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D E C I S I O N
of 18 January 2005

Case Number: T 0278/03 - 3.3.8

Application Number: 91309595.6

Publication Number: 0481790

IPC: C12N 15/13

Language of the proceedings: EN

Title of invention:
Antibody production

Patentee:
THE WELLCOME FOUNDATION LIMITED

Opponents:

1. F. HOFFMANN-LA ROCHE & CO. Aktiengesellschaft
2. Boehringer Ingelheim GmbH Patente
3. Cambridge Antibody Technology Limited
4. Novartis AG Patent and Trademark Dept.
5. IDEC Pharmaceuticals Corpn
6. Schering AG
7. SmithKline Beecham plc, Corporate Intellectual Property,
SB House
8. Chugai Pharmaceutical Co., Ltd.

Headword:
Antibody production/WELLCOME

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main request and first to fifth auxiliary requests: inventive step (no)"
"Sixth auxiliary request: admissible (no), abuse of procedure (yes)"

Decisions cited:
T 0187/93, T 0207/94

Catchword:

-



Case Number: T 0278/03 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 18 January 2005

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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 18 October 2002
revoking European patent No. 0481790 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
C. Rennie-Smith

Summary of Facts and Submissions

- I. The patentee (appellant) lodged an appeal against the decision of the opposition division given at oral proceedings on 16 January 2002, with written reasons posted on 18 October 2002, by which the patent was revoked on the basis of the granted claims (as the main request), and two auxiliary requests, referred to as request B(i) and request B(iv), both filed with the patentee's letter of 14 December 2001.
- II. Of the eight opponents which had initially opposed the patent, opponent 7 withdrew its opposition on 25 April 2001, ie during the written phase of the opposition procedure, while opponents 1 and 8 withdrew their oppositions on 5 and 6 November 2003, respectively, ie during the appeal phase. These two latter opponents were parties to the present appeal proceedings only for cost purposes. Opponents 2 to 6 were respondents I to V, respectively.
- III. Reasons for the revocation were as follows. Claim 1 of the main request was considered to contain **added matter** (see Article 123(2) EPC). The subject-matter of claim 1 of auxiliary request B(i), while regarded as meeting the requirements of Article 123(2) EPC, was considered to **lack novelty**. Finally, claim 1 of auxiliary request B(iv), while regarded as meeting the requirements of Articles 123(2) and 54 EPC, was found to **lack inventive step** (see Article 56 EPC) over document D17, regarded as the closest state of the art, taken into combination with document D54 (see Section XVII, *infra*). With respect to both auxiliary requests, it was held that

the **priority** had not been validly claimed (see Article 87 EPC).

- IV. The patent had also been opposed on the further ground that the invention was not sufficiently disclosed (see Article 83 EPC). At the oral proceedings before the opposition division, the issue of sufficiency of disclosure was not discussed and, thus, was not a reason for revocation.
- V. Together with its statement of grounds of appeal, the appellant filed an amended main request and an auxiliary request which corresponded to previous auxiliary request B(iv).
- VI. In reply to the statement of grounds of appeal, observations were filed by respondents I, II and V.
- VII. Together with a letter faxed to the EPO on 14 April 2003, the appellant filed a second, third, fourth and fifth auxiliary requests as well as further observations.
- VIII. The Board issued a communication pursuant to Article 11 of the Rules of Procedure of the Boards of Appeal in which provisional and non-binding opinions were expressed. In reply to that communication respondents II and V submitted further observations in letters dated 17 December 2004 and 5 October 2004, respectively, in which they submitted that the requirements of Articles 123(2), 83, 54 and 56 EPC were not met by any of the claim requests on file. Together with a letter of 17 December 2004, the appellant filed a new main request and five new auxiliary requests (first to fifth;

also referred to infra as "the five auxiliary requests of 17 December 2004") to replace all the previous requests. The first auxiliary request (claims 1 to 5) corresponded to claims 1 to 3, 7 and 8 of auxiliary request B(iv).

IX. Oral proceedings took place on 18 January 2005 at which the appellant filed a sixth auxiliary request. The oral proceedings were not attended by respondent I, as indicated in a fax-letter on 12 January 2005, nor by respondent IV which duly received the summons on 19 July 2004.

X. The **main request** consisted of 5 claims. Claim 1 read:

"1. Use of an antibody which has antigen binding capability and the effector function of binding an Fc receptor of a cell and mediating complement activation, having chinese hamster ovary cell glycosylation in the manufacture of a medicament for the treatment of cancer."

