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Datasheet for the decision of 20 March 2007

Case Number: T 0491/04 - 3.3.04

Application Number: 91121806.3

Publication Number: 0492448

IPC: C12P 21/08

Language of the proceedings: EN

Title of invention:
Monoclonal antibodies against human tumor necrosis factor alpha

Patentee:
Pharmacia & Upjohn S.p.A.

Opponents:
Centocor, Inc.
Abbott Laboratories

Headword:
Anti-TNF α antibody/PHARMACIA & UPJOHN

Relevant legal provisions:
EPC Art. 123(2), 123(3)

Keyword:
"Main request - added subject-matter (yes)"
"Auxiliary request - extention of scope of protection (yes)"

Decisions cited:
G 0003/89, G 0001/93

Catchword:
-

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Case Number: T 0491/04 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 20 March 2007

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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 5 February 2004 revoking European patent No. 0492448 pursuant to Article 102(1) EPC.

Composition of the Board:

Chair: U. Kinkeldey
Members: B. Claes
G. Weiss

Summary of Facts and Submissions

I. European patent No. 0 492 448 with the title "Monoclonal antibodies against human tumor necrosis factor alpha" was granted on the basis of the European patent application 91121806.3.

II. Claims 1 and 2 as originally filed read:

"1. A monoclonal antibody or a binding fragment thereof which is able to neutralize human Tumor Necrosis Factor α, characterized in that said antibody is able to precipitate human TNF α forming high molecular weight antigen-antibody complexes."

"2. A monoclonal antibody or a binding fragment thereof according to claim 1, wherein the smallest antigen-antibody complexes formed with human TNF α contain substantially at least two molecules of said antibody and at least one human TNF α molecule and have molecular weight of at least 400 kD."

III. Claim 1 of the set of claims for the designated Contracting States AT *et al.* contained in the patent as granted read:

"1. A monoclonal antibody or a binding fragment thereof which is able to neutralize human Tumor Necrosis Factor alpha, characterized in that said antibody is able to precipitate human TNF alpha forming high molecular weight antigen-antibody complexes, whereof the smallest antigen-antibody complexes formed with human TNF alpha contain substantially three molecules of said antibody

and two human TNF alpha molecules and have a molecular weight of at least 400 kD."

IV. The patent had been opposed in its entirety on the grounds of Article 100(a) EPC, combined with Articles 52(2)(a), 54 and 56 EPC as well as Articles 100(b) and 100(c) EPC.

V. Against the decision of the opposition division to revoke the patent under Article 102(1) EPC the appellant (patent proprietor) filed an appeal. With the statement of grounds of appeal a main and auxiliary request both comprising 13 claims for the designated Contracting States AT *et al.* and 12 claims for ES and GR were submitted.

VI. Claim 1 of the set of claims of the main request for the designated Contracting States AT *et al.* read:

"1. A monoclonal antibody which is able to neutralize human Tumor Necrosis Factor alpha, characterized in that said antibody is able to precipitate human TNF alpha forming high molecular weight antigen-antibody complexes, whereof the smallest antigen-antibody complexes formed with human TNF alpha contain substantially three molecules of said antibody and two human TNF alpha molecules and have a molecular weight of at least 400 kD, wherein said monoclonal antibody is able to provide complete protection in mice from an otherwise lethal dose of human TNF alpha at antibody doses lower than 1 μg/mouse."

Claim 1 of the set of claims of the auxiliary request for the designated Contracting States AT *et al.* read:

"1. A monoclonal antibody which is able to neutralize human Tumor Necrosis Factor alpha, characterized in that said antibody is able to precipitate human TNF alpha forming high molecular weight antigen-antibody complexes, whereof the antigen-antibody complexes formed with human TNF alpha typically contain substantially three molecules of said antibody and two human TNF alpha molecules and have a molecular weight of at least 400 kD, wherein said monoclonal antibody is able to provide complete protection in mice from an otherwise lethal dose of human TNF alpha at antibody doses lower than 1 μg/mouse."

