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**Datasheet for the interlocutory decision
of 24 April 2008**

Case Number: T 0601/05 - 3.3.04

Application Number: 94102560.3

Publication Number: 0614984

IPC: C07K 16/24

Language of the proceedings: EN

Title of invention:

Anti-TNF alpha human monoclonal antibodies

Patentee:

Bayer Corporation

Opponents:

- 01 Centocor, Inc.
02 Abbott Laboratories

Headword:

Anti-TNF alpha human monoclonal antibodies/BAYER II

Relevant legal provisions:

EPC Art. 56

Keyword:

"Main Request - inventive step (yes)"

Decisions cited:

T 0939/92, T 0450/95, T 1329/04

Catchword:

-



Case Number: T 0601/05 - 3.3.04

I N T E R L O C U T O R Y D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 24 April 2008

Appellant: Bayer Corporation
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Decision under appeal: Decision of the Opposition Division of the European Patent Office posted 16 February 2005 revoking European patent No. 0614984 pursuant to Article 102(1) EPC 1973.

Composition of the Board:

Chairman: M. Wieser
Members: G. Alt
R. Moufang

Summary of Facts and Submissions

I. This is the second interlocutory decision in appeal case T 601/05. The first interlocutory decision was announced at the oral proceedings held on 18 October 2007. At the same oral proceedings, the board, after having heard the parties with respect to the inventive step of the main request, closed the debate on that issue, which is dealt with in the present decision. As far as the procedural facts in general are concerned, reference is made to the section entitled "Summary of facts and submissions" in the reasoned first interlocutory decision.

II. Claim 1 of the main request read:

"1. A pharmaceutical composition containing a human monoclonal antibody that binds to human tumor necrosis factor alpha."

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

ID8: Scand. J. Immunol., vol. 30, 1989, pages 219-223, Fomsgaard, A. et al.

ID9: Bendtzen K. et al. in "The Physiological and Pathological Effects of Cytokines"; Eds. Dinarello, C. A. et al.; 1990, pages 447-452

ID25: J. Immunol. Meth., vol. 100, 1987, pages 5-40, James, K. and Bell, G.T.

ID26: WO 89/00607

- ID29: The Lancet, vol. 26, No. 335, 1990, pages 1275-1277, Exley, A.R. et al.
- ID32: EMBO J., vol. 12, No. 2, 1993, pages 725-734, Griffiths, A.D. et al.
- ID35: Declaration by Prof. Paolo Casali dated 01 May 2004
- ID46: Declaration by Prof. Sander van Deventer dated 19 October 2004
- ID57: Nature, vol. 349, 1991, pages 293-299, Winter, G. and Milstein, C.

IV. The appellant's submissions in writing and during the oral proceedings, as far as they are relevant for the present decision, may be summarised as follows:

Document ID29 did not represent the closest prior art because it did not disclose the pharmaceutical usefulness of the murine monoclonal anti-tumour necrosis factor (TNF) alpha antibody CB0006.

At the priority date of the patent a skilled person would not have attempted to provide human monoclonal antibodies because of the known difficulties in generating them as evidenced by documents ID25, ID32 and ID57.

If the view was accepted on the basis of declarations ID35 and ID46 that, generally, low-affinity antibodies lacked pharmaceutical usefulness, it had to be

considered as an indication of inventive step to provide such antibodies for pharmaceutical purposes.

- V. Respondent I's and respondent II's (hereinafter: the respondents) submissions in writing and during the oral proceedings, as far as they are relevant for the present decision, may be summarised as follows:

Either any one of documents ID8 and ID9 or document ID29 represented the closest prior art.

The problem to be solved was the provision of a further therapeutically useful antibody binding to tumour necrosis factor alpha.

This problem was not solved by the patent because it merely disclosed a low-affinity antibody. It was however generally recognised, as evidenced by declarations ID35 and ID46, that low-affinity antibodies were not pharmaceutically useful. The patent did not contain evidence of a therapeutic application either, because the data in Table 10 were doubtful.

Even if the problem was considered as solved, there was lack of inventive step because the provided solution was obvious. Methods to produce human antibodies were well-known, for example from document ID26.

Reasons for the decision

Main Request

Inventive step

1. To assess inventive step, this board, in line with the normal practice of the boards of appeal of the European Patent Office, will apply the "problem and solution approach". This involves as a first step identifying the closest prior art.

