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Datasheet for the decision of 6 March 2008

Case Number: T 0580/05 - 3.3.04

Application Number: 94202090.0

Publication Number: 0626390

IPC: C07K 16/46

Language of the proceedings: EN

Title of invention:
Humanised antibodies

Patentee:
CELLTECH THERAPEUTICS LIMITED

Opponents:
01: Protein Design Labs Inc
02: MedImmune Inc.
03: Chugai Pharmaceutical Co., Ltd.

Headword:
Humanised Antibodies/CELLTECH

Relevant legal provisions:
EPC Art. 123(2)
EPC R. 139

Keyword:
"Correction of errors (yes)"
"Too broad disclaimer, added subject-matter - (yes)"

Decisions cited:
G 0003/89, G 0001/03

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0580/05 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 6 March 2008

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 17 February 2005 revoking European patent No. 0626390 pursuant to Article 102(1) EPC (1973).**

Composition of the Board:

Chair: U. Kinkeldey
Members: M. Wieser
G. Weiss

Summary of Facts and Submissions

I. The appeal was lodged by the Patent Proprietor (Appellant) against the decision of the Opposition Division, whereby the European patent No. 0 626 390 was revoked pursuant to Article 102(1) EPC (1973).

II. The patent had been opposed by Opponent 01 (Respondent I), Opponent 02 (Respondent II) and Opponent 03 under Article 100(a) on the grounds of lack of novelty and lack of inventive step and under Article 100(b) and (c) EPC.

III. The Opposition Division had decided that the main request before them did not meet the requirements of the EPC as claim 1 contained a correction which was not considered to fulfil the requirements of Rule 88 EPC (1973). Moreover they decided that the sole auxiliary request before them contravened the requirements of Article 123(3) EPC.

IV. With letter dated 24 December 2007 Opponent 03 informed the Board that the opposition was withdrawn. Opponent 03 ceased to be a party to the procedure as to substantive issues.

V. Oral proceedings were held on 6 March 2008 in the absence of Respondent II, who had informed the Board that it will not attend the oral proceedings.

VI. The Appellant requested that the decision under appeal be set aside and the patent be maintained in amended form on the basis of claims 1 to 7 of the main request filed with letter dated 21 June 2005.

In the course of the oral proceedings the Appellant withdrew all auxiliary requests filed before during the written procedure.

Respondent I requested that the appeal be dismissed.

Respondent II did not file any request during the appeal procedure.

VII. Claims 1 to 7 of Appellant's main request are identical to claims 1 to 7 of the main request before the Opposition Division. Claim 1 read as follows:

"An antibody molecule having affinity for a predetermined antigen and comprising:

a CDR-grafted heavy chain wherein, according to the Kabat numbering system, residues 31 to 35, 50 to 65 and 95 to 102 are donor residues; and

a complementary light chain,

said CDR-grafted heavy chain having a variable domain comprising predominantly acceptor antibody heavy chain framework residues and donor antibody heavy chain antigen-binding residues, said donor antibody having affinity for said predetermined antigen,

wherein, according to the Kabat numbering system, in said CDR-grafted heavy chain, amino acid residues 23, 24, 26 to 30 and 49 at least are additionally donor residues,

provided that the antibody molecule does not have a heavy chain having a variable domain having the sequence (numbered according to the Kabat numbering system):

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1       5        10        15        20
Q V Q L V Q S G A E V K K P G S S V K V
       25        30        35        40
S C K A S G Y T F T S Y R M H W V R Q A
       45        50        55        60
P G Q G L E W I G Y I N P S T G Y T E Y
         65        70        75
N Q K F K D K A T I T A D E S T N T A Y
80  82a b c    85        90        95
M E L S S L R S E D T A V Y Y C A R G G
   100       105       110
G V F D Y W G Q G T L V T V S S
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and a light chain having a variable domain having the sequence (numbered according to the Kabat numbering system):

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1       5        10        15        20
D I Q M T Q S P S T L S A S V G D R V T
       25        30      35        40
I T C S A S S S I S Y M H W Y Q Q K P G
     45        50        55        60
K A P K L L I Y T T S N L A S G V P A R
     65        70        75        80
F S G S G S G T E F T L T I S S L Q P D
     85        90        95        100
D F A T Y Y C H Q R S T Y P L T F G Q G
     105
T K V E V K."
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VIII. Dependent claims 2 to 6 referred to preferred embodiments of the antibody molecule; claim 7 related to a therapeutic or diagnostic composition comprising the antibody molecule.