Claims 2 to 5 were dependent on claim 1 and were directed to specific embodiments of the use of an antibody according to claim 1.

XI. The **first auxiliary request** (I) consisted of 5 claims. Claim 1 read:

"1. Use of an antibody comprising a variable domain capable of binding to an antigen of a cell and a constant domain wherein the antibody has the ability of lysing via complement the cell to which it is bound and has chinese hamster ovary cell glycosylation in the

manufacture of a medicament for the treatment of cancer."

Claims 2 to 5 were dependent on claim 1 and were directed to specific embodiments of the use of an antibody according to claim 1.

XII. The **second auxiliary request** (II) consisted of 3 claims.

Claim 1 read:

"1. Use of an antibody which has the antigen binding capability of binding to a tumour cell marker antigen and the effector function of binding an Fc receptor of a cell and mediating complement activation, having chinese hamster ovary cell glycosylation in the manufacture of a medicament for the treatment of non-Hodgkins lymphoma."

Claims 2 and 3 were dependent on claim 1 and were directed to specific embodiments of the use of an antibody according to claim 1.

XIII. The **third auxiliary request** (III) consisted of 3 claims.

Claim 1 read:

"1. Use of an antibody comprising a variable domain capable of binding to a tumour cell marker antigen and a constant domain wherein the antibody has the ability of lysing via complement the cell to which it is bound and has chinese hamster ovary cell glycosylation in the manufacture of a medicament for the treatment of non-Hodgkins lymphoma."

Claims 2 and 3 were dependent on claim 1 and were directed to specific embodiments of the use of an antibody according to claim 1.

XIV. The **fourth auxiliary request** (IV) consisted of one claim which read:

"1. Use of a CDR-grafted antibody which has the antigen binding capacity to bind the CDw52 antigen and the effector function of binding an Fc receptor of a cell and mediating complement activation, having chinese hamster ovary cell glycosylation in the manufacture of a medicament for the treatment of non-Hodgkins lymphoma."

XV. The **fifth auxiliary request** (V) consisted of one claim which read:

"1. Use of a CDR-grafted antibody comprising a variable domain capable of binding to the antigen CDw52 and a constant domain wherein the antibody has the ability of lysing via complement the cell to which it is bound and has chinese hamster ovary cell glycosylation in the manufacture of a medicament for the treatment of non-Hodgkins lymphoma."

XVI. The **sixth auxiliary request** (VI) consisted of one claim which read:

"1. The antibody Campath IH comprising a variable domain capable of binding to CDw52 antigen, having Chinese hamster ovary cell glycosylation, for use in human immunotherapy of pathological disorders."

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

- (D17) G. Hale et al., *Lancet*, Vol. 2, No. 8625, 17 December 1988, Pages 1394 to 1399
- (D29) EP-A-0 365 997 (published on 2 May 1990)
- (D34) Michael Neumaier et al., *Cancer Res.*, Vol. 50, 1 April 1990, Pages 2128 to 2134
- (D54) Martin J. Page and Mark A. Sydenham, *Bio/Technology*, Vol. 9, January 1991, Pages 64 to 68
- (D83) Declaration of James Scott Crowe dated 2.11.1994
- (D84) Masato Nose and Hans Wigzell, *Proc. Natl. Acad. Sci. USA*, Vol. 80, November 1983, Pages 6632 to 6636
- (D85) Robin J. Leatherbarrow et al., *Mol. Immunol.*, Vol. 22, No. 4, 1985, Pages 407 to 415
- (D86) T.W. Rademacher et al., *Ann. Rev. Biochem.*, Vol. 57, 1988, Pages 785 to 838
- (D87) Declaration of Geoffrey Hale dated 16 November 1994
- (D88) Declaration of Robert Lively dated 6.4.1994

- (D102) Steven A. Carr et al., J. Biol. Chem.,
Vol. 264, No. 35, 15 December 1989,
Pages 21286 to 21295
- (D118) Confidential Progress Report by Geoff Hale
for the period from 1 May 1990 to
31 December 1990
- (D119) Melvin S. Oka and Randall G. Rupp,
Bioprocess Technol., Vol. 10, 1990,
Pages 72 to 92

XVIII. The submissions made by the appellant, insofar as they are relevant for the present decision, may be summarised as follows:

Priority

It was accepted that the effective date for the subject-matter of the main request and the five auxiliary requests of 17 December 2004 was the date of filing of the European patent application, ie 17 October 1991.

Inventive step of the main request and of the first, second, third, fourth and fifth auxiliary requests

The technical problem solved by the invention was that of providing antibodies which maintained full activity in vivo in humans without undue immunological reaction.

