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D E C I S I O N
of 15 September 2005

Case Number: T 0236/01 - 3.3.08

Application Number: 89301052.0

Publication Number: 0327378

IPC: C12N 15/00

Language of the proceedings: EN

Title of invention:

Domain-modified constant region antibodies

Patentee:

The Trustees of Columbia University in the City of New York

Opponent:

Celltech Therapeutics Ltd.

Headword:

Domain-modified antibodies/COLUMBIA UNIVERSITY

Relevant legal provisions:

EPC Art. 54, 113(1), 123(2)

Keyword:

"Main request and first auxiliary request - appeal not substantiated"

"Second and third auxiliary requests - undisclosed disclaimer not allowable - added matter (yes)"

"Auxiliary requests IV to IX - added matter (yes)"

Decisions cited:

G 0001/03, G 002/03, T 0939/92, T 1050/99

Catchword:

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Case Number: T 0236/01 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 15 September 2005

Appellant: The Trustees of Columbia University in the
(Proprietor of the patent) City of New York
West 116th Street and Broadway
New York
New York 10027 (US)

Representative: Denison, Christopher
Mewburn Ellis LLP
York House
23 Kingsway
London WC2B 6HP (GB)

Respondent: Celltech Therapeutics Ltd.
(Opponent) 216 Bath Road
Slough
Berkshire SL1 4EN (GB)

Representative: Mercer, Christopher Paul
Carpmaels & Ransford
43, Bloomsbury Square
London WC1A 2RA (GB)

Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 13 December 2000
revoking European patent No. 0327378 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
S. Perryman

Summary of Facts and Submissions

- I. The appeal lies against the decision of the opposition division posted 13 December 2000 revoking European patent No. 0 327 378, entitled "Domain-modified constant region antibodies" and granted with 21 claims for all designated Contracting States on the basis of European patent application No. 89 301 052.0.
- II. An opposition had been filed on the grounds of Article 100(a) EPC and Article 100(b) EPC, in particular lack of novelty (Article 54 EPC), lack of inventive step (Article 56 EPC) and insufficient disclosure of the claimed subject-matter in the patent as granted. The opposition division found that the main request (claims as granted) did not fulfil the requirements of Article 54 EPC, the subject-matter of claim 1 lacking novelty over documents D6 and D10. Furthermore, the opposition division held that none of the three auxiliary requests on file (first auxiliary request based on an amended claim 1 filed on 30 July 1998, and second and third auxiliary requests as filed on 18 August 2000) was allowable, the negative features introduced into their respective claims 1 being in breach of Article 123(2) EPC. Claim 1 of the first auxiliary request was found also not to fulfil the requirements of Article 84 EPC.
- III. Granted claim 1 (**main request**) read as follows:
- "1. An antibody chain having at least one binding site region and a domain-modified constant region, wherein said domain-modified constant region comprises a modification selected from the group consisting of

(1) an insertion of at least eighty percent of the amino acids of at least one of the domains of C_L, C_{H1}, hinge, C_{H2}, C_{H3}, and C_{H4}, wherein the rest of the domain-modified constant region has the same amino acid sequence as that of a constant region of a mammalian antibody,

(2) a substitution of at least eighty percent of the amino acids of at least one of the domains of C_L, C_{H1}, hinge, C_{H2}, C_{H3}, or C_{H4} by at least eighty percent of the amino acids of at least one but less than all of said domains from a different mammalian antibody chain, wherein the rest of the domain-modified constant region has at least eighty percent the same amino acid sequence as that of a constant region of a mammalian antibody and

(3) a deletion of at least eighty percent of the amino acids of more than one of the domains C_{H1}, hinge, C_{H2}, C_{H3}, or C_{H4}, wherein the remaining amino acids of the domain-modified constant region have at least eighty percent the same amino acid sequence as that of at least one domain of a constant region of a mammalian antibody."

Claims 2 to 11 as granted were directed to different embodiments of the antibodies of claim 1. Claims 12 to 18 concerned DNA constructs encoding domain-modified antibody chains, and claims 19 and 20 a cell containing the claimed DNA constructs. Finally, claim 21 related to a method for producing a domain-modified constant region antibody.