The closest prior art

2. The respondents considered either document ID29 or any one of documents ID8 and ID9 as the closest prior art documents.
 - 2.1 The boards of appeal have developed certain criteria that should be adhered to in order to identify the closest state of the art. One such criterion is that the closest prior art is a document disclosing subject-matter conceived for the same objective as the claimed invention and having the most relevant technical features in common (Case Law of the Boards of Appeal of the European Patent Office, 5th edition 2006, I.D.3.1).
 - 2.2 In the light of the claims, the objective of the patent is to provide pharmaceutically useful antibodies binding to tumor necrosis factor (TNF) alpha.
3. Document ID29 discloses the results of a phase I clinical trial conducted with the murine monoclonal, TNF-alpha binding antibody CB0006. In the board's view, the fact that the antibody is submitted to a phase I clinical trial unambiguously conveys that the antibody CB0006 is intended for a pharmaceutical purpose.

- 3.1 The appellant argues that the results reported in document ID29 indicated that the antibody CB0006 was not actually pharmaceutically effective. However, for the determination of the closest prior art the purpose objectively derivable from a document is taken into account. Therefore, since document ID29 is considered to disclose the pharmaceutical purpose (see point 3 above), the appellant's perceived pharmaceutical non-effectiveness of the antibody CB0006 is not relevant with regard to the determination of the purpose underlying that document.
- 3.2 Documents ID8 and ID9 report on the presence of auto-antibodies to TNF-alpha in human sera. In none of the two documents is it suggested to exploit these sera or isolated antibodies therefrom for pharmaceutical purposes.
- 3.3 Therefore, the board concludes that document ID29, and not any one of documents ID8 or ID9, represents the closest prior art with regard to the present invention.

The problem

4. In view of the closest prior art, the problem to be solved is therefore the provision of pharmaceutically useful TNF-alpha-binding monoclonal antibodies being less immunogenic in humans than the murine monoclonal antibody CB0006.

Is the problem solved?

5. With reference to decision T 1329/04 of 28 June 2005 the respondents submit that the patent does not solve

the posed problem because it does not contain evidence about pharmaceutically active antibodies.

5.1 According to decision T 1329/04 "[t]he definition of an invention as being a contribution to the art, i.e. as solving a technical problem and not merely putting forward one, requires that it is at least made plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve" (see point 12 of the reasons).

5.2 Hence, in view of this approach and the respondents' argument, the question in the present case arises whether the patent contains enough evidence to make it plausible that human monoclonal TNF-alpha binding antibodies with therapeutic value have indeed been generated.

5.3 The patent describes in paragraph [0088] an assay testing the influence of antibodies B5, 6F11 and 7T1 on the lipopolysaccharide (LPS)-stimulated secretion of TNF-alpha from a human monocyte cell line. Two series of experiments are disclosed. In the first series, the inhibition of secretion was tested in the absence of an antibody, in the presence of 40µg/ml of monoclonal antibody 6F11, 40µg/ml of monoclonal antibody 7T1, and of 40, 20, 10 and 5µg/ml of antibody B5. In the second series, inhibition of secretion was tested in the absence of antibody, in the presence of 40µg/ml of antibody 6F11 and of 40, 20, 10 and 5µg/ml of antibody B5.

5.4 Table 10 presents the results inter alia in terms of % of inhibition of secretion of TNF-alpha:

Inhibition was 0% in the absence of antibody. In the presence of 40µg/ml of antibody 6F11, inhibition was 1% and 3%, respectively. In the presence of 40µg/ml of antibody 7T1, inhibition was 3%. The presence of antibody B5 at the different concentrations resulted (in descending concentration order) in 90/93%, 59/62%, 19/38% and 4/-10% inhibition.

5.5 In the board's view, the data demonstrate that the antibody B5 inhibits LPS-induced secretion of TNF-alpha specifically (see the near absence of inhibition with the control antibodies) and in a dose-dependent manner (see inhibition of B5 at different concentrations).

5.6 According to paragraph [0005] of the patent TNF-alpha is one of the factors secreted during septic shock as well as inflammatory diseases. Given therefore that secretion of TNF-alpha from the cell may be regarded as one of the reasons for its deleterious effects, the demonstration in the patent of the inhibition of secretion of TNF-alpha by the human monoclonal antibody B5 is for the board convincing evidence to make the pharmaceutical usefulness of the B5 antibody plausible.

5.7 It is disclosed in the patent that the antibody B5 binds to TNF-alpha with low affinity. With reference to documents ID35 and ID46 the respondents maintain that, at the priority date of the patent, low-affinity antibodies would not have been considered as pharmaceutically useful by the skilled person. However, in view of the finding of the board above, i.e. that the evidence in the patent makes the pharmaceutical

usefulness of the specific low-affinity antibody B5 plausible, the respondents' argument fails.