An evaluation of the scientific facts to hand at the filing date (17 October 1991) would have given the skilled person no expectation of success. This was in

line with the teaching of decisions T 207/94 (OJ EPO 1999, 273) and T 187/93 of 5 March 1997. There were a series of documents cited in the present proceedings (such as D29, D34, D84, D85, D86, D102, and D119), as well as three declarations prepared for the purpose of parallel proceedings before the USPTO (D83, D87 and D88 used as expert opinions) and a report not available to the skilled person at the filing date (D118 also used as expert opinion), which showed that antibodies produced from Chinese hamster ovary (CHO) cells would not be appropriate for therapy.

It was only derivable with hindsight that document D54, which was the closest state of the art, could provide the solution to the technical problem. The document referred only to the need to produce enough antibody and described the production of the Campath®-1H antibody in CHO-cells which differed from the same antibody produced in rat myeloma cells, as described in document D17, by its glycosylation pattern.

It had not been established in document D17 that the Campath®-1H antibody as produced in rat myeloma cells was suitable for the treatment of humans without undue immunological reaction. Knowing furthermore from document D86 that the glycosylation of a protein might contribute to and be an intrinsic part of its physiological activity, the skilled person would not have embarked on the testing of the Campath®-1H antibody as produced in CHO-cells, ie with a different glycosylation pattern.

Sixth auxiliary request

The appellant had been given an opportunity by the Board to submit a further request. This request should therefore be introduced into the proceedings. The only claim of the request related to limited subject-matter which had not yet been discussed. It contained no added matter and could be examined without consideration of document D54, which, since the priority date of 17 October 1990 was valid for the non-claimed subject-matter, was not part of the state of the art under Article 54(2) EPC.

- XIX. The submissions made by the respondents, insofar as they are relevant for the present decision, may be summarised as follows:

Priority

As admitted by the appellant, the effective date of the subject-matter of the main request and the five auxiliary requests of 17 December 2004 was the date of filing of the European patent application, ie 17 October 1991.

Inventive step of claim 1 of the main request and of each of the first, second, third, fourth and fifth auxiliary requests

The results presented in the patent did not actually show that the antibody Campath®-1H produced in CHO-cells was therapeutically useful. There were no results of any clinical tests of the antibody for the

treatment of cancer, the only medical indication referred to in the claims.

Document D54 was the closest state of the art. There was no gap in the knowledge contained therein. One of the authors had contributed to the clinical tests described in document D17. Therefore, the authors must have been convinced that Campath®-1H as previously produced in rat myeloma cells was useful for the treatment of cancer in humans. They were looking for a cellular system for the industrial production of an antibody which they also expected to be suitable for the treatment of cancer in humans. It was certainly not their intention just to test CHO-cells, which they knew they were going to produce the antibody with a different glycosylation pattern, in order to determine only whether such cells were appropriate to produce enough antibody. As it could be derived from the sentence bridging the two columns on page 67 of document D54, they were convinced that they had produced clinically important antibodies. Thus, document D54 on its own provided a strong incentive to test clinically Campath®-1H as produced in CHO-cells for the treatment of cancer in humans.

The incentive provided by document D54 was amplified by a series of documents forming part of the state of the art.

Sixth auxiliary request

Whereas the previous claims on file were directed to the use of an antibody generally defined and having Chinese ovary cell glycosylation in the manufacture of

a medicament for the treatment of cancer such as non-Hodgkins Lymphoma, the only claim of the sixth auxiliary request was directed to the antibody Campath®-1H having Chinese hamster ovary cell glycosylation for use in human immunotherapy of pathological disorders. This was a completely new request which changed the nature of the appeal. As such it should not be admitted into the proceedings.

XX. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or auxiliary requests I to V filed on 17 December 2004, or auxiliary request VI filed at the oral proceedings.

XXI. The respondents (opponents) requested that the appeal be dismissed.

Reasons for the Decision

Procedural matters

1. Common to all requests on file except the sixth auxiliary request are claims centred on the use of an antibody having Chinese hamster ovary (CHO) cell glycosylation, in particular a CDR-grafted antibody against the CDw52 antigen (see the only claim of the fifth auxiliary request), in the manufacture of a medicament for the treatment of cancer such as non-Hodgkins lymphoma. In view of this, the Board found it expedient to deal with the key question whether that use involves an inventive step in the light of the prior art and to leave aside the disputed issues of

compliance of the requests with Articles 123, 83 and 54 EPC.