IV. The **first auxiliary request** (claims 1 to 21) differed from the main request solely in that its claim 1 included the following provisos:

"...

- (a) that the insertion of (1) is not a duplication of a hinge domain;
- (b) that the deletion is other than deletion of constant region containing the domains CH2 and CH3; and
- (c) that the substitution of (2) is not the substitution of the hinge of IgG1 with the hinge of IgG4."

V. Claim 1 of the **second auxiliary request** (claims 1 to 7) read:

"1. A secreted monoclonal antibody which comprises two heavy chains and two light chains assembled into a Y-shape configuration wherein:

- (A) the antibody has a desired antigen specificity; and
- (B) each heavy chain of the antibody comprises at least one binding site region from a mammalian source and a domain-modified human constant region, wherein said domain-modified constant region comprises a modification relative to an unmodified heavy chain of a human antibody from a human source, which modification is selected from the group consisting of:

- (1) an insertion of at least 80% of the amino acids of at least one of the domains of C_L, C_{H1}, hinge, C_{H2}, C_{H3}, and C_{H4} from said human antibody or from a different human antibody, wherein the rest of the domain-modified human constant region has the same amino acid sequence as that of a constant region of said unmodified heavy chain of said human antibody,
- (2) a substitution of at least 80% of the amino acids of at least one of the domains of C_{H1}, hinge, C_{H2}, and C_{H3} by at least 80% of the amino acids of at least one but less than all of C_L, C_{H1}, hinge, C_{H2}, C_{H3}, and C_{H4} from a different human antibody, wherein the rest of the domain-modified constant region has at least 80% of the same amino acid sequence as that of a constant region of said unmodified heavy chain of said human antibody, and
- (3) a deletion of at least 80% of the amino acids of more than one of the domains C_{H1}, hinge, C_{H2}, and C_{H3} of said human antibody, wherein the remaining amino acids of the domain-modified constant region have at least 80% the same amino acid sequence as that of at least one domain of a constant region of said unmodified heavy chain of said human antibody;

and wherein said human antibody is an IgG1 through IgG4 subclass antibody with the proviso that said human antibody is not an IgG3 subclass antibody."

Claims 2 to 6 were directed to embodiments of the antibody of claim 1, and claim 7 to a method for producing the claimed antibody.

VI. The **third auxiliary request** (claims 1 to 7) differed from the previous request in that the additional feature

"(C) the antibody has carbohydrate attached to it"

was inserted at the end of claim 1.

VII. The appellant (proprietor of the patent) filed an appeal against the revocation of the patent and paid the appeal fee. With the statement of grounds of appeal, the appellant filed six new auxiliary requests (auxiliary requests IV to IX), the main request and the auxiliary requests I to III on which the decision of the opposition division was based, being maintained on appeal. As a subsidiary request, oral proceedings pursuant to Article 116 EPC were requested.

VIII. Claim 1 of **auxiliary request IV** (claims 1 to 9) reads:

"1. An antibody fragment which comprises a half antibody formed from a single light chain and a single heavy chain assembled to produce a specific binding site,

which heavy chain has at least one binding site region from a mammalian source and a domain-modified human constant region,

which domain-modified human constant region comprises a deletion of at least 80% of the amino acids of more than one of the domains CH1, hinge, CH2, and CH3,

wherein the remaining amino acids of the domain-modified human constant region have at least 80% the same amino acid sequence as that of at least one domain of the original human constant region,

wherein the antibody fragment is an IgG class antibody fragment with the proviso that it does not have an IgG3 heavy chain."

Independent claim 2 is also directed to an antibody fragment, but differs from claim 1 in that the domain-modified human constant region comprises "a deletion of the amino acids of the domains hinge, CH2, and CH3", the proviso with respect to IgG3 having been deleted. Independent claim 3 is identical to claim 1 of the second auxiliary request, except for the phrase "and wherein said human antibody is an IgG1 through IgG4 subclass antibody with the proviso that said human antibody is not an IgG3 subclass antibody" being replaced by "and wherein the antibody is an IgG class antibody with the proviso that it does not have an IgG3 heavy chain." Dependent claims 4 and 5 relate to different embodiments of the antibodies/antibody fragments of claims 1 to 3. Dependent claims 6 to 8 concern various embodiments of the antibody of claim 3, and independent claim 9 is directed to a method for

producing the antibodies/antibody fragments of claims 1 to 3.