Claims 1 to 7 differed from the claims as granted only in so far as in claim 1 the amino acid sequence of the disclaimed heavy chain variable domain had "L" in position 45, being the symbol for the amino acid Leucine, instead of "R", being the symbol for the amino acid sequence Arginine.

IX. The present decision refers to the following documents:

(8) PNAS, vol.86, December 1989, pages 10029 to 10033;

(10) WO 90/07 861;

(18) Appellant's letter to the EPO, dated 27 April 2001.

X. The submissions made by the Appellant, as far as relevant to the present decision, may be summarised as follows:

The correction of claim 1 as granted met the requirements of Rule 139 EPC (corresponding to Rule 88 EPC 1973) in that it was obvious that the claim contained an error and the obviousness was in the sense that it was immediately evident that nothing else was intended than what was offered as the correction.

Document (10) disclosed, besides complete antibody molecules, also Fv, Fab and $F(ab)_2$ fragments as well as single chain antibodies. The disclaimer contained in

claim 1, whereby "antibody molecules" having the depicted heavy- and light-chain variable domain sequences were excluded from the scope of protection, was therefore not to broad and did not remove more than what was necessary to restore novelty over document (10). The requirements of Article 123(2) EPC were therefore not violated.

XI. The submissions made by Respondent I, as far as relevant to the present decision, may be summarised as follows:

A claim of a European patent might be corrected under Rule 139 EPC only within the limits of what a skilled person would derive directly and unambiguously from the patent application as originally filed.

In the present case the application as originally filed, and in particular the original claims, did not contain a suggestion of the original disclaimer as found in the granted claim, let alone the amended version which the Appellant tried to achieve through the provisions of Rule 139 EPC, whose requirements were therefore not satisfied.

Document (10) disclosed in its experimental part a specific complete antibody molecule having the heavy- and light-chain variable domains shown in its figures 1 and 2. Although the document also referred to antibody fragments it did not disclose any such fragment having these specific heavy- and light-chain variable domains.

The disclaimer in claim 1 was therefore too broad. As it removed more than what was necessary to restore

novelty over document (10) the requirements of Article 123(2) EPC were violated.

Reasons for the decision

Amendments - Correction of errors - Rule 139 EPC

1. "If the description, a claim or a drawing comprised in a European patent application contains an error on the date of filing, correction of the error under Rule 88, second sentence, EPC has the effect of amending the European patent application as filed. If a European patent application or a European patent which has been amended compared with the version as filed is corrected under Rule 88, second sentence, EPC, the same applies to the amended version. Both are special cases involving an amendment within the meaning of Article 123 EPC and are likewise subject to the prohibition of extension laid down in Article 123(2) EPC." (see decision of the Enlarged Board of Appeal G 3/89, OJ EPO 1993, 117; point (1) of the reasons).

In the present case Appellant's request concerns a correction of "an error of transcription" in the disclaimer in claim 1 of the European patent. Article 123 EPC is therefore applicable.

Under Article 1(1), first sentence, of the Decision of the Administrative Council of 28 June 2001 on the transitional provisions under Article 7 of the Act revising the European Patent Convention of 29 November 2000 (OJ EPO 2007, Special edition No. 1, 197), the revised version of Article 123 EPC is applicable to

European patent already granted at the time of their entry into force. It follows that the new version EPC 2000 is applicable in the present case. Under Article 2, first sentence, of the Decision of the Administrative Council of 7 December 2006 amending the Implementing Regulations to the European Patent Convention 2000 (OJ EPO 2007, Special edition No. 1, 89), the Implementing Regulations to EPC 2000 apply to all European patents subject to EPC 2000. Since the subject-matter of Rule 139 EPC relates to Article 123 EPC, the Board considers also that Rule 139 EPC applies.

2. During the examination procedure of the patent in suit, the Appellant, with letter dated 27 April 2001 (document (18)), filed a new set of claims 1 to 8. Claim 1 of this request was identical to claim 1 as granted later in the procedure, with the only exception that it did not require that amino acid residues 26 to 30 in the CDR-grafted heavy chain were donor residues. This was a preferred embodiment of the invention according to dependent claim 2 (27 April 2001).

Thus, claim 1 (27 April 2001) contained the disclaimer of claim 1 as granted (with "R" (Arginine) in position 45 of the heavy chain variable domain).

3. Document (18) (see page 3, sixth to eighth paragraph and page 5, seventh paragraph) read:

"It is worth noting that the filing date of D3 ["D3" corresponds to document (10) in the present appeal procedure; remark by the Board] is 28th December 1989 which is after the priority date for the present application. Therefore, only material which is entitled

to either of the two priority dates claimed in D3 could be detrimental to novelty.

