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Datasheet for the decision of 5 October 2011

Case Number: T 0341/09 - 3.3.08

Application Number: 02076251.4

Publication Number: 1247865

IPC: C12N 15/13

Language of the proceedings: EN

Title of invention:
Antibody for use in therapy

Patentee:
THE WELLCOME FOUNDATION LIMITED

Opponents:
Medimmune Limited
Amgen, Inc
AstraZeneca AB
Bayer Pharma Aktiengesellschaft
Merck Serono SA
Biovitrum AB / Symphogen A/S
Bioinvent International AB
Genentech, Inc.
Boehringer Ingelheim Pharma GmbH & Co KG
Novartis AG
Abbott Laboratories
Wyeth
Genmab A/S

Headword:
Antibody/WELLCOME

Relevant legal provisions:
EPC Art. 76(1)

Relevant legal provisions (EPC 1973):
-

Keyword:
"Main request: added matter (yes)"
"Auxiliary request: added matter (yes)"

Decisions cited:
T 0461/05

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0341/09 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 5 October 2011

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 3 February 2009 revoking European patent No. 1247865 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman: M. Wieser
Members: T. J. H. Mennessier
R. Moufang

Summary of Facts and Submissions

I. The patentee (appellant) lodged an appeal against the decision of the opposition division dated 3 February 2009, whereby European patent 1 247 865 was revoked. The patent had been granted on European patent application No. 02 076 251.4 entitled *"Antibody for use in therapy"*. The application was filed as a divisional application from the earlier applications No. 97 201 842.8 (parent application) and No. 91 309 595.6 (grandparent application).

II. The patent had been opposed by thirteen opponents. The grounds for opposition relied on were lack of novelty (Articles 54 and 100(a) EPC), lack of inventive step (Articles 56 and 100(a) EPC), insufficiency of disclosure (Articles 83 and 100(b) EPC), and presence of added matter (Article 100(c) EPC) with objections raised under Articles 76(1) and 123(2) EPC.

III. The decision of the opposition division was based on a main request (claims as granted) and four auxiliary requests filed under cover of a letter of 17 October 2007. The patent was revoked for reasons of non-compliance with the requirements of Article 76(1) EPC.

IV. Together with its statement of grounds of appeal, the appellant submitted a first auxiliary request, identical to the first auxiliary request before the opposition division, consisting of claims 1 to 3 as granted. Claims 1 to 7 as granted remained appellant's main request.

V. Claim 1 as granted read:

"1. A method for the production of a pharmaceutical composition comprising an antibody capable of activating complement ***in vitro*** which antibody is effective in the therapy of humans, which method comprises the steps of:

(a) suspension culturing a recombinant CHO cell in a serum free media which secretes into said media, a glycosylated antibody comprising a light and heavy chain;
(b) recovering said immunoglobulin of step (a);
(c) incorporating said immunoglobulin of step (b) into said composition."

VI. Opponents 01 to 07 (respondents I to VII) replied to the statement of grounds by filing new submissions. They requested oral proceedings in case the board did not intend to dismiss the appeal. Opponent 10 (respondent X) and opponent 13 (respondent XIII), in their respective replies, only generally referred to their submissions filed in the proceedings before the first instance. Opponents 08, 09 and 12 (respondents VIII, IX and XII) did not file any submissions in these appeal proceedings.

VII. With letter of 26 October 2009, opponent 11 (respondent XI) withdrew its opposition. The status of respondent XI as a party to the proceedings is unaffected insofar as the question of apportionment of costs under Article 104 EPC is at issue.

VIII. On 23 March 2011, the board issued a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal attached to the summons to oral proceedings in which its provisional and non-binding opinion, in particular as regards the issue of compliance with the requirements of Article 76(1) EPC, was expressed.

IX. With a letter dated 4 May 2011, respondents VI and VII requested the board to postpone the appointed oral proceedings.

X. In reply thereto, with a communication dated 13 May 2011, the board informed the parties that the request for postponement was refused.

XI. In a letter dated 12 July 2011, the appellant withdrew its request for oral proceedings.

XII. Each with a letter dated 3 August 2011, respondents VI and VII conditionally requested the scheduled oral proceedings be cancelled.