- IX. **Auxiliary request V** (claims 1 to 9) differs from the previous request in that the negative proviso in independent claims 1 and 3 has been replaced by a positive formulation to the effect that the claimed antibody/antibody fragment is an IgG1, IgG2 or IgG4 subclass antibody/antibody fragment.
- X. In **auxiliary request VI**, independent claim 2 includes a proviso by which antibody fragments having an IgG3 heavy chain are excluded from the scope of the claim, all other claims being identical to those of the previous request.
- XI. **Auxiliary request VII** differs from the previous request in that the proviso has been replaced by a limiting feature analogous to that in claim 1 (cf. Section IX above).
- XII. The claims of **auxiliary request VIII** have been limited to antibodies/antibody fragments of the IgG1 or IgG4 subclass (claims 1 to 8) and to a method for producing the same (claim 9).
- XIII. Claims 1 to 4 of **auxiliary request IX** are identical to claims 2, 4, 5 and 9 of the previous request.
- XIV. The respondent (opponent) submitted its comments on both the grounds of appeal and the new sets of claims filed by the appellant, and requested that oral proceedings be held in the event that the board did not intend to reject the appeal.

XV. The parties were summoned to oral proceedings to take place on 15 September 2005. In a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal sent with the summons, the board stated its provisional opinion on the issues decided by the opposition division and, in connection with the allowability of claim 1 of the second and third auxiliary requests under Article 123(2) EPC, drew the attention of the parties to decisions G 1/03 and G 2/03 (OJ EPO 2004, 413 and 448) of the Enlarged Board of Appeal, as well as to decision T 1050/99 of 25 January 2005. With regard to the auxiliary requests IV to IX filed on appeal, the board expressed its concerns as to the compliance of the new auxiliary requests with the requirements of Rule 57a and Articles 84, 123(2) and (3) EPC, and advised the appellant to submit new claim request(s) and to indicate the basis in the application as filed for each of the amendments introduced into these claims. Finally, the board commented on the issue of inventive step, referring in particular to decision T 939/92 (OJ EPO 1996, 309).

XVI. With letter dated 2 September 2005, the appellant withdrew its request for oral proceedings and requested instead that a decision be taken on the basis of the submissions in writing. No submissions were made in reply to the board's communication, nor were amended claim requests filed. The respondent also withdrew its request for oral proceedings, provided that the appeal would be rejected. On 12 September 2005 the parties were informed per fax letter that the oral proceedings were cancelled.

XVII. Following documents are referred to in the present decision:

D6: S. Cabilly et al., Proc. Natl. Acad. Sci. USA, June 1984, Vol. 81, pages 3273 to 3277;

D10: S.L. Morrison et al., Annals N.Y. Acad. Sci., December 1987, Vol. 507, pages 187 to 198.

XVIII. The submissions made by the appellant in writing, as far as they are relevant to this decision, were as follows:

The impugned decision stated that claim 1 of the second auxiliary request did not meet the requirements of Article 123(2) EPC because there was no specific disclosure of an IgG3 subclass human antibody. However, the application did disclose an IgG3 subclass antibody in Examples 1-3 of the specification, *inter alia* on page 16, lines 36-37; page 17, line 5; page 17, lines 17-19; page 18, line 5; and Figures 1 and 3. The proviso specifying that the claimed human antibody did not have an IgG3 heavy chain, was to disclaim cited reference D10, which described antibodies having deletions of domains wherein the antibody has an IgG3 heavy chain, for instance on page 193, line 22. Thus, the proviso conformed as a disclaimer to the requirements of Article 123(2) EPC. Consequently, the decision was incorrect in refusing to allow maintenance of the patent on the basis of the second auxiliary request.

