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DECISION
of 12 November 2003

Case Number: T 0500/01 - 3.3.4

Application Number: 90903576.8

Publication Number: 0451216

IPC: C12P 21/08

Language of the proceedings: EN

Title of invention:

Humanized Immunoglobulins and their production and use

Patentee:

PROTEIN DESIGN LABS, INC.

Opponents:

02. ICOS Corp.
03. Novartis AG
04. Celltech Therapeutics Ltd
05. Bayer AG
06. Chiron Corporation
08. Genentech, Inc.
09. IDEC Pharmaceuticals Corpn
10. Biotest Pharma GmbH
11. Biotransplant, Inc
12. Bristol-Myers Company
13. GLAXO GROUP LIMITED
14. Boehringer Ingelheim GmbH
17. Schering Corporation
18. Ixsys, Inc

Headword:

Humanized Immunoglobulins/PROTEIN DESIGN LABS, INC.

Relevant legal provisions:

EPC Art. 111, 123(2), 123(3), 84

Keyword:

"Main request and auxiliary request I - added matter (yes)"

"Auxiliary request II - added matter (no), clarity (yes)"

"Remittal - (yes)"

Decisions cited:

G 0009/91, G 0010/91, J 0016/90, T 0243/99, T 0577/97,

T 0190/99

Catchword:

According to Article 123(2) EPC, a European patent application or a European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. A claim, the wording of which is essentially identical to a claim as originally filed, can nevertheless contravene the requirements of Article 123(2) EPC, if it contains a feature whose definition has been amended in the description in a non-allowable way. The specific definition of a feature, which according to the description is an overriding requirement of the claimed invention, is applied by a skilled reader to interpret this feature whenever it is mentioned in the patent (see points (11) to (15) of the Reasons for the Decision).



Case Number: T 0500/01 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 12 November 2003

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Decision under appeal:

Interlocutory decision of the Opposition
Division of the European Patent Office posted
14 February 2001 concerning maintenance of
European patent No. 0451216 in amended form.

Composition of the Board:

Chairwoman: U. Kinkeldey
Members: M. Wieser
S. Hoffmann

Summary of Facts and Submissions

- I. The appeal was lodged by the Patent Proprietors (Appellants) against the decision of the opposition division, whereby the European Patent No. 0 451 216 was maintained in amended form pursuant to Article 102(3) EPC after the Patent was opposed by eighteen parties under Articles 100(a), (b) and (c).
- II. Opponents 18 filed a notice of appeal on 11 April 2001 and paid the fee for appeal on the same day. No statement of grounds was filed.

By a communication dated 12 July 2001 sent by registered letter with advice of delivery, the registry of the Board informed the Opponents 18 that no statement of grounds had been filed and that the appeal could be expected to be rejected as inadmissible.

Opponents 18 were invited to file observations within two months. Attention was also drawn to Article 122 EPC. No answer was given to the registry's communication.

- III. The patent originates from the international patent application with the number PCT/US89/05857, which was filed on 28 December 1989 with claims 1 to 22.

Claim 19 thereof read:

"A method of designing a humanized immunoglobulin chain having a framework region from a human acceptor immunoglobulin and complementarity determining regions (CDRs) from a donor immunoglobulin capable of binding

to an antigen, said method comprising the steps of substituting at least one human framework amino acid of the acceptor immunoglobulin with a corresponding amino acid from the donor immunoglobulin at a position in the immunoglobulins where:

(a) the amino acid in the human framework region of the acceptor immunoglobulin is rare for said position and the corresponding amino acid in the donor immunoglobulin is common for said position in human immunoglobulin sequences; or

(b) the amino acid is immediately adjacent to one of the CDRs; or

(c) the amino acid is predicted to have a side chain atom within about 3Å of the CDRs in a three-dimensional immunoglobulin model and to be capable of interacting with the antigen or with the CDRs of the humanized immunoglobulin."

IV. The patent was granted with claims 1 to 21. Claims 1 and 7 read:

"1. The use of at least one amino acid substitution outside of complementarity determining regions (CDRs) as defined by Kabat et al ("Sequences of Proteins of Immunological Interest", Kabat, E., et al., US Department of Health and Human Services, (1983)) together with Chothia et al (Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987)) in the production of a humanized immunoglobulin, wherein said amino acid substitution is from the non-CDR variable region of a non-human donor immunoglobulin, and in which humanized

immunoglobulin the variable region amino acid sequence other than the CDRs comprises at least 70 amino acid residues identical to an acceptor human immunoglobulin variable region amino acid sequence, and the CDRs are from the variable region of said non-human donor immunoglobulin.