VII. Opponents 01 and 02, who are respondents I and II respectively, in the present appeal proceedings, filed submissions in answer to the appellant's grounds of appeal.

VIII. The board issued a communication pursuant to Article 12 of the Rules of Procedure of the Boards of Appeal indicating its preliminary non-binding opinion.

IX. Oral proceedings took place on 20 March 2007.

X. The appellant's arguments relevant for the present decision may be summarised as follows:

Main request; claim 1 of the set of claims for the designated Contracting States AT et al.;
Ground of opposition under Article 100(c) EPC

The amendment "whereof the smallest antigen-antibody complexes formed with human TNF alpha contain

substantially three molecules of said antibody and two human TNF alpha molecules" characterising the ability of the claimed antibodies to form high molecular weight antigen-antibody complexes with human TNF alpha, had been made to the claim in the course of the examination proceedings to emphasise a "distinctive feature" of the invention, namely that the complexes formed, even at low concentrations, typically contain three molecules of antibody to two human TNF alpha molecules. This resulted in beneficial properties of the claimed antibodies such as a more efficient human TNF alpha clearance.

The skilled person interpreted claim 1 as being directed to monoclonal antibodies that form small amounts of complexes both bigger and smaller than those having the 3 to 2 stoichiometric ratio. Furthermore, the claim was directed to a biological system, which was never completely definable with regard to the size of the aggregates as formed therein. Accordingly, an antibody that forms "smallest" antigen-antibody complexes that contain "substantially" three molecules of antibody to two molecules of TNF alpha will necessarily also form small amounts of other complexes, both bigger and smaller.

Claim 1 could only be read as to cover a monoclonal antibody wherein the smallest complex which is substantially present has the 3 to 2 stoichiometric ratio whereby small amounts of other forms may also be present. This interpretation was fully supported by the description of the application as filed on page 4, lines 17 to 24 and the last sentence of example 8.

Claim 1 of the main request therefore did not contain subject-matter which extended beyond the content of the application as filed.

Auxiliary request, claim 1 of the set of claims for the designated Contracting States AT et al.;
Article 123(3) EPC

Claim 1 did not infringe the requirements of Article 123(3) EPC. The claim merely defined, in explicit terms, the subject-matter of claim 1 as granted.

XI. The respondents' arguments relevant for the present decision may be summarised as follows:

Main request; claim 1 of the set of claims for the designated Contracting States AT et al.;
Ground of opposition under Article 100(c) EPC

The feature "whereof the smallest antigen-antibody complexes formed with human TNF alpha contain substantially three molecules of said antibody and two human TNF alpha molecules" characterising the ability of the claimed antibodies to form high molecular weight antigen-antibody complexes with human TNF alpha extended beyond the content of the application as filed. The amendment therefore did not comply with the requirement of Article 123(2) EPC.

Auxiliary request, claim 1 of the set of claims for the designated Contracting States AT et al.;
Article 123(3) EPC

The deletion of the "lowest" limit of the possible antigen-antibody complexes capable of being formed between the claimed antibody and human TNF alpha containing substantially three molecules of said antibody and two human TNF alpha molecules, extended the protection conferred by the patent also to antibodies having as the lowest limit of the possible antigen-antibody complexes capable of being formed consisting of two claimed antibodies and one human TNF alpha molecule.

XII. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 13 for AT *et al.* and claims 1 to 12 for ES and GR (main request) or, alternatively, on the basis of claims 1 to 13 for AT *et al.* and claims 1 to 12 for ES and GR, both requests filed with letter dated 14 June 2004. The appellant furthermore requested that, in the event that the board found the claims formally allowable, the case be remitted to the department of first instance for further prosecution on the grounds under Articles 100(a) and 100(b) EPC.