The application clearly described half antibodies as claimed in claim 1 of auxiliary requests IV to IX. It was stated on page 16, lines 18-20 of the application as filed that the term "antibody" referred to both whole antibodies and fragments thereof, while page 16, lines 22-24 stated that antibody fragments included half antibodies formed from single light and heavy chains that have assembled to produce a specific binding site. Accordingly, the application provided an antibody fragment which comprised a half antibody formed from a single light chain and a single heavy chain assembled to produce a specific binding site.

XIX. The submissions made by the respondent in writing were essentially as follows:

No valid appeal was filed in respect of the main, first and third auxiliary requests, as the appellant did not provide any grounds on which the appeal was based. Therefore, these requests should be removed from consideration in the present proceedings.

There was no basis in the application as filed for excluding IgG3 antibodies from the claims. The application as filed mentioned IgG3 antibodies, but there was no statement in the application that it was preferred not to use IgG3 antibodies.

Document D10 was relevant for both novelty and inventive step issues. It was relevant also for questions of Article 123(2) EPC in connection with claim 1 of the second auxiliary request, since according to the established case law of the boards of

appeal the use of a disclaimer in respect of a document relevant for obviousness was not possible.

Claim 1 of auxiliary request IV related to half antibodies. However, the passage of the application indicated by the appellant as support for this claim gave no details at all as to the structure of the half antibody. There was no disclosure in the application that half antibodies were only produced by making deletions in the constant region, as specified in claim 1. There was also no support for half antibodies in connection with the limitation to an IgG subclass. The combination claimed in claim 1 could not be derived directly and unambiguously from the application as filed. To come up with the wording of claim 1, the appellant had to take disclosures from disparate parts of the application and cobble them together. The same applied *mutatis mutandis* to claim 1 of the remaining auxiliary requests.

The amendments introduced in the claims raised deficiencies under Article 84. As regards conciseness, auxiliary requests IV to VIII contained three independent product claims. As regards clarity, when read in connection with the further features in claims 1 and 2, the phrase "the antibody fragment is an IgG class antibody" in these claims had no clear meaning.

The patent did not provide any guidance as to how to obtain half antibodies having certain combinations of deletions in the constant region specified in claim 1, for instance, a deletion of only C_H2 and C_H3. Such half antibodies could not be obtained, because the heavy

chain containing a hinge region would dimerize to form a $F(ab')_2$ molecule. A dimer having the features specified in claim 1 was already known from D10. Consequently, to the extent that the subject-matter of claim 1 was supported or enabled, it lacked novelty over D10. Furthermore, in view of this prior art document the subject-matter of all claims did not involve an inventive step.

XX. The appellant requests that the decision under appeal be set aside and the patent be maintained on the basis of the main request or any of the first auxiliary request filed on 30 July 1998, the second and third auxiliary requests filed on 18 August 2000 and auxiliary requests IV to IX filed with the statement of grounds of appeal.

XXI. The respondent requests that the appeal be dismissed.

Reasons for the Decision

Main request and first auxiliary request - Article 54 EPC

1. No reasons have been given by the appellant in its statement of grounds of appeal to substantiate its allegation that the findings of the opposition division with respect to the main request and the first auxiliary request were wrong. Since the board has been given no grounds, as would be required by Article 108 EPC, as to why the decision of the first instance on the present main request and first auxiliary request is wrong, these requests will not be considered by the board. It is not part of the function of the board of

appeal to reconsider refused requests in the absence of any substantiation of their allowability under the EPC by the appellant.

Second and third auxiliary request - Article 123(2) EPC

2. Claim 1 of both the second and third auxiliary requests includes the feature "*with the proviso that said human antibody is not an IgG3 subclass antibody*", which was not present in claim 1 as granted. The opposition division found that this feature had no basis in the application as filed, the limitation to a human antibody of the IgG1 through IgG4 subclass, as disclosed on page 5, line 22 of the application as originally filed (corresponding to line 33 on page 3 of the application as published) not being considered to amount to a specific disclosure of an **IgG3** subclass **human** antibody. Furthermore, the opposition division held that, even if the negative feature at issue were to be considered as a "disclaimer", no indication had been given by the proprietor as to which specific prior art disclosure might have served as a basis for it. Consequently, the amendment to claim 1 was found not to conform to Article 123(2) EPC (cf. point 4.3 of the impugned decision).