7. A method of producing a humanized immunoglobulin chain having a framework region from a human acceptor immunoglobulin and complementarity determining regions (CDRs) from a donor immunoglobulin capable of binding to an antigen, said method comprising substituting at least one non-CDR framework amino acid of the acceptor immunoglobulin with a corresponding amino acid from the donor immunoglobulin at a position in the immunoglobulins where:

(a) the amino acid in the human framework region of the acceptor immunoglobulin is rare for said position and the corresponding amino acid in the donor immunoglobulin is common for said position in human immunoglobulin sequences; or

(b) the amino acid is immediately adjacent to one of the CDRs; or

(c) the amino acid is predicted to have a side chain atom capable of interacting with the antigen or with the CDRs of the humanized immunoglobulin."

V. The description of the granted patent contained the following text on page 3, lines 7 to 50. This passage was not contained in the application as originally filed:

"The hypervariable regions (also called Complementarity Determining Regions, abbreviated to "CDRs") of immunoglobulins were originally defined by Kabat et al., ("Sequences of Proteins of Immunological Interest" Kabat, E., et al., U.S. Department of Health and Human Services, (1983)) based on extent of sequence variability, to consist of residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the light chain variable domain (V_L) and 31-35(H1), 50-65 (H2) and 95-102 (H3) in the heavy chain variable domain (V_H), using Kabat's standard numbering system for antibody amino acids. The CDRs are believed to contact the target antigen of an antibody and to be primarily responsible for binding. More recently Chothia et al (Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987)) have given an alternate definition of the hypervariable regions or CDRs as consisting of residues 26-32(L1), 50-52 (L2), 91-96 (L3) in V_L and residues 26-32 (H1), 53-55 (H2), 96-101 (H3) in V_H . The Chothia definition is based on the residues that constitute the loops in the 3-dimensional structures of antibodies. It is particularly important to note that for each of the six CDRs the Chothia CDR is actually a subset of (i.e. smaller than) the Kabat CDR, with the single exception of H1 (the first heavy chain CDR), where the Chothia CDR contains amino acids 26-30 that are not in the Kabat CDR.

Riechmann et al ("Reshaping human antibodies for therapy", Nature, Vol. 332, pp 323-326, (March 1988)) describe work in which precisely the Kabat CDRs were transferred to a pre-determined human framework (NEW again for the heavy chain and REI for the light chain). However, they found that an antibody containing the

humanized heavy chain lost most of its binding affinity and ability to lyse target cells. They therefore made a new humanized antibody containing the Kabat CDRs from the mouse antibody and two amino acid changes in Chothia CDR H1, but no other mouse amino acids.

Summary of the Invention

The invention provides the use of at least one amino acid substitution outside of complementarity determining regions (CDRs) as defined by Kabat et al ("Sequences of Proteins of Immunological Interest", Kabat, E., et al., US Department of Health and Human Services, (1983)) together with Chothia et al (Chothia and Lesk, J. Mol. Biol., 196:901-917 (1987)) in the production of a humanized immunoglobulin, wherein said at least one amino acid substitution is from the non-CDR variable region of a non-human donor immunoglobulin, and in which humanized immunoglobulin the variable region amino acid sequence other than the CDRs comprises at least 70 amino acid residues identical to an acceptor human immunoglobulin variable region amino acid sequence, and the CDRs are from the variable region of said non-human donor immunoglobulin. In another aspect, the invention provides a method of producing a humanized immunoglobulin chain having a framework region from a human acceptor immunoglobulin and complementarity determining regions (CDRs) from a donor immunoglobulin capable of binding to an antigen, said method comprising the steps of substituting at least one non-CDR framework amino acid of the acceptor immunoglobulin with a corresponding amino acid from the donor immunoglobulin at a position in the immunoglobulins where:

(a) the amino acid in the human framework region of the acceptor immunoglobulin is rare for said position and the corresponding amino acid in the donor immunoglobulins common for said position in human immunoglobulin sequences; or

(b) the amino acid is immediately adjacent to one of the CDRs; or

(c) the amino acid is predicted to have a side chain atom capable of interacting with the antigen or with the CDRs of the humanized immunoglobulin."