XIII. With a communication dated 11 August 2011, the board informed the parties that the oral proceedings scheduled on 10 November 2011 were cancelled.

XIV. The submissions made by the appellant (patent proprietor), insofar as they are relevant to the present decision, may be summarised as follows:

Claim 1 of the main and the first auxiliary requests: compliance with the requirements of Article 76(1) EPC in view of the grandparent application

The method of claim 1 was described in the general part of the description, in claim 16 and in example 4 of the grandparent application.

The production of proteins by recombinant CHO cells in general and the provision of a CHO cell line capable of producing antibodies in particular were described on page 1, lines 1 to 2 and page 4, lines 22 to 23, respectively.

Co-transfection of the CHO cells was only an option. This was clear from the general part of the description, in particular from the sentences and phrases reading *"At least one of the selectable markers preferably also provides the basis upon which the genes encoding the light and heavy chains may be amplified."* (see page 7, lines 8 to 10), *"In co-transfection of a CHO cell line, the vector DNAs are often integrated into the chromosome of the cell at the same locus."* (see page 7, lines 10 to 11), *"Construction of the expression vectors may be carried out in accordance with procedures known in the art"* (see page 8, lines 14 to 15) and *"Co-transfection of the CHO cell line with the expression vectors may be carried out simply by using equimolar quantities of both vectors"* (see page 8, lines 19 to 20). Moreover, claim 16 was relevant in this respect, as it was directed to a process for the preparation of an antibody comprising culturing a CHO cell engineered in such a way - without any indication that it had been co-transfected by two vectors - to express the antibody.

In the passage reading "*It has now been found that antibody glycosylated by CHO cells maintains antigen binding capability and effector functionality. This has been demonstrated in in vitro complement lysis assays and in vivo in a human patient.*" (see page 9, lines 25 to 28), the wording "*effector functionality*" was to be interpreted as "*complement activation*". In Example 5, (see from line 28 on page 22 to line 1 on page 24), complement lysis was successfully assayed *in vitro* for three samples of an antibody produced by the method of Example 4. Therefore, the disclosure in the general part of the description in combination with the specific examples provided a basis for the feature "*an antibody capable of activating complement in vitro*" in claim 1.

The term "cell suspension" was literally referred to in the sentence of Example 4 reading "*Three 25 cm^2 flasks were set up with 10ml of cell suspension + hypoxanthine (H), thymidine (T) or HT.*" (see page 19, lines 11 to 12). It was further disclosed that the cells were grown either in a Techner spinner for a period of over five months or in a fermenter equipped with a stainless steel angled paddle for more than 50 days and were found to secrete antibodies in excess of 60 and 100 µg/ml, respectively (see line 19 on page 19 to line 8 on page 20). In view of decision T 461/05 of 10 July 2007, the disclosure on pages 19 to 20, although it referred to an example, provided support for the feature "*suspension culturing*" in claim 1.

The phrases reading "*Cells continued growing serum free for a period over five months*" on page 19, lines 20 to 21 (part of Example 4) and "*Cells from a) above*

which had been growing serum-free for over 2 months" on page 19, lines 34 to 35 (part of Example 4) were a clear indication that the medium for the production of antibodies should be without serum. Combining this feature, taken from an example, with other features taken from the general part of the description should be permitted in view of decision T 461/05 (*supra*).

XV. The submissions made by respondents I to VII, insofar as they are relevant to the present decision, may be summarised as follows:

Claim 1 of the main and the first auxiliary requests: compliance with the requirements of Article 76(1) EPC in view of the grandparent application

The method of claim 1 was not described in the grandparent application, which contained no support for the technical features "*a recombinant CHO cell*", "*an antibody capable of activating complement in vitro*", "*suspension culturing*" and "*serum free media*".

None of the passages referred to by the appellant described the use of a system that did not require co-transfection. Furthermore, it was clear from page 4 that the invention specifically related to a process that enabled balanced expression of antibody chains by virtue of co-transfecting CHO cells with two vectors, one encoding a heavy chain and the other encoding a light chain.