5.8 The respondents further argue that the data presented in Table 10 are questionable:

- (a) It is submitted that the antibody 6F11, which is an anti-Pseudomonas lipopolysaccharide (LPS) monoclonal antibody (see for example the patent paragraph [0058]), should only bind to LPS and not to TNF-alpha. Therefore, it should not inhibit TNF-alpha secretion. Firstly, the board notes that the inhibiting effect of the antibody 6F11 is minor (1% and 3%, respectively). Secondly, the data on the binding of the antibody 6F11 to the surfaces of cells from various cell lines reported in Table 2 appear to indicate that the antibody is not free of cross-reactivity.
- (b) It is submitted that antibody 7T1 should bind better to TNF-alpha than it does according to Table 10. However, it is stated in paragraph [0048] of the patent that the antibody 7T1 fails to bind to TNF-alpha complexed to mouse monoclonal antibodies. In the board's view, this statement rather points away from the alleged good binding properties.
- (c) It is further submitted that the high level of inhibition of antibody B5 at 40µg/ml reported in Table 10 is dubious in view of the results in Table 4. However, the appellant submitted at the oral proceedings that, in the experiments leading to the results in Table 4, binding of the antibody

was determined instantaneously after its addition, while in the experiment leading to the results in Table 10 the incubation time of the antibody was four hours. Thus, the board considers that the increased binding can be explained as the result of the increased incubation time.

(d) Finally, it is submitted that Table 6 shows an unspecific binding of the antibody B5 to TNF-alpha. However, the results presented in Table 6 are unrelated to those of Table 10 and have therefore no effect on their interpretation.

5.9 Hence, the board considers that none of the respondents' submissions is appropriate to cast doubt on the credibility of the data in Table 10.

6. Finally, the board notes the following:

6.1 With respect to their argument that the patent does not solve the problem posed, the respondents cited, together with decision T 1329/04 (supra), decision T 450/95 of 18 July 2000 which, as far as the reasoning relevant in the present context is concerned, refers to decision T 939/92 (OJ EPO 1996, 309), points 2.6 and 2.6.1 of the reasons (see decision T 450/95, point 2.12).

6.2 However, in the board's view, the considerations in decision T 1329/04 and T 939/92 concerning the question whether the subject-matter of a patent solves a problem relate to different circumstances.

- 6.3 According to decision T 1329/04 it is examined whether the **description** of the patent application provides plausible evidence that the posed problem is solved (see point 5.1 above).
- 6.4 In decision T 939/92, the board stated that "[the] technical problem could only be taken into account if it could be accepted as having been solved, ie if, in deciding the issue under Article 56 EPC, it would be credible that substantially all **claimed** compounds possessed this activity" (third paragraph of point 2.6; emphasis added by this board). In point 2.7 the board stated that "only those of the **claimed** chemical compounds could possibly involve an inventive step which could be accepted as solutions of the technical problem"(emphasis added by this board). Thus, in the board's view, the approach of decision T 939/92 is only applicable in situations where the problem to be solved consists in the achievement of an effect which effect is not stated in the claim. Only then does the question arise whether or not all of the claimed compounds, which may be defined in the claim, for instance, by their structure or by a way for their production, achieve the required effect.
- 6.5 Present claim 1 relates to a "pharmaceutical composition". Thus, the pharmaceutical effect of the composition is a feature of claim 1. Therefore, the question to be answered in the context of Article 56 EPC is not whether all the compositions covered by the claim are pharmaceutically useful since compositions not meeting this criterion are not encompassed by the claim due to its wording. Hence, the situation

underlying decision T 939/92 is different and the decision is not applicable here.

7. The board thus decides that the patent provides sufficient evidence that pharmaceutically useful TNF-alpha-binding monoclonal antibodies being less immunogenic in humans than the murine monoclonal antibody CB0006 are provided and that, accordingly, the problem underlying the patent has been solved.

Obviousness of the solution

8. The appellant submits that the skilled person would not have attempted to generate human monoclonal antibodies binding to human TNF-alpha at the priority date of the patent in view of the known difficulties of generating human monoclonal antibodies by immortalisation of B-lymphocytes, i.e. by the hybridoma technique, as for example disclosed in documents ID25, ID32 or ID57. He/she would rather have chosen an alternative technology, such as for example humanising a mouse antibody, as for example disclosed in document ID32 or document ID57.

On the other hand, the respondents submit that methods of generating fully human monoclonal antibodies were known, for example from document ID26. Therefore, the solution according to claim 1 was obvious.