VI. The opposition division decided that claim 1 as granted did not meet the requirements of Article 123(2) EPC, as the feature "... complementarity determining regions (CDRs) as defined by Kabat et al ... together with Chotia et al ..." did not have a basis in the application as originally filed.

They disagreed with the Appellants (Patent Proprietors), who considered the following passage on page 9, line 37 to page 10, line 7 of the application as originally filed as basis for this definition of CDRs:

"The variable regions of each light/heavy chain pair form the antibody binding site. The chains all exhibit the same general structure of relatively conserved framework regions joined by three hypervariable regions, also called CDRs (see, "Sequences of Proteins of Immunological Interest," Kabat, E., et al., U.S. Department of Health and Human Services, (1983); and

Cholthia and Lesk, J. Mol. Biol., 196:901-917 (1987), which are incorporated herein by reference)."

(The incorrect spelling of the name "Chotia" is contained in the original document).

- VII. The opposition division concluded in point (A)(7) on page 27 of the reasons for the decision, that besides claim 1 also claims 2 to 6, directly dependent thereon, and claim 11 as granted contravened the requirements of Article 123(2) EPC.

Moreover, they added the following statement to their conclusion:

"This opinion also applies to claim 7 and 12 where no particular definition of the CDR has been given; however, in the absence of such definition, and since it is assumed that the same invention is under consideration, the Proprietor is clearly bound by the definition he has provided in claim 1."

- VIII. While the opposition division considered, that claim 1 of auxiliary requests I and II before them, also did not meet the requirements of Article 123(2) EPC, they decided that the patent according to auxiliary request III met the requirements of the EPC.

- IX. With the grounds of appeal the Appellants filed a new main request and auxiliary requests I and II. Claim 1 of each of these requests read:

Main request

"1. A method of producing a humanized immunoglobulin chain having a framework region from a human acceptor immunoglobulin and complementarity determining regions (CDRs) from a donor immunoglobulin capable of binding to an antigen, said method comprising substituting at least one non-CDR framework amino acid of the acceptor immunoglobulin with a corresponding amino acid from the donor immunoglobulin at a position in the immunoglobulins where:

(a) the amino acid in the human framework region of the acceptor immunoglobulin is rare for said position and the corresponding amino acid in the donor immunoglobulin is common for said position in human immunoglobulin sequences; or

(b) the amino acid is immediately adjacent to one of the CDRs; or

(c) the amino acid is predicted to have a side chain atom capable of interacting with the antigen or with the CDRs of the humanized immunoglobulin; and

wherein said immunoglobulin chain is not a heavy chain having the variable region amino acid sequence 1 to 113 of the upper lines of sequence information in Figure 2a of EP-A-0 328 404, wherein the serine at position 27 is replaced by phenylalanine and/or the serine at position 30 is replaced by threonine."

Auxiliary Request I

"1. A method of producing a humanized immunoglobulin chain having a framework region from a human acceptor immunoglobulin and complementarity determining regions (CDRs) from a donor immunoglobulin capable of binding to an antigen, said method comprising substituting at least one non-CDR framework amino acid of the acceptor immunoglobulin with a corresponding amino acid from the donor immunoglobulin at a position in the immunoglobulins where:

(a) the amino acid in the human framework region of the acceptor immunoglobulin is rare for said position and the corresponding amino acid in the donor immunoglobulin is common for said position in human immunoglobulin sequences; or

(b) the amino acid is immediately adjacent to one of the CDRs; or

(c) the amino acid is predicted to have a side chain atom capable of interacting with the antigen or with the CDRs of the humanized immunoglobulin;

wherein there are at least three of said non-CDR framework amino acids substituted by amino acids from the donor immunoglobulin chosen by criteria (a), (b) or (c)."