In any event, as D3 is clearly a novelty-only citation, it is appropriate to use a disclaimer in respect of it.

It is well accepted that novelty can only be destroyed by a disclosure which is enabling. It is submitted that the disclosure in D3 is only enabling in respect of the disclosure of the specific humanised antibody shown in Figures 1 and 2 of D3."

"In the light of the above, it is submitted that it is only necessary to insert into claim 1 a disclaimer of the specific antibody disclosed in D3 in order to solve the "novelty-only citation" problem. Thus, the only proviso in claim 1 now recites the heavy and light chain variable domain sequences of the specific antibody disclosed in D3."

4. With letter dated 29 October 2003, the Appellant, during the opposition procedure, requested to correct "an error of transcription" in the disclaimer in claim 1 as the residue at position 45 of the heavy chain sequence recited in claim 1 should be "L" rather than "R", which would have been obvious to a skilled person reading the patent. The only place in which an antibody having a sequence similar to that given in the claim was found was in document (10), which was referred to on page 3 of the patent (corresponding to page 5 of the application as originally filed. A skilled person would have readily seen that the heavy chain sequence disclaimed in claim 1 was identical with the one given in document (10), with the sole exception of the

residue at position 45 of the heavy chain and would thus have had immediately seen that there was an error.

5. Respondent I argued that the correction of claim 1 did not fulfil the criteria for corrections under Rule 88 EPC (1973) defined by the Enlarged Board of Appeal in decision G 3/89 (supra), where it is stated that "The parts of a European patent application or of a European patent relating to the disclosure (the description, claims and drawings) may be corrected under Rule 88, second sentence, EPC only within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of these documents as filed. Such a correction is of a strictly declaratory nature and thus does not infringe the prohibition of extension under Article 123(2) EPC." (see conclusion (1)).

Respondent I referred in this respect to page 6, lines 25 to 27 of the application as filed (page 3, lines 44 to 45 of the granted patent) which read:

"The set of residues which we have identified as being of critical importance does not coincide with the residues identified by Queen et al (9)."

Reference (9) in the above citation refers at the same time to documents (8) and (10) in the present appeal procedure (see page 25, line 30 of the patent).

6. Furthermore, Respondent I argued that the skilled reader would have concluded that the relevant "set of

residues" referred to in this passage was that identified in the claims as originally filed and that accordingly no need for a disclaiming or limiting amendment could objectively and unambiguously have been ascertained from the application as originally filed. As not even the introduction of the "original" disclaimer in granted claim 1 could be derived from the application as filed, a correction of the disclaimer which the Appellant seeks to achieve through the provisions of Rule 139 EPC cannot meet the requirements set by decision G 3/89 (supra).

7. Claim 1 of Appellant's present request refers to an antibody molecule wherein the three CDRs of the heavy chain according to the Kabat numbering system and eight additional residues, outside the Kabat CDRs, are donor residues. Neither the antigen for which the antibody molecule has affinity nor the nature of the donor or the acceptor are defined. Considering that the amino acid residues of certain "donor" and certain "acceptor" antibodies at the required positions may be different but that they also can be identical, the claim covers an almost infinite number of antibody molecules.

In this situation the Board does not agree with Respondent I, that it can be derived from the sentence on page 6, lines 25 to 27 of the application as filed (see point (5) above) that no need for a disclaiming or limiting amendment could objectively and unambiguously have been ascertained from the application as originally filed. As a result of the immense scope of claim 1, it is quite realistic that an antibody disclosed in a prior art document may be encompassed by the wording of the claim, without said prior art

document describing exactly the same set of residues as being of critical importance than the patent in suit.

8. In decision G 1/03 (OJ EPO 2004,413) the Enlarged Board of Appeal decided that an amendment to a claim by the introduction of a disclaimer resulting in the incorporation therein of a "negative" feature, excluding from a general feature specific embodiments or areas, may not be refused under Article 123(2) EPC for the sole reason that neither the disclaimer nor the subject-matter excluded by it from the scope of the claim have a basis in the application as filed (see Order, point (1)). In the Order, point (2) the Enlarged Board of Appeal stated the criteria to be applied for assessing the allowability of a disclaimer which is not disclosed in the application as filed. According to the Order, point (2.1) a disclaimer may be allowable in order to restore novelty by delimiting a claim against state of the art under Article 54(3) and (4) EPC (1973), which are earlier applications which have not been published at the filing or priority date of the later application.

9. Respondent I has argued that the claimed priority date of the patent in suit was not valid. However, for the reasons outlined below the Board sees no need to decide this issue.