3. In the statement of grounds of appeal, the appellant contested these findings, pointing to further passages of the application as filed, which, in its view, provided a basis for the negative feature in amended claim 1. Thus, the first issue to be decided by the board in connection with Article 123(2) EPC is whether or not the application as filed, in particular the passages referred to in the impugned decision and/or

cited by the appellant in its statement of grounds of appeal, disclose the negative feature in question.

4. The passage referred to in the decision of the opposition division (cf. point 4.3) is found in the application as filed under the heading "Description of the specific embodiments", and describes specific embodiments of the claimed antibodies. The whole sentence including this passage reads:

"The antibodies include IgM, IgG, IgA, IgD and IgE classes as well as the various subclasses of the individual classes (e.g., human IgG1 through IgG4)."

Further passages cited by the appellant in its statement of grounds of appeal read:

"IgG₃ genes have been constructed and expressed."
(page 16, lines 36-37 of the application as filed, corresponding to page 7, line 23 of the published application.)

"Exchanging the hinge region from IgG3 and IgG4 did not alter the ability of these molecules to fix complement and to bind the Fc receptor." (page 17, lines 5-7 of the application as filed, corresponding to page 7, lines 26-27 of the published application.)

"To determine if there is an upper limit on the size of an antibody molecule which could be produced, an IgG₃ heavy chain in which C_H1 and the hinge region were duplicated was constructed." (page 17, lines 16-19 of the application as filed, corresponding to page 7, lines 35-36 of the published application.)

"IgG₃ heavy chain genes encoding proteins with deletions of

C_{H2};

hinge + C_{H2};

C_{H1} + hinge; and

C_{H1} + hinge + C_{H2}

were constructed and transfected into myeloma cells" (page 18, lines 5-10 of the application as filed, corresponding to page 7, lines 50-55 of the published application.)

The appellant cited also Figures 1 and 3 as disclosing an IgG3 subclass antibody. In Figure 1, four different cloning cassettes used to exchange constant regions are shown, each cassette corresponding to one of the four IgG subclasses, ie IgG1, IgG2, IgG3 and IgG4. Figure 3 illustrates a cloning cassette used to delete or duplicate constant region domains, in particular of an antibody of the IgG3 subclass.

5. When judging whether or not amendments introduced in the claims conform to Article 123(2) EPC, the Boards of Appeal of the EPO take a strict approach (cf. "Case Law of the Boards of Appeal of the EPO", 4th edition 2001, chapter III.A). An amendment is only considered to be allowable if the skilled person can derive the subject-matter of the amended claim from the application in a clear and unambiguous manner. This board does not see any reason to deviate from this jurisprudence when judging whether or not a **negative** feature introduced in the claims adds subject-matter contrary to Article 123(2) EPC.

6. In the present case, the board notes that, although IgG3 subclass antibodies are in fact mentioned in all the passages of the application quoted above, no explicit formal basis for the introduced amendment as such, ie for a **negative** feature excluding specifically IgG3 subclass antibodies can be found in the cited passages or elsewhere in the application as filed. Moreover, the board is not able to find an implicit support for the claimed subject-matter in the cited passages, as the embodiments being excluded by the negative feature in question (ie IgG3 subclass antibodies) are presented as being part of the invention disclosed in the application, rather than as an area which should be excluded or avoided, as it is the case in claim 1 (cf. decision T 1050/99 of 25 January 2005, in particular point 7(c) of the reasons). For these reasons, the passages of the application as filed cited by the appellant cannot be accepted as an explicit or implicit basis for the negative feature introduced in claim 1.
7. On appeal, the appellant has alleged that the negative feature in claim 1 is intended to disclaim the subject-matter disclosed in document D10, and, as a disclaimer, conforms to the requirements of Article 123(2) EPC. In view of the appellant's submission, a further question to be decided by the board in this respect is whether in the present case the introduction of the undisclosed disclaimer in claim 1 conforms to Article 123(2) EPC.
8. In decisions G 1/03 and G 2/03 (OJ EPO 2004, 413 and 448), the Enlarged Board of Appeal established the criteria for assessing whether an amendment to a claim