The phrase reading "*Construction of the expression vectors may be carried out in accordance with procedures known in the art*" (see page 8, lines 14

to 15) taught that multiple expression vectors were required for the invention to work. The phrase reading "*Co-transfection of the CHO cell line with the expression vectors may be carried out simply by equimolecular quantities of both vectors*" (see page 8, lines 19 to 20) described how co-transfection was achieved. Taken together these two phrases actually provided a clear disclosure that multiple vectors were required and that these vectors were co-transfected into the CHO cells.

Hence, a method using any recombinant CHO cell without the requirement for co-transfection with two vectors was not described in the grandparent application.

The feature "*antibody capable of activating complement in vitro*" was not disclosed in the grandparent application in combination with the other features of claim 1. The disclosure in the experimental part of the grandparent application referred to specific subject-matter, the "Campath-1H" antibody, not to antibodies in general.

The sentence in Example 4 reading "*Three 25cm^2 flasks were set up with 10ml of cell suspension + hypoxanthine (H), thymidine (T) or HT.*" (see page 19, lines 11 to 12) did not refer to a method for culturing cells in a suspension. The disclosure immediately preceding this sentence showed that the cells were cultured adherently. It was clear from the context of this passage that the "*cell suspension*" referred to therein was only a transition stage, whereby the adherent cells were placed into suspension in order to move them from one culture vessel to another. Whether or not the cells

were subsequently grown adherently or in suspension was simply not disclosed. A Techner spinner as referred to on page 19, line 19 could be used to grow cells in suspension or adherently. Fermenters as referred to on page 19, lines 30 and 35 could equally be used for both cell culture methods.

In only one passage the description contained a general disclosure of a media being "*serum-containing or preferably serum and protein free media*" (see page 8, lines 28 to 29). It is evident that the serum free media disclosed in this sentence had also to be protein free. The serum free growth media referred to in example 4, WCM4 or WCM5, were specific media with defined nutrient composition.

Furthermore, taking the features "*suspension culturing*" and "*serum free media*" out of their context in example 4, i.e. the only place in the grandparent application where they were referred to, and combining them with features disclosed in the general part of the description would lead to an inadmissible generalisation. Decision T 461/05 (*supra*) related to a different situation and was not applicable in the present case.

XVI. The appellant requests that the decision under appeal be set aside and the case be remitted to the first instance for further prosecution on the basis of the main request (claims 1 to 7 as granted) or of the first auxiliary request (claims 1 to 3 as granted).

XVII. Respondents I to VII, X and XIII request that the appeal be dismissed. Furthermore, respondent II

requests that, should any request filed by the appellant be found to comply with Articles 76(1) and 123 EPC, the case be remitted to the first instance.

Reasons for the Decision

Compliance with the requirements of Article 76(1) EPC

Main request (claims 1 to 7 as granted)

1. In the decision under appeal, objections under Article 76(1) EPC were raised against claims 1 and 3 to 7 of the claims as granted. These claims were considered to contain subject-matter extending beyond the content of both the parent and the grandparent applications. As a first point the board will examine whether claim 1 complies with the requirements of Article 76(1) EPC in view of the grandparent application.

2. Claim 1 is directed to a method for the production of a pharmaceutical composition comprising an antibody capable of activating complement ***in vitro*** which antibody is effective in the therapy of humans. The antibody is glycosylated and comprises a light and a heavy chain. For its production use is made of a recombinant CHO cell which is capable of secreting the antibody. The claim does not specify how the cell has been recombinantly engineered. The claimed method comprises three steps, firstly, the recombinant CHO cell is cultured in suspension in a serum free media into which it secretes the antibody, secondly, the secreted antibody is recovered from the media and

thirdly, the recovered antibody is incorporated into a pharmaceutical composition.

3. The general part of the description of the grandparent application describes primarily a process for the balanced expression of the light and heavy chains of an antibody from CHO cells (see page 4, lines 13 to 14). The antibody which may be the active ingredient of a pharmaceutical composition (see from line 33 on page 10 to line 9 on page 11) is glycosylated and capable of activating the complement ***in vitro*** (see page 9, lines 25 to 28).