The claimed priority date of the patent in suit lies between the two priority dates and the publication date of document (10). Therefore, as long as the Board has not decided that the priority date of the patent in suit is not valid, document (10) belongs to the state of the art under Article 54(3) EPC.

Thus, in order to restore novelty against the disclosure in document (10) and when following the criteria given in decision G 1/03 (supra), a disclaimer may be introduced into the claims of the patent in suit, even if neither the disclaimer nor the excluded subject-matter have a basis in the application as filed. Therefore, Respondent I's argument, that the correction of the disclaimer under Rule 139 EPC is not allowable, as, in the first place, the application as originally filed contains no basis from which the need for a disclaiming or limiting amendment could objectively and unambiguously have been ascertained, must fail.

10. If the disclaimer introduced during the examination procedure may be corrected later according to the provisions set out in Rule 139 EPC, will now be investigated taking into account the exact wording of this Rule.

Rule 139 EPC is concerned with the correction of linguistic errors, errors of transcription and mistakes in **any document filed with the European Patent Office.** A correction concerning the description, claims or drawings must fulfil the requirement that the correction must be obvious in the sense that it is immediately evident that nothing else would have been intended than what is offered as the correction.

11. In the present case, **the document filed with the European Patent Office,** which according to the Appellant contained an error of transcription, was the letter dated 27 April 2001 (document (18)) accompanied by claims 1 to 8 of the newly filed main request (see points (1) and (2) above.

Therefore, the claims filed with this document have to be examined for the requirements of Rule 139 EPC, namely if it is immediately evident that they contain an error of transcription and if so if it is also immediately evident that nothing else would have been intended than what was offered as the correction with letter dated 29 October 2003 (see point (4) above).

The Board emphasises that the consideration of any document filed with the European Patent Office before document (18), by which the error was introduced for the first time, would make no sense.

12. Document (18), on pages 3 and 5 (see point (2) above), clearly expresses the intention to restore novelty of claim 1 by delimiting it against the disclosure in document (10). It is said that the specific humanised antibody shown in Figures 1 and 2 of document (10) should be excluded from the scope of the claim.

Figures 1 and 2 of document (10) show the amino acid sequences of the heavy chain and light chain variable domains of a specific humanised antibody, whose preparation is described in the experimental part of document (10), starting on page 26 thereof.

13. The skilled reader looking at claim 1 of the new request submitted with document (18), would therefore expect that nothing else than exactly the amino acid sequences of the heavy chain and light chain variable domains shown in Figures 1 and 2 of document (10) were excluded from the scope of the claim by the introduced disclaimer.

Due to the complex structure of the disclaimer, which contains two amino acid sequences each containing more than 100 residues, the skilled reader would not become aware of the difference between the disclaimed sequences and the disclosure in Figures 1 and 2 of document (10) at first glance. However, this cannot be a criterion for considering the allowability of a correction under Rule 139 EPC, as the Appellant in document (18) has left no doubt what exactly he intended to disclaim from the scope of claim 1.

Upon a closer look, i.e. a comparison of the sequences in the disclaimer of claim 1 and the sequences of Figures 1 and 2 of document (10), the skilled reader would become aware that the heavy chain variable domain sequence contained in the disclaimer differs in position 45 from the sequence of Figure 1 of document (10). Not only would it immediately be evident to him/her that there **exists** an error of transcription, but he/she, from the disclosure in document (10) would immediately know that **nothing else** would have been intended than what was offered as the correction in the letter dated 29 October 2003, namely to replace "R" in position 45 of the heavy chain by "L".

As a consequence, the Board arrives at the decision that the amendment of claim 1 meets the criteria defined in Rule 139 EPC.

Amendments - Article 123(2) EPC

14. As already discussed in point (7) above, the Enlarged Board of Appeal in decision G 1/03 (supra) has developed the criteria to be applied for assessing the

allowability of a disclaimer which is not disclosed in the application.

One of said criteria requires that a disclaimer should not remove more than is necessary either to restore novelty or to disclaim subject-matter excluded from patentability for non-technical reasons (G 1/03, Order, point (2.2)).

The Enlarged Board of Appeal found that an allowable disclaimer merely restricts the required protection and is outside the scope of Article 123(2) EPC, which does not allow the subject-matter of an application to be extended beyond the content of the application as filed. However, the only justification for the disclaimer is to exclude a novelty-destroying disclosure or subject-matter not eligible for patent protection. The necessity for a disclaimer is not an opportunity for the applicant to reshape his claims arbitrarily. Therefore, the disclaimer should not remove more than is necessary to restore novelty or to disclaim subject-matter excluded from patentability for non-technical reasons (G 1/03, point (3) of the reasons).