The respondents (opponents 01 and 02) requested that the appeal be dismissed.

Reasons for the Decision

Main request; claim 1 of the set of claims for the designated Contracting States AT et al.;
Ground of opposition under Article 100(c) EPC

1. Claim 1 is directed to a monoclonal antibody which is able to neutralize human Tumor Necrosis Factor alpha. The characterising part of this claim consists essentially of two groups of features, namely that the antibody

(a) "is able to precipitate human TNF alpha forming high molecular weight antigen-antibody complexes,

whereof the smallest antigen-antibody complexes formed with human TNF alpha

(i) contain substantially three molecules of said antibody and two human TNF alpha molecules and

(ii) have a molecular weight of at least 400 kD",

and

(b) "wherein said monoclonal antibody is able to provide complete protection in mice from an otherwise lethal dose of human TNF alpha at antibody doses lower than 1 μg/mouse."

2. Claim 1 of the set of claims for the designated Contracting States AT *et al.* as granted (see section III above) differs from this claim merely by the

addition of feature (b). The group (a) features are identically contained in claim 1 as granted. The ground of opposition under Article 100(c) EPC has been invoked in the opposition proceedings. Accordingly, the board is competent to examine the group (a) features for their compliance with the requirements of Article 123(2) EPC.

3. The monoclonal antibody as subject-matter of claim 1 combined with that of dependent claim 2 of the set of claims of the application as filed for the designated Contracting States AT *et al.* (see section II above) differs in respect of feature (a)(i) from the monoclonal antibodies of claim 1 of the main request. Feature (a)(i) in the former defines the monoclonal antibody as being able to precipitate antigen-antibody complexes whereof the smallest complexes formed contain substantially **two** molecules of antibody and **one** human TNF alpha molecule in the former, whereas in the latter it defines the antibodies as being able to precipitate antigen-antibody complexes whereof the smallest complexes formed substantially **three** molecules of antibody and **two** human TNF alpha molecules.

4. The underlying idea of Article 123(2) EPC is that an applicant is not allowed to improve his position by adding subject-matter not disclosed in the application as filed, which would give him an unwarranted advantage and could be damaging to the legal security of third parties relying on the content of the original application (see decision G 1/93, OJ EPO 1994, 541, point 9 of the reasons). In accordance with established case law of the Boards of Appeal, this is generally taken to mean that the relevant question to be decided

when assessing whether an amendment adds subject-matter extending beyond the content of the application as filed is whether the amendments are **directly** and **unambiguously** derivable from the application as filed (see decision G 3/89, OJ EPO 1993, 117, point 2 of the reasons and Case Law of the Boards of Appeal of the European Patent Office, 5th edition, III.A.2 and 2.1).

5. Accordingly, in the present case it needs to be determined whether the change of the lower limit of the antigen-antibody complex stoichiometric ratio of 2 antibodies to 1 antigen to a ratio of 3 antibodies to 2 antigens adds subject-matter to the claim which extends beyond the content of the application as filed and thus whether the amended feature that the monoclonal antibody is "able to precipitate antigen-antibody complexes whereof the smallest complexes formed substantially three molecules of antibody and two human TNF alpha molecules" constitutes added subject-matter within the meaning of Article 123(2) EPC .

6. The board notes that the application as filed refers, in the form of claim 2, to the feature concerning the composition ratio of the *smallest* high molecular weight complexes formed between the monoclonal antibody and TNF alpha molecules. Accordingly, the application as filed explicitly draws the attention of the skilled person to the particular characterizing nature of the feature of stoichiometric ratio of the smallest high molecular weight antigen-antibody complexes of which the claimed antibodies are capable of forming.