- 8.1 Document ID25, published in 1987, mentions in the introductory part on page 5 that "the development of human monoclonal antibody technology has been a slow, laborious and often unrewarding exercise", and on page 29 that "[f]rom our previous comments it is

obvious that the production of human monoclonals is still a chance affair involving considerable effort and dedication. It is also equally apparent that at the present time there is no simple answer to the many problems which beset this work."

However, on the other hand, document ID25 sets out and evaluates in detail on nearly 23 pages the different methods that had so far been used for producing human monoclonal antibodies. Moreover, Table XII lists 78 antigens, including 27 autoantigens (tumour necrosis factor is an autoantigen; see for example documents ID8 and ID9 reporting on the presence of autoantibodies against TNF-alpha), against which human monoclonal antibodies were raised. In addition, a book is recommended on page 5 of document ID25 which contains a "detailed methodological appendix" on the techniques of producing human monoclonal antibodies by the hybridoma technique.

- 8.2 Document ID26, a patent application having a priority date in the year 1987, also discloses a method for the generation of human monoclonal antibodies and that antibodies were indeed successfully produced by it. It is stated on page 19: "Table 3 shows several cell lines making antibody of the IgG, IgA and IgM class to Tg, Ins, and TT. These clones produced 5-20 µg/ml of IgG, 10-40 µg/ml IgA, and 5-160 µg/ml IgM. Many clones have been expanded in culture for up to six months without alteration in their rate of growth or immunoglobulin secretion. Over 40 antibody-producing clones have now been constructed."

8.3 The board considers that, in view of documents ID25 and ID26, a skilled person would have been confident at the priority date that, though not being free of difficulties, the production of human monoclonal antibodies to a selected antigen, including autoantigens, such as TNF-alpha, was a feasible affair.

8.4 In order to support further its view that, at the priority date of the patent, the prior art taught away from generating fully human monoclonal antibodies, the appellant cited documents ID32 and ID57 and referred in his written submissions inter alia to the following passages:

Document ID32, page 725:

"Human monoclonal antibodies (mAbs) have huge potential for therapy, but are difficult to make by immortalizing B-lymphocytes (for reviews ...). Furthermore, it is especially difficult to generate human mAbs directed against human antigens (anti-self antibodies), for example antibodies against soluble TNF to block septic shock..."

Document ID57, page 298:

"Gene technology offers alternatives. The 'humanizing' of rodent monoclonal antibodies is currently the most practical approach."

Document ID57, page 299:

"We see a jungle of technologies, old and new, stimulating each other: in the immediate future, most of them start with immunized animals."

8.5 However, these statements have to be seen in the whole context of documents ID32 and ID57 which focus on the new methods of preparing antibodies by gene technology. Therefore, in the board's view, the skilled person would have perceived said statements as a means to stimulate a positive attitude vis-à-vis the new methods, rather than as a signal to abolish the "old" method of preparing human monoclonal antibodies by immortalising B-lymphocytes. The board thus concludes that the disclosure in documents ID32 and ID57 would not have discouraged the skilled person from generating human monoclonal antibodies by the hybridoma technique.

8.6 This conclusion is supported by a statement at the end of the discussion section in document ID57:

"But all these methods will have to compete with immortalization by Epstein-Barr virus and cell fusion, which themselves are constantly improving, particularly as they start to incorporate ideas and techniques involving DNA manipulations."

8.7 Further support comes from document ID35. Prof. Casali states therein in points 11 and 12:

"11. Due to my expertise in the field, in approximately 1992, while employed at New York University, I was contracted by a large multi-national corporation to obtain a fully human, high affinity, neutralizing monoclonal antibody to the human autoantigen TNF- α .

12. I used the same hybridoma technology I had used previously because I had been successful in producing fully human neutralizing monoclonal antibodies to different antigens and fully expected that this technology would lead to a fully human, high affinity, neutralizing monoclonal antibody to TNF- α ."

Thus, before the earliest priority date of the patent in March 1993, and although alternative technologies had existed, Prof. Casali nevertheless made an attempt to generate human monoclonal antibodies to TNF-alpha by hybridoma technology.

8.8 Hence, the board is not convinced by the appellant's argument that a skilled person would not have attempted to generate human monoclonal antibodies binding to human TNF-alpha at the priority date of the patent in view of known difficulties connected with the production of fully human monoclonal antibodies.

9. However, since claim 1 does not refer merely to a composition containing a human monoclonal antibody, but to "a **pharmaceutical** composition containing a human monoclonal antibody", it is not only necessary to examine whether it had been obvious to prepare a composition as such, but also whether or not it would be obvious to provide a **pharmaceutical** composition containing the antibody.