by introduction of an undisclosed disclaimer offends against Article 123(2) EPC. According to these decisions, the introduction of an undisclosed disclaimer may be allowable under certain circumstances, *inter alia*, in order to restore novelty by delimiting a claim against state of the art under Article 54(3) and (4) EPC or against an accidental anticipation under Article 54(2) EPC (cf. G 1/03, *supra*, Headnote II.1).

9. None of these exceptional circumstances apply in the present case. Document D10, which belongs to the prior art citable under Article 54(2) EPC and discloses human domain-modified constant region antibodies, has been considered to be possibly the "closest prior art", ie the starting point for the assessment of inventive step, by both the appellant and the respondent. Therefore, this document can hardly be considered to be an "accidental anticipation" as defined in the decisions G 1/03 and G 2/04 (*supra*), ie a prior art document which is so unrelated to and remote from the claimed invention that the person skilled in the art would never have taken it into consideration when making the invention. Moreover, if one takes this document as starting point for the assessment of inventive step, the negative feature included in claim 1 becomes relevant in this respect as, at least for certain embodiments encompassed by claim 1, it constitutes the only difference over the disclosure of the prior art.

10. In the light of these considerations, the board concludes that the amendment to claim 1 of the second and third auxiliary requests by introduction of the disclaimer in question is not allowable, as it adds subject-matter contrary to Article 123(2) EPC.

Auxiliary requests IV to IX - Article 123(2) EPC

11. With the statement of grounds of appeal, the appellant filed six new auxiliary requests, all of which include at least one independent claim directed to an antibody fragment which comprises a half antibody (cf. Sections VIII to XIII above). The respondent has protested against the introduction of the new requests, raising numerous objections under Articles 123(2), 84, 83, 54 and 56 EPC.

12. In its communication pursuant to Article 11(1) of the Rules of Procedure, the board indicated that, in spite of the references to the original application given by the appellant in the statement of grounds of appeal, the origin and rationale of the amendments introduced in the new auxiliary requests in comparison to the claims as granted and to the claims submitted before the opposition division, was not clear. The board also indicated that it was an undue burden for the reader to establish: 1) in response to which objection any given feature had been introduced in the claim, 2) whether a given feature found its origin in the application as filed in relation to the whole of the other features specified in the claim, and 3) whether the scope of protection had remained the same.

13. The board also indicated that the auxiliary requests IV to IX might raise serious issues under Rule 57a and Articles 84, 123(2) and 123(3) EPC. Specifically, in connection with Article 123(2) EPC the board pointed to claims 1 and 2 of auxiliary requests IV to VIII, and claim 1 of auxiliary request IX, which read: "An

*antibody fragment which **comprises** a half antibody...*", and took the view that, whereas it was stated on page 16, lines 22-24 of the application as filed that antibody fragments within the meaning of the application may be half antibodies formed from single light and heavy chains that have assembled to produce a specific binding site, none of the passages cited by the appellant in its statement of grounds of appeal appeared to provide a fair basis for antibody fragments including anything else than a half antibody.

14. As this particular deficiency under Article 123(2) EPC, which has been mentioned in the board's communication, affects claim 1 of each of the auxiliary requests IV to IX, none of these claim requests can serve as a basis for the maintenance of the patent. Consequently, in the absence of an allowable claim request the board cannot set aside the impugned decision as requested by the appellant.

Article 113(1) EPC

15. The reasons given in the present decision were apparent from the communication sent by the board in preparation for the oral proceedings. The appellant withdrew its request for oral proceedings, and chose not to file a reply to the board's communication or amended claim requests. The respondent's request for oral proceedings is conditional, and the matter is decided in its favour. Thus, the provisions of Article 113(1) EPC are complied with.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

A. Wolinski

L. Galligani