Inventive step

Priority

2. In consideration of the subject-matter of the main request and of the five auxiliary requests of 17 December 2004, claim 1 of each of them being directed to the use of an antibody with specific features in the manufacture of a medicament for the treatment of cancer such as non-Hodgkins lymphoma, the appellant has admitted that the patent is not entitled to its priority date (17 October 1990). Indeed the priority document fails to refer to any use of an antibody in the treatment of cancer. Thus, the priority is not valid. Consequently, document D54 which has been published between the priority date and the filing date of the European application (17 October 1991) is part of the state of the art as defined in Article 54(2) EPC.

Main request

3. Claim 1 is in the form of a second medical use. It is directed to the use of an antibody with specific features in the manufacture of a medicament for the treatment of cancer. Therefore, it should be assessed whether the use of such antibody in the treatment of cancer is inventive.
4. In the patent the production of the preferred antibody Campath®-1H (a known antibody; see document D17) in CHO-cells is illustrated (see Examples 1 to 4 on pages 5 to 9 in the patent specification). Production

of Campath®-1H in CHO-cells is described in document D54. The document, however, does not directly point to its use in the therapy of cancer. Thus, strictly speaking, novelty of claim 1 vis-à-vis document D54 can be acknowledged.

5. Document D54 is regarded as the closest state of the art. It describes the use of CHO-cells as hosts for expression of the known antibody Campath®-1H and the evaluation of two alternative amplification procedures for the production of up to 200 µg/ml of Campath®-1H antibody from non-lymphoid CHO-cells. Comments are made therein on the Campath®-1H antibody as previously produced in rat myeloma cells. Emphasis is put on the fact that this antibody as produced in such cells has been shown to eliminate large numbers of tumour cells, resulting in remission for patients with non-Hodgkins lymphoma, reference being made in this respect on page 64 (see bottom of the left-hand column) to citation 7 which is document D17 in the present proceedings.

6. Document D17, which can thus be seen as part of the disclosure of document D54, actually describes the use of the antibody Campath®-1H as produced in rat myeloma cells to treat two patients with non-Hodgkins lymphoma. The authors note (see the "Discussion" on page 1398) that the remission achieved in these two patients shows that it is possible to clear large numbers of tumour cells with small amounts of the antibody. As to the immunogenicity of the antibody, the authors regard it as encouraging that two courses of antibody treatment could be given, even in the patient who had previously had unusually severe reactions to the original antibody

Campath[®]-1G of which Campath[®]-1H is a reshaped human version (see same page 1398).

7. In the light of this prior art, the technical problem to be solved may be regarded as finding a use for an antibody, such as the Campath[®]-1H antibody, produced at high levels of expression in CHO-cells. The solution thereto is the proposal for its use in the manufacture of a medicament for the treatment of cancer.

8. When reading document D54 as starting point, the skilled person would have known from its introduction, in particular from the reference to document D17 (citation 7), that the known antibody Campath[®]-1H as produced in rat myeloma cells would have been suitable for manufacturing a medicament for the treatment of cancer. The high levels of expression of the same antibody in CHO-cells as described in document D54 and the optimistic views expressed in the same document about the many advantages of that system for producing proteins of therapeutic value on an industrial scale (see the passage bridging left and right columns on page 67 which puts emphasis on the demonstration given in the document of the use of "engineered CHO-cells to express and secrete high levels of clinically important recombinant antibodies, such as Campath-1H") would have readily encouraged the skilled person to propose precisely what is now claimed, ie the use of Campath[®]-1H as produced in CHO-cells in the manufacture of a medicament for the treatment of cancer.

9. The appellant argues that there was a body of scientific facts to hand at the filing date (17 October 1991) an evaluation of which, as set forth in decisions

T 207/94 (see Section XVIII, supra) and T 187/93 (see Section XVIII, supra), would have left the skilled person with no expectation of success, when considering the therapeutic use of an antibody produced in CHO-cells. Prior art documents D29, D34, D84, D85, D86, D102 and D119 are relied upon in order to support this view. Moreover, the appellant also relies upon three declarations and a report as expert opinions. These documents however were not available to the skilled person at the filing date and thus cannot be taken into consideration in the afore-mentioned evaluation.