Auxiliary Request II

"1. A method of producing a humanized immunoglobulin light chain having a framework region from a human acceptor immunoglobulin and complementarity determining regions (CDRs) from a donor immunoglobulin capable of binding to an antigen, said method comprising substituting at least one non-CDR framework amino acid of the acceptor immunoglobulin chain with a corresponding amino acid from the donor immunoglobulin chain at a position in the immunoglobulins where:

(a) the amino acid in the human framework region of the acceptor immunoglobulin is rare for said position and the corresponding amino acid in the donor immunoglobulin is common for said position in human immunoglobulin sequences; or

(b) the amino acid is immediately adjacent to one of the CDRs; or

(c) the amino acid is predicted to have a side chain atom capable of interacting with the antigen or with the CDRs of the humanized immunoglobulin."

X. Opponents 01, 07, 15 and 16 withdrew their oppositions before 14 February 2001, the date of the decision of the Opposition Division was given and, thus, are no longer parties to the proceedings.

XI. Opponents 02, 06, 09, 10 and 13 have not made written submissions during the appeal proceedings and were not represented at the oral proceedings held on 11 and 12 November 2003.

Opponents 18 have not made any written submissions after filing notice of appeal (see section II above) and were also not represented at the oral proceedings.

- XII. The Appellants (Patent Proprietors) requested that the decision under appeal be set aside and that the European Patent be maintained on the basis of the main request (claims 1 to 14), or auxiliary request I (claims 1 to 14), or auxiliary request II (claims 1 to 15), all filed on 22 June 2001, and that the case be remitted to the first instance for further prosecution.

They further requested the urgent referral to the Enlarged Board of Appeal of questions concerning the admissibility of the introduction of the disclaimer into claim 1 of the main request.

- XIII. Respondents III, IV, V, VIII, XI, XII, XIV and XVII (Opponents 03, 04, 05, 08, 11, 12, 14 and 17) requested that the appeal by the Patent Proprietors be dismissed and, as an auxiliary measure, that the case not be remitted to the first instance.

Respondents IV, V and XI further requested that auxiliary request II not be allowed into the proceedings and, in case of remittal, that the Opposition Division be ordered to expedite the matter and consider only auxiliary request II and claims more limited than that.

XIV. The following documents are mentioned in this decision:

- (1) Wu et al., J.Exp.Med., vol.132, 1970, pages 211 to 250
- (7) Kabat E., J.Immunol., vol.125, 1980, pages 961 to 969
- (15) Kabat E., et al., extracts from "Sequences of Proteins of Immunological Interest", 1983 Edition, US Department of Health and Human Services
- (28) Chotia C., et al., J.Mol.Biol., vol.196, 1987, pages 901 to 917
- (36) Riechmann L., et al., Nature, vol.332, March 1988, pages 323 to 327
- (84) Declaration C. Chotia, 18 October 1996

XV. The arguments of the Appellants, relevant for the present decision, may be summarised as follows:

Claim 1 of the main request corresponded to claim 7 as granted but differed therefrom in that it ended with a final disclaiming clause. Claim 1 of auxiliary request I corresponded to granted claim 7, wherein the subject-matter of granted claim 8 had been incorporated. The subject-matter of claim 1 of auxiliary request II has been restricted to the production of humanized immunoglobulin light chains.

The application as originally filed was in perfect agreement with Kabat's CDR definition in document (27).

Thus, unless CDRs were specifically defined as in granted claim 1, the person skilled in the art would have inevitably understood that this term had to be interpreted according to Kabat.

Claims 1 and 7 as granted defined two different embodiments of the invention. For that reason the CDRs have been specifically defined in granted claim 1, while in granted claim 7 they were never intended to refer to CDRs other than those defined by Kabat in document (15).

It was expressly stated in the minutes that the Appellants on request at the oral proceedings before the Opposition Division maintained that claim 7 as granted referred to CDRs as defined by Kabat.

A skilled person reading the definition of CDRs given on page 3 of the description as granted and studying the publications of Kabat and Chotia cited, i.e. documents (15) and (28) respectively, would have recognized immediately that document (28) did not give a definition of CDRs. He would have realized that the definition of CDRs on page 3, lines 29 to 32 was not correct, and would have concluded that CDRs according to Kabat were meant wherever the term occurred in the granted patent and was not directly followed by a specific definition.

Granted claim 7 was an independent claim that had to be assessed independently from claim 1. It referred to a framework region and to CDRs. The description as granted on page 5, lines 50 to 52 (page 10, line 37 to page 11, line 3 as originally filed) defined the term

"framework region" as those portions of immunoglobulins other than the CDRs as defined by Kabat. This made it immediately clear that CDRs in claim 7 could have only been interpreted as meaning Kabat CDRs. This was also evident from the example where the CDRs are defined according to Kabat.

Since claim 1 of the main and auxiliary request I corresponded almost word for word to claim 19 as originally filed (with the exception of the disclaimer introduced in claim 1 of the main request, and the introduction of claim 8 as granted into claim 1 of auxiliary request I), they did not contravene the requirements of Article 123(2) EPC.

Auxiliary request II represented an attempt to overcome objections raised during the opposition procedure and its filing could not be interpreted as an abuse of the procedure. Considering that this request referred to a general method to humanise immunoglobulin light chains, a subject-matter which has not been substantially examined by the first instance yet, remittal to the opposition division seemed to be justified in the light of the established case law of the Boards of Appeal. The claims of auxiliary request II were considered to meet the requirements of Articles 123(2) and (3) and 84 EPC. In detail, page 5, lines 25 to 27 and page 6, lines 18 to 20 of the description as originally filed were indicated as being the basis for claim 1.

XVI. The arguments relevant for the present decision of the Respondents may be summarised as follows:

The application as originally filed defined CDRs as was generally accepted in the art, namely according to Kabat in document (15). This was no longer the case in the patent as granted since in order to distinguish the claimed subject-matter from the state of the art, especially from document (36), the Patent Proprietors had introduced a new definition for this technical term, which, as correctly decided by the Opposition Division, had no basis in the application as originally filed and thus contravened the requirements of Article 123(2) EPC.

The patent as granted contained only one definition for CDRs. The skilled person did not have any reason to assume that the term when used in the patent had to be interpreted differently. Thus, not only when the term CDRs was directly followed by the newly introduced definition, like in claim 1, but also when it was used without further explanation, as in claim 7, CDRs had to be understood as defined on page 3 of the granted patent.

The definition of the term "framework region", on page 5, lines 50 to 52 was not considered to contain information that would have forced the reader to adopt a definition for CDRs different from the one on page 3.

Moreover claim 14 as granted showed that the Patent Proprietors did not intend to attribute a different meaning to the term CDRs in claims 1 and 7 as granted. This claim referred to polynucleotides comprising sequences coding for CDRs. Upon expression the polynucleotides encoded an immunoglobulin chain of claim 11 or claim 12, which referred to immunoglobulin

chains obtainable by a use of claim 1, and by a method of claim 7, respectively.

Upon considering the balance of interests of the parties in the light of the length of the procedure, the Board should not remit the case back to the first instance for further prosecution of auxiliary request II. This request did not meet the formal requirements of Articles 123(2) and (3) and 84 EPC.

XVII. The following further arguments were submitted by Respondents IV, V and XI:

Auxiliary request II had been introduced by the Patent Proprietors at a very late stage in the proceedings. The claims of this request, referring to subject-matter essentially different from the subject-matter discussed so far, could have been introduced much earlier, for instance during the opposition procedure when the Patent Proprietors were already aware of the problems resulting from the introduction of a new definition of CDRs. Since this request was considered to be used to deliberately stall the procedure, it should be disregarded by the Board according to Article 114(2) EPC.

In order not to delay the matter any further, the Board, in case of remittal, should order that the case be treated by the Opposition Division in an expeditious manner, and that only claims according to the second auxiliary request be considered, or claims more limited than that.

Reasons for the Decision

Admissibility of the appeals

1. No written statement setting out the grounds of appeal has been filed by Opponents 18. The notice of appeal contained nothing that could be regarded as a statement of grounds pursuant to Article 108 EPC. Therefore, their appeal has to be rejected as inadmissible (Rule 65(1) EPC in conjunction with Article 108, sentence three, EPC).

The appeal of the Patent Proprietors (Appellants) complies with Articles 106 to 108 and Rules 1 and 64 EPC and is thus admissible.

Main Request

Article 123(2) EPC

2. Claim 1 refers to a method of producing a humanized immunoglobulin chain having a framework region from a human acceptor immunoglobulin and CDRs from a donor immunoglobulin wherein at least one non-CDR framework amino acid is also from the donor.

The claim ends with a disclaiming clause, which is the only difference to claim 7 as granted. Its wording is almost identical to claim 19 as originally filed (see sections III and IV above).

3. When examining whether or not claim 1 has nevertheless been amended in such a way that it contains subject-matter which extends beyond the content of the

application as filed, contrary to the requirements of Article 123(2) EPC, the meaning of the term CDRs plays a critical role.

4. The parties do not dispute that said term in the application as originally filed was defined according to the definition generally used and accepted by a skilled person working in the field of humanised immunoglobulins at the filing date of the application, 28 December 1989, namely the definition of **Kabat**, given in document (7) (see figure 1 and page 962, left column), which is based on previous work published in document (1).

5. In the passage bridging pages 9 and 10, the application as originally filed contains a reference to two prior art documents (see section VII above). One is a later publication of **Kabat** (document (15)), the other is document (28) published by **Chotia**.

These citations, when read in the context of the description, could make a reader believe that **Kabat** and **Chotia** give different definitions of the term CDRs.

This is an assumption which is not based on technical facts. Document (28) does not give a definition of CDRs, but refers to hypervariable regions or loops, who's "... limits are somewhat different from those of the complementary determining regions defined by Kabat et al. ..." (document (28), page 904, left column). Moreover, the author of document (28) declares in document (84), that there are no "Chotia CDRs". He states that "the CDRs are regions in antibodies of sequence variation that were identified in 1970 by

Kabat who predicted correctly that they would be the regions that bind antigen" (document (84), sentence bridging pages 6 and 7). Thus, the board concludes that only Kabat provides a definition of the term CDRs (see reasons for the decision of the Opposition Division, point (A)(6) on pages 15 to 24).

6. During the examination of the patent application the definition of the term CDRs underwent a major change.

By referring to the citation of documents (15) and (28) on pages 9 to 10 of the application as originally filed, the Appellants, in order to distinguish the claimed subject-matter from the disclosure in document (36), on 26 August 1994 (see page 3, third full paragraph of the letter) introduced a definition of CDRs into the description and into independent claim 1, according to which this term is to be understood "...as defined by **Kabat** et al... **together** with **Chotia** et al..." (emphases added by the Board).

A patent, being a legal document, may be its own dictionary and may define technical terms and determine how a skilled person has to interpret a specific word when used in the description or in the claims. This will not be necessary if the patent does not depart from the meaning a word normally has in the respective technical field and which a skilled person would attribute to it. If however it is intended to use a word which is known in the art to define a specific subject-matter to define a different matter, the description may give this word a special, overriding meaning by explicit definition.

7. As mentioned in section VII above, the Opposition Division decided that claims 1 to 6 and 11 as granted contravened the requirements of Article 123(2) EPC, and added that in their opinion the same applied to claim 7, though unamended, as the term CDRs contained therein had to be understood as defined in the amended description.

The Appellants consider this statement to be unjustified and argue that claim 7 as granted, thus in essence claim 1 of the main request, refers now and always referred to CDRs according to Kabat, and is therefore in perfect agreement with the application as originally filed and thus not open for consideration under Article 123(2) EPC.

8. Claim 1 refers to complementary determining regions, abbreviated to CDRs. The legal issue here is to establish which meaning this term has in the light of the amended description.

The subject of the appeal proceedings is the patent as granted along with the amended claims, according to Appellants' requests filed with the grounds of appeal. Thus, the description that has to be considered is the description of the patent as granted, and in the context to be considered here page 3, lines 7 to 50, which were not contained in the application as originally filed (see section V above).

9. Complementarity determining regions, abbreviated to CDRs, are mentioned for the first time on page 3, line 8. It is stated that CDRs were first defined by Kabat. Document (15) is cited and a short summary of

its content is given. The description goes on to say that "More recently Chotia et al... have given an alternative definition of the hypervariable regions or CDRs..". Reference is made to document (28) and to the amino acid positions which are defined therein as hypervariable regions or loops. By repeatedly referring to the term "Chotia CDR", which, as has been shown in point (5) above, results from a wrong interpretation of document (28), it is shown that the first CDR on the heavy chain, which according to Kabat consists of residues 31 to 35, differs from the first hypervariable region according to Chotia consisting of amino acids 26 to 32.

This passage is followed by an analysis of document (36). The content thereof is described as referring to "...a new humanized antibody containing the Kabat CDRs from the mouse antibody and two amino acid changes in Chotia CDR H1, **but no other mouse amino acids**" (emphasis added by the board).

10. Immediately thereafter, under the heading "Summary of the invention" starting with the words: "**The invention provides...**", the wording of claim 1 is cited once again, referring to CDRs as defined by **Kabat together with Chotia**. This is followed by a further citing of claim 7, starting with the words: "**In another aspect, the invention provides...**", wherein the term CDRs is used without any further definition.

The board concludes therefrom that claim 7 as granted (in essence claim 1 of the present main request) referred to **another aspect of the same invention** according to claim 1 as granted, which included that

the term CDRs has the same meaning in both claims, a position that was disputed by the Appellants.

11. The question arises whether the term CDRs is understood by the skilled reader according to the newly introduced definition (**Kabat together with Chotia**) whenever it is used throughout the patent, or, whether the description contains a disclosure that allows the same term to be interpreted differently in a claim which does not specifically contain the new definition.
12. The Appellants relied on page 5, lines 50 to 54, of the granted patent, which according to them provides a basis to define the term CDRs according to Kabat only. This passage reads:

"As used herein, the term "framework region" refers to those portions of immunoglobulin light and heavy chain variable regions that are relatively conserved (i.e., other than the CDRs) among different immunoglobulins in a single species, as defined by Kabat, et al., op. cit. As used herein a "human-like framework region" is a framework region that in each existing chain comprises at least about 70 or more amino acid residues, typically 75 or 85 or more residues, identical to those in a human immunoglobulin."

The first sentence of this passage states that, according to Kabat, framework regions, other than CDRs, are relatively conserved. Thus, the information given does not concern the actual extent of framework regions, by disclosing those amino acid residues that are part thereof, but concerns their degree of

conservation. The second sentence defines the term "human like framework regions".

Therefore, this passage does not provide a definition of the term CDRs.

13. The Board concludes therefrom that the definition of the term CDRs given on page 3, lines 29 to 32 of the description, and contained in claim 1 as granted, is an overriding requirement of the invention and is thus convinced that the skilled reader applies this definition to interpret the term CDRs whenever it is used in the amended patent without any further accompanying definition.

14. In figures 1 and 2 of the application as filed (see also page 7, lines 1 to 19) the CDRs of the anti-Tac and Eu heavy and light chains, which are used in the experimental part of the patent specification for the production of a humanized anti-Tac antibody, are underlined and match with those as defined according to Kabat. Thus, CDR1 of the heavy chain consists of amino acids 31 to 35. This is a subset of CDR1 of the heavy chain as defined on page 3, lines 39 to 42 and in claim 1 of the patent as granted, namely according to Kabat **together** with Chotia, which consists of amino acids 26 to 35.

However, according to the established case law of the boards of appeal, the disclosure in an example, which represents a specific embodiment of the claimed invention, is no basis for formulating generic claims not restricted to said specific embodiment.

15. Accordingly, claim 1 of the main request is considered to refer to CDRs as defined on page 3, lines 29 to 32 of the description of the granted patent (see section V *supra*).

16. In the passage bridging pages 9 and 10 of the application as originally filed, two prior art documents are cited (see section VI above; "... *Kabat, E., et al., .. and Cholthia and Lesk, ..*"; emphasis added by the board). It has been shown in point 5 above that one of them only provides a definition of the term CDRs while the other refers to hypervariable regions or loops. On the basis of this conclusion alone, it follows that there is no basis in the application as filed for an amendment by which the teaching in two documents referring to different entities is combined.

Even if CDR1 of the heavy chain according to Kabat consisted of amino acid residues 31 to 35 (page 3, line 11 of the granted patent), while "CDR1" of the heavy chain according to Chotia consisted of amino acid residues 26 to 32 (page 3, line 15 of the granted patent), one would arrive at the same conclusion, because the provision of a reference to two different definitions of the same entity does not constitute a supporting disclosure for their combination that would result in CDR1 of the heavy chain consisting of amino acid residues 31 to 35 **plus** 26 to 32, thus amino acid residues 26 to 35. The listing of several alternatives by using the conjunction "and", does not imply that the listing provides the additive information contained in all items of the list.

Thus, the definition of the term CDRs on page 3, lines 29 to 32 of the granted patent has no basis in the application as originally filed.

Therefore, claim 1 does not meet the requirements of Article 123(2) EPC. The main request has to be rejected.

17. It results from the above that the questions which the Appellants sought to be referred to the Enlarged Board of Appeal in application of Article 112(1)(a) EPC and which relate to the allowability of a disclaimer contained in claim 1 of the main request are no longer decisive for the present decision.

Under Article 112(1)(a) EPC, the Board of Appeal making the referral must consider a decision by the Enlarged Board to be "required". It is not sufficient for the point referred to be of general interest. An answer to it must also be necessary to a decision on the appeal in question (cf J 16/90 OJ EPO 1992, 260).

For this reason this request is rejected.

Auxiliary Request I

18. Claim 1 of auxiliary request I is distinguished from the main request by not having the final disclaimer and by the feature that at least three non-CDR framework amino acids of the acceptor immunoglobulin are substituted. However, it contains the term CDR as claim 1 of the main request.

Therefore, the above reasons for claim 1 of the main request apply in the same way to claim 1 of auxiliary request I which is also not allowable under Article 123(2) EPC.

Auxiliary Request II

Procedural matter

19. Auxiliary request II was filed by the Appellants on 22 June 2001 with their written statement setting out the grounds of appeal.

A board has discretion to accept amended claims at any stage of the appeal proceedings (cf decision T 577/97, 5 April 2000).

Contrary to claim 1 of all other requests, which refers to a method of producing a humanized immunoglobulin chain encompassing both heavy and light chains, claim 1 of auxiliary request II is restricted to the production of a humanized immunoglobulin light chain only.

This restriction has to be considered as a *bona fide* attempt to overcome objections under Article 123(2) EPC resulting from the introduction of a new definition of the term CDRs, which objections apply to the CDRs of the heavy chain only, and which resulted in the rejection of Appellants' main and auxiliary requests I and II in opposition proceedings.

The board does not see this as an abuse of procedural rights to delay the procedure as maintained by the Respondents.

Thus, the board at its discretion accepts auxiliary request II into the proceedings.

Article 123(2) and (3) EPC

20. Several objections have been raised by the Respondents under this Article.

21. All Respondents argued that the production of light chains alone, without corresponding heavy chains, was not disclosed in the application as filed, which referred to the production of complete immunoglobulins only.

However, the application as originally filed states on page 5, lines 8 to 9 that the invention provides methods for designing human-like immunoglobulins, and says in lines 26 to 27 that "the donor immunoglobulin may be either a heavy chain or a light chain (or both), and the human collection will contain the same kind of chain", and thus *expressis verbis* discloses light chains as design targets.

Therefore, the Board does not agree with the Respondents.

22. Respondents III, VIII and XIV considered that claim 1 contravenes the requirements of Article 123(2) EPC for the same reasons as the main request and auxiliary request I, as it refers in point (c) to "..the CDRs of the human immunoglobulin;..", which has to be interpreted as containing heavy chain CDRs.

Claim 1 refers to "... a method of producing a humanized immunoglobulin light chain **having** ... complementary determining regions (CDRs).." (emphases added by the board). The claim goes on to state that at least one **non-CDR framework** amino acid is derived from the donor chain also, and defines three criteria by which said **non-CDR framework** amino acid is to be selected. The wording in the introductory part of the claim defines that the term CDRs in claim 1 means light chain CDRs. Within one and the same claim a term cannot have different meanings. In this respect it should be borne in mind that according to the case law of the boards of appeal a claim must be construed by a mind willing to understand not a mind desirous of misunderstanding (cf T 190/99, 6 March 2001).

23. Respondent III and XIV took the view that auxiliary request II in the absence of a corrected version of the description still contains, on page 3 lines 29 to 32, the definition of CDRs deemed to be an unallowable extension, and therefore contravenes the requirements of Article 123(2) EPC.

The board is of the opinion that the newly introduced definition for CDRs, namely "Kabat together with Chotia", in place of the definition used in the application as originally filed, namely "Kabat only", created a problem under Article 123(2) EPC with regard to the CDRs of the heavy chain only. For all three CDRs of the light chain the so-called "Chotia CDRs" are subpopulations of the Kabat CDRs, so that "Kabat together with Chotia" for the light chain CDRs is identical in meaning to "Kabat only", and thus even if

one accepts the Respondent's position, there