15. Present claim 1, referring to an **antibody molecule**, contains the proviso that said antibody molecule does not have a heavy chain variable domain having the sequence of Figure 1 of document (10) and a light chain variable domain having the sequence of Figure 2 of document (10).

The term "antibody molecule" is defined in paragraph [0025] of the patent where it is said that it may comprise: "a complete antibody molecule, having full

length heavy and light chains; a fragment thereof, such as a Fab, $(Fab')_2$ or FV fragment; or a single chain antibody, e.g. a single chain FV in which heavy and light chain variable regions are joined by a peptide linker. Similarly the CDR-grafted heavy and light chain variable region may be combined with other antibody domains as appropriate."

16. Thus, the disclaimer contained in claim 1 not only excludes a complete antibody molecule having the specific heavy and light chain variable domain sequences of Figures 1 and 2 of document (10) from the scope of protection, but also fragments and single chain antibodies according to paragraph [0025] of the patent containing the specific sequences disclosed in document (10).

17. Document (10), an earlier application belonging to the state of the art under Article 54(3) EPC (see point (9) above), refers to humanised immunoglobulins having CDRs from a donor immunoglobulin and a framework region from a human immunoglobulin, wherein each humanized immunoglobulin chain may comprise about three or more amino acids from the donor immunoglobulin in addition to the CDRs.

In the general part of the description it is said that "[t]he immunoglobulins may exist in a variety of forms besides antibodies; including, for example, Fv, Fab, $F(ab)_2$, as well as in single chains ..." (page 10, lines 15 to 17). On pages 12 to 15 certain criteria are developed to be considered when designing such humanised antibodies, in particular which residues, in addition to the CDRs should be from the donor.

18. The experimental part of the document (see page 26 and following and the figures and their description on pages 7 and 8) describes the preparation of a specific humanized antibody for p55 Tac protein of the IL-2 receptor.

The sequence of the human antibody Eu was used to provide the framework of the humanized antibody. The heavy chain variable domains of the Eu antibody and of a mouse anti-Tac antibody are aligned in Figure 1, the light chain variable domains of the two antibodies are aligned in Figure 2. The CDRs of the heavy and light chain variable regions of the humanized antibody were derived from the mouse anti-Tac antibody. In addition twelve amino acids in the heavy chain variable domain and three amino acid residues in the light chain variable domain of the Eu antibody were replaced by residues from the donor antibody. These residues are denoted in figures 1 and 2 by an "*".

The construction of humanized heavy and light chain genes is described on pages 28 and 29 and the amino acid and nucleotide sequences of the full length heavy and light chains of the complete humanised antibody are shown in figures 3 and 4. The construction of plasmids to express the full length heavy and light chains is described on page 30 and the synthesis of the complete humanised anti-Tac antibody is on pages 30 to 31 of document (10).

No other individualised immunoglobulin, neither in the form of an antigen fragment or of a single chain antibody, having the specific heavy and light chain variable domain sequences shown in figures 1 and 2 is

described in document (10). Thus, although the document in its general part mentions that such entities fall within the term "immunoglobulins", the only disclosure of a concrete immunoglobulin comprising these specific sequences is the complete humanised antibody whose preparation is described on pages 26 to 31 and only this precisely described molecule can be considered to be novelty destroying for the subject-matter of the patent in suit.

19. To the contrary, according to the patent's interpretation of the term "antibody molecule", which includes antibody fragments such as Fab, $(Fab')_2$ or FV fragment, single chain antibodies and CDR-grafted heavy and light chain variable regions combined with other antibody domains as appropriate (see point (15) above), claim 1 is not restricted to a complete antibody molecule having full length heavy and light chains. This has the effect that the disclaimer contained in claim 1 not only excludes a complete antibody molecule having the specific heavy and light chain variable domain sequences disclosed in Figures 1 and 2 of document (10), but also other entities falling within the definition of "antibody molecule" given in the patent which have these specific sequences.

As such entities, different from a complete antibody molecule, are not described in document (10), the Board comes to the conclusion that the disclaimer contained in claim 1 of the patent in suit removes more than what is necessary to restore novelty of the claimed subject-matter over the disclosure in document (10).

20. Consequently, in the light of decision G 1/03 (see Order, point 2.2 and point (3) of the reasons; supra) this disclaimer does not fulfil the requirements of Article 123(2) EPC.

Order

For these reasons it is decided:

The appeal is dismissed.

Registrar: Chair:

P. Cremona U. Kinkeldey