4. The described process relies on the use of a CHO cell line which has been co-transfected with two vectors capable of expressing the light and heavy chains of the antibody, respectively (see pages 4, lines 22 to 33). Pages 4 to 8 describe in detail the construction of the vectors and the selection of the cells after co transfection using the selected markers which are part of the vectors. This disclosure includes the four passages referred to by the appellant in the statement of its grounds for appeal (see Section XIV, ***supra***). Two of them relate ***expressis verbis*** to co-transfection with the disclosed vectors (see page 7, lines 10 to 11 and page 8, lines 19 to 20), the other two relate to the selectable markers encoded by the vectors (see page 7, lines 8 to 10) and the construction of the vectors (see page 8, lines 14 to 15). Thus, none of these passages provides any support for the appellant’s argument that co-transfection is only an optional embodiment of the claimed invention. In the same way, also the introductory paragraph on page 1, lines 1 to 3, which states that the invention relates "***to Chinese hamster***

ovary (CHO) cell lines", "*to the production of proteins, in particular antibodies from such cell lines*", and "*to antibodies having CHO glycosylation*", does not support appellant's argument.

5. To summarise, the general part of the description describes a method which clearly and exclusively refers to a method using recombinantly engineered CHO cells which have been co-transfected with two vectors capable of expressing the light and heavy chains of the antibody, respectively.

6. The experimental part of the description illustrates the method described in the general part, by disclosing the production of *Campath-1H*, a humanized antibody capable of activating complement *in vitro* (see Examples 1 to 4), and its use as part of a pharmaceutical composition (see Example 5). For this purpose a CHO cell line is co-transfected, as detailed in Examples 2 and 3 on pages 13 to 18, with two vectors, one vector, denoted pLD9, comprising a Campath-1H light chain cDNA, and the other one, denoted pNH316, comprising a Campath-1H heavy chain cDNA.

7. In a further attempt to support its argument, the appellant refers to claim 16 of the grandparent application. This claim is directed to a method for the production of an antibody "*as defined in any of claims 13 to 15*", which method comprises culturing a CHO cell "*engineered to express the antibody*". The appellant argues that claim 16 is not limited to any specific way of engineering the CHO cell, let alone to its co-transfection with two vectors capable of expressing

the light and the heavy chains of the antibody, respectively.

8. However, the board considers that the subject-matter defined by claim 16 of the grandparent application is, in several aspects, much broader than the subject-matter of granted claim 1. In particular, it does not contain several features of the method steps specified in granted claim 1. Moreover, the antibodies according to claims 13 to 15 (to which claim 16 refers back) are not defined as being capable of activating complement ***in vitro*** and as being useful in a medical treatment as part of a pharmaceutical composition, as required in claim 1. Thus, only a combination of the teaching of claim 16 of the grandparent application with more specific technical teaching in the description of the grandparent application can arguably form a basis for the proposition that Article 76(1) EPC is complied with. However, since the description of the grandparent application clearly and exclusively refers to a method using recombinantly engineered CHO cells which have been co-transfected with two specific vectors (see above, point 5), a selective combination of claim 16 with specific other parts of the description without limiting the subject-matter by the above-mentioned "co-transfection" feature amounts to an unallowable intermediate generalisation. Therefore, claim 16 of the grandparent application does not form a basis for the subject-matter of claim 1.

9. The board concludes that claim 1, at least for the reason that the claimed method is not restricted to the use of a CHO cell co-transfected with two vectors capable of expressing respectively the light and heavy

chains of the antibody, respectively, but encompasses the use of any recombinant CHO cell, contains subject-matter which has not been described in the grandparent application as filed. Therefore, the main request does not comply with the requirements of Article 76(1) EPC.

10. In view of this conclusion, there is no need for the board to further assess whether in example 4 the CHO cells were indeed cultured in suspension using a serum free medium and whether these features can be taken from their initial context, the specific conditions of the example, and combined with other features described in the general part of the description, without violating the requirements of Article 76(1) EPC. In this respect, the board sees also no reason to discuss whether or not decision T 461/05 (*supra*) applies for the present case. There is also no need to examine whether claim 1 contains subject-matter which extends beyond the content of the parent application.

First auxiliary request

11. As claim 1 of the first auxiliary request is identical to claim 1 of the main request, the conclusion reached in point 8 above with respect to the main request applies in the same way. Thus, the first auxiliary request does not comply with the requirements of Article 76(1) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar | The Chairman

A. Wolinski | M. Wieser