10. At any rate, a detailed review of the said prior art does not support the appellant's position. Indeed:
 - 10.1 Document D29 describes a family of high affinity, modified antibodies optionally **produced in CHO-cells** (see page 18, lines 45 to 50) which are **suitable for cancer treatment**.
 - 10.2 Document D34 predicts that the chimeric antibodies **produced** upon expression of chimeric human/mouse T84.66 genes **in CHO-cells** will only be weakly immunogenic and will make **excellent reagents for repeated therapy** (see last paragraph on page 2133).
 - 10.3 Document D84 concludes that **removal of carbohydrate chains** from IgG molecules may have a profound and highly select impact on the biological activity of these antibodies.
 - 10.4 Document D85 describes the production of a monoclonal **aglycosylated** IgG2a and the purification of this IgG2a to homogeneity.

- 10.5 Document D86 acknowledges that, on the basis of observations of glycoforms of proteins such as TSH, hormone receptors and antithrombin III (**no antibodies referred to**), the glycosylation of a protein may contribute to and be an intrinsic part of its physiological activity (see pages 792 to 795).
- 10.6 Document D102 describes the protein and carbohydrate structural analysis of a recombinant soluble CD4 receptor by mass spectrometry.
- 10.7 Document D119 states that the traditional selection of a cell type for expressing heterologous proteins has generally been limited to the more "common" cell types such as CHO-cells, without consideration of questions such as how the carbohydrate side chain affects the performance of the molecule or how the expression of carbohydrate moieties on the molecule can be controlled (see page 82).
- 10.8 In the Board's view, none of the above documents establishes or suggests that the use of CHO-cells as an expression system would result in a glycosylation pattern affecting or at risk of affecting the effector function of an antibody like Campath[®]-1H as produced in rat myeloma cells in such a way that the antibody as produced in CHO-cells would not be useful in the treatment of cancer in humans. Thus, the positive expectations of the skilled person based on document D54 would not have been lessened by any of the citations, alone or in combination.

11. The appellant also argues that document D17 does not show that the antibody Campath[®]-1H as produced in rat myeloma cells is useful for the treatment of cancer in humans.
12. This is not convincing. Document D17 actually reports on clinical tests performed on two patients with cancer and the achievement of remission. This is regarded as sufficient by the board which notes that, a contrario, the patent does not contain any clinical data concerning the treatment of patients with cancer.
13. These remarks lead the Board to conclude that a skilled person faced at the filing date with the afore-mentioned technical problem would have found in document D54 a strong incentive to test clinically in patients with cancer the antibody Campath[®] 1H as produced in CHO-cells. The only possible reservation would have been the doubt inherent in the field of biological research but such doubt is reasonable and absolute certainty of success is not required.
14. Therefore, claim 1 of the main request does not involve an inventive step. Thus, the main request does not meet the requirements of Article 56 EPC and cannot form a basis for the maintenance of the patent.

First, second, third, fourth and fifth auxiliary requests

15. As claim 1 of the main request, claim 1 of each of the five auxiliary requests of 17 December 2004 covers the use of the preferred Campath[®]-1H antibody as produced in CHO-cells in the manufacture of a medicament for the treatment of cancer (see the main and the first

auxiliary requests) or more specifically of non-Hodgkins lymphoma (see the second, third, fourth and fifth auxiliary requests). For the same reasons given above in respect of the main request, these auxiliary requests do not involve an inventive step and, thus, they cannot form a basis for the maintenance of the patent.

Sixth auxiliary request

16. This request, filed during the oral proceedings after the discussion on the main request and the five auxiliary requests of 17 December 2004, differs from the other requests in several respects. It is not in the second medical use format. It contains a combination of features which had not been presented previously. As the appellant explained in argument, it had been drafted in terms which fell within the priority document. Thus, if the request were to be held admissible, some of the prior art cited against the other requests would not be prior art for this request including document D54, the closest prior art in the case of the other requests (see points 5 and 15, supra).

17. This request represents an entirely fresh case. The appellant made no attempt to present it in any other light. While it may on occasions be permissible for a patentee to file a new request at a very late stage of the proceedings, such a request would usually be a limited version of an earlier request or requests (for example, limited by the introduction of a feature from a dependent claim) which would not entail much consideration by other parties or the Board. Even a late request of that nature is, as with all late

requests, only admissible at the discretion of the Board. In the present case the late request marks a total departure from all other requests filed in the appeal proceedings; it is unsupported by any arguments in the grounds of appeal or any subsequent written submission of the patentee; it reintroduces an issue (priority) on which the appellant lost at first instance but which it has not previously challenged upon appeal; and it has beyond any doubt taken the respondents by surprise. The Board considers such a complete change of case at such a late stage amounts to an abuse of procedure and the Board's discretion cannot be exercised so as to sanction such an abuse. The sixth auxiliary request is accordingly inadmissible.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

A. Wolinski

L. Galligani