7. The only passage in the application as filed which explicitly discloses antigen-antibody complexes containing substantially **three** molecules of antibody and **two** human TNF alpha molecules is on page 4, lines 17 to 24 in the description of the application as originally filed. This passage reads:

"As a *third aspect, the present invention shows that the smallest antigen-antibody complex formed upon incubation of said monoclonal antibody with human TNF α is a high molecular weight antigen-antibody complex, containing substantially at least 2 molecules of said monoclonal antibody and at least 1 human TNF α molecule; typically three monoclonal antibody molecules link together two molecules of human TNF α. The term "high molecular weight antigen-antibody complex" is used to denote antigen-antibody complexes of at least 400 kD, typically from about 570 kD to about 600 k*D." (emphasis added by the board)

The "said monoclonal antibody" in the passage refers to "the monoclonal antibody provided by the present invention", as can be taken from the application as filed on page 3, lines 33 to 34.

8. The board is satisfied that the skilled person would have learned from the recited passage that the monoclonal antibody as claimed has the capability of forming a mixture of high molecular weight complexes of different sizes with a lower composition ratio of 2 antibodies to 1 antigen and that a typical representative of this mixture is a complex of three antibodies and two antigens. The board judges however that from the cited passage the skilled person cannot

directly and **unambiguously** derive that the specification of the application also contemplated that monoclonal antibodies of the invention also included such antibodies which are characterised by being able to form a mixture of high molecular weight complexes of different sizes with the lowest composition ratio of 3 antibodies to 2 antigens, i.e. a feature which the board considers to exclude from the subject-matter of claim 1 all such monoclonal antibodies which are able to form the complexes having the composition ratio of 2 antibodies to 1 antigen.

9. The appellant has argued that in view of the fact that an antibody that forms "smallest" antigen-antibody complexes that contain "substantially" three molecules of antibody to two molecules of TNF alpha will necessarily also form small amounts of other complexes, both bigger and smaller, and therefore also such which contain substantially two molecules of antibody and one human TNF alpha molecule.

10. The board cannot however concur with this argument in view of the clear wording of the claim that the **smallest** complexes formed contain substantially **three** molecules of antibody and **two** human TNF alpha molecules, thereby excluding from the subject-matter of claim 1 all such monoclonal antibodies which are able to form the complexes having the composition ratio of e.g. two antibodies to 1 antigen.

11. The appellant has furthermore referred to example 8 contained in the application as filed as supporting the feature relating to the stoichiometric ratio of three antibodies to two human TNF alpha molecules. The board

cannot concur with the appellant's argumentation in this context as it considers that this example makes no direct and unambiguous reference to such a stoichiometric ratio but merely refers, in general terms, to the molecular weight of the complexes formed under the conditions of the example.

12. In view of the above considerations, the board considers that claim 1 of the set of claims for the designated Contracting States AT et al. of the main request extends beyond the content of the application as filed.

Auxiliary request, claim 1 of the set of claims for the designated Contracting States AT et al.;
Article 123(3) EPC

13. Claim 1 differs from claim 1 of the set of claims as granted for the designated Contracting States AT *et al.* (see section III above) by a combination of an insertion amendment (insertion of the term "typically") and a deletion amendment (deletion of the term "smallest"). These amendments result in the feature defining the ability of the claimed monoclonal antibody to form high molecular weight complex whereby such complexes "**typically**" contain substantially **three molecules** of said antibody and **two** human TNF alpha molecules and have a molecular weight of at least 400 kD.

14. The board judges that the feature that the monoclonal antibodies are able to form a mixture of high molecular weight complexes of different sizes with the lowest stoichiometric composition ratio of 3 antibodies to 2

antigens, no longer excludes from the scope of the claim such monoclonal antibodies which are able to form high molecular weight complexes having the composition ratio of e.g. 2 antibodies to 1 antigen, i.e. such antibodies which the board judges not to fall within the scope of protection provided by granted claim 1.

15. In view of the above considerations claim 1 of the set of claims for the designated Contracting States AT *et al.* of the auxiliary request therefore infringes the requirements of Article 123(3) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

P. Cremona U. Kinkeldey