chain shuffling, random mutagenesis and backmutation / "germlining", all techniques referred to in the patent in suit in paragraphs [0086] to [0088]. Therefore, the most important and primary feature of any human antibodies obtained directly from the guided selection step was that they recognise a particular epitope (i.e. the same epitope as is recognised by the mouse template antibody). The skilled person, knowing he could improve these at a later stage by routine techniques, would regard the exact kinetic properties of an antibody thus obtained directly from the guided selection step as being of secondary importance. The two steps could be thought of as an initial "high throughput" screen (i.e. the guided selection step) to select candidate "lead compounds", followed by lead

optimisation (i.e. improvements in the kinetic properties of the antibody) to obtain antibodies which recognise the desired epitope and which have optimal kinetics, i.e. which fall under the scope of the claims.

40. The appellant accordingly argued that the claimed-subject matter lacked inventive step by stating that there was a **reasonable expectation** that guided selection would allow, in principle, the conversion of a murine neutralising anti-TNFα antibody to a human neutralising anti-TNFα antibody, even if the human antibody obtained directly from the guided selection step had poor kinetic properties at that stage, seeing that there would have been a **reasonable expectation** that the kinetic properties of that antibody could have been further optimised.

41. Document (D5), entitled "Human anti-self antibodies with high specificity from phage display libraries", elaborates on the huge potential of human monoclonal antibodies for therapy and notes however that it is "*especially difficult to generate human mAbs directed against human antigens (anti-self antibodies), for example to block septic shock (…). This difficulty results from immunological tolerance mechanisms that prevent the antigen-driven expansion of B-cell clones with self specificities (…).*" (see document (D5), page 725, left-hand column line 1 to right-hand column, line 3). The document discloses nevertheless the isolation of human scFv fragments of high specificity against a small number of human antigens, including human TNFα, by the use of the phage display libraries disclosed (see page 726, left hand column, lines 21 to 23, page 730, right-hand column, lines 25 to 30,

figures 1 and 2, Table IV). Although the binding to the antigens is reported to be highly specific, the kinetics of association of the antibody fragments are reported to be "fast off-rate" (see page 730, right-hand column, lines 33 to 34 and 47 to 58). As already referred to above document (D8) (and document (D3) similarly) also discloses a non-neutralising human anti-hTNFα antibody. Also document (D1) discloses a human anti-hTNFα antibody, B5, which is of low affinity and does not neutralise the cytotoxicity of rhTNFα.

42. The board notes therefore that low affinity, human anti-hTNFα antibodies had been identified in the prior art. However none of these prior art antibodies are neutralising the activity of hTNFα, let alone are they reported as recognising an epitope on hTNFα which has the potential of being the key to such neutralisation. The board therefore concludes that although the skilled person, based on the disclosures in the prior art, may have had a reasonable expectation that the method as disclosed in document (D8) could provide further low affinity non-neutralising anti-hTNFα antibodies, there is no teaching in the available prior art that human antibodies can be isolated by this method which recognise epitopes on a given protein which, when the antibody binds to it, can neutralise the activity of this protein. On the contrary, the board is of the opinion that the skilled person would be sceptical in this respect, certainly in view of the statements in document (D5) referred to in point 41, above. This must also apply, if not even more, to the expectation to identify human anti-hTNFα antibodies having hTNFα neutralising capacity, which when present in the human body would be expected to have even more pronounced

deleterious effects to the human organism than non-neutralising ones.

43. A number of decisions of the boards of appeal in the technical field of biotechnology have pointed out that, in evaluating the attitude of the skilled person, one should not confuse the "hope to succeed", which is linked to the wish that a result be achieved, with the "reasonable expectation of success", which is linked to the ability to predict reasonably, based on the particular technical circumstances, a successful conclusion of the project within acceptable time limits (see e.g. decisions T 296/93, OJ EPO 1995, 627, T 923/92 and OJ EPO 1996, 564). In this respect, each case has to be assessed on its own merits, and any hindsight has to be avoided. Thus evaluating the "reasonable expectation of success" involves analysing the prior art to determine the degree of confidence it gives the skilled person that an envisaged result will be obtained. If that degree of confidence is too low, the reasonable expectation turns into a mere "hope to succeed". A skilled person working on that basis follows a non-obvious course of action.

44. For the board the circumstances referred to above indicate that at the priority date the skilled person could in general not make any reliable rational predictions about the likelihood of obtaining human antibodies recognising epitopes on hTNFα and which, when bound to the epitope, can neutralise the activity of hTNFα. Consequently, the board considers that the skilled person's level of confidence in finding any human antibodies recognising epitopes on hTNFα with the ability to neutralise hTNFα too low to perceive a

reasonable expectation of success. Hence, the board concludes that if the skilled person, in the light of the prior art, had embarked on the project of isolating such antibodies starting from the murine antibody disclosed in document (D7) and using the guided selection method as disclosed in document (D8), this would have been done in the hope of succeeding and not because there was any reason to expect a favourable outcome.

45. The conclusion reached above renders superfluous an assessment of the appellant's further argument that even if the human antibody obtained directly from the guided selection step had poor kinetic properties at that stage, seeing that there would have been a reasonable expectation that the kinetic properties of that antibody could have been further optimised.

46. Accordingly, the board concludes that the skilled person would not have obtained the subject-matter of the independent claims with a reasonable expectation of success. Consequently, the requirement of Article 56 EPC is fulfilled.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar The Chairman

P. Cremona C. Rennie-Smith