10. The respondents, in the context of their submission that the patent does not solve the posed problem, argue that at the priority date the skilled person would not have regarded low-affinity antibodies as

pharmaceutically useful compounds. They relied on declarations from Prof. Casali (ID35) and from Prof. van Deventer (ID46) to support this view.

- 10.1 Prof. Casali states in his declaration (document ID35, points 14 and 15):

"14. During the course of this laboratory work, however, I was able to develop fully human, moderate affinity IgM antibodies to TNF- α (....).

15. I did not submit the above results for publication due to the fact that these antibodies are scientifically uninteresting due to them having only moderate affinity levels. I suspect that other scientists obtaining similar moderate affinity antibodies to TNF-a likewise would not publish due to a lack of scientific significance."

- 10.2 Prof. van Deventer declares (document ID46, point 18):

"18. In my experience a low affinity, non neutralizing antibody to TNF α is not therapeutically useful. Only high affinity, neutralizing antibodies are therapeutically useful."

- 10.3 For the purpose of the argumentation of non-obviousness, the appellant adopts the respondents' view and maintains that, if it was accepted that the skilled person had attempted to generate human monoclonal TNF-alpha binding antibodies, it was not obvious to provide a **pharmaceutical** composition containing such antibodies, given that low-affinity antibodies were not considered to have any pharmaceutical value.

- 10.4 The board concludes from the parties' submissions (points 10 to 10.3 above) that they all agree that at the priority date of the patent the skilled person would not consider human monoclonal antibodies binding to TNF-alpha with low affinity as pharmaceutically useful.
- 10.5 On the other hand, it is not in dispute between the parties that at the priority date the skilled person would have considered human monoclonal antibodies binding to TNF-alpha with high affinity as pharmaceutically useful.
- 10.6 However, as to the possibility of generating such high-affinity antibodies, it is stated in declaration ID35, points 13, 16 and 17:
- "13. However, I was unsuccessful in generating fully human, high affinity, neutralizing monoclonal antibodies to TNF- α utilizing hybridoma techniques.
- [...]
16. In order to produce a fully human, high affinity, neutralizing TNF- α antibody using hybridoma technology, one needs to isolate a human B-cell from a human donor that actually produces high affinity, neutralizing TNF- α antibodies and [...].
17. However, the reason hybridoma technology is unable to produce fully human, high affinity, neutralizing monoclonal antibodies to TNF- α is that humans in

general do not make B-cells capable of producing neutralizing antibodies to TNF- α ."

- 10.7 The observation that the human immune system does not raise high-affinity antibodies to autoantigens is also made in document ID32 (page 725, second column):

"However, the 'natural autoantibodies' produced do not lend themselves to therapeutic use as they are often IgM, low affinity and polyreactive (see...)."

- 10.8 The board derives from the statements in documents ID32 and ID35 that, at the priority date, the skilled person would not have considered to be able to generate antibodies binding to TNF-alpha with high affinity.

- 10.9 Consequently, in summarizing the above (see points 8.3, 10 to 10.8), the board concludes that at the priority date the skilled person, on the one hand, would have considered it possible to generate human monoclonal antibodies binding to TNF-alpha with low affinity. However, he/she would not have considered them as pharmaceutically useful. On the other hand, the skilled person was convinced that antibodies binding to TNF-alpha with high affinity would be pharmaceutically useful. However, he/she would not have had a reasonable expectation to succeed in generating them. Therefore, it follows that, at the priority date of the patent, the skilled person would have thought that pharmaceutically useful TNF-binding human monoclonal antibodies could not be generated and would therefore not have attempted to provide them with a reasonable expectation of success.

10.10 Inventiveness can be established, for example, by demonstrating that a prevailing opinion has been overcome. Given the skilled person's opinion at the priority date of the patent that pharmaceutically useful antibodies binding to TNF-alpha could not be generated (see point 10.9 above), it follows in the board's view that the subject-matter of claim 1 relating to a **pharmaceutical** composition containing a human monoclonal antibody binding to TNF-alpha is not obvious.

10.11 Hence, the board concludes that the subject-matter of claim 1 could not be derived in an obvious way from the teaching in the closest prior art document ID29 alone or in combination with the teaching in document ID26 or in any other document on file. Therefore, the subject-matter of claim 1 involves an inventive step. This finding also applies to the subject-matter of claims 2 to 6 which are all dependent on claim 1.

Order

For these reasons it is decided that:

1. The main request of the appellant fulfils the requirements of Article 56 EPC.
2. The procedure is continued in writing.

The Registrar:

The Chair:

P. Cremona

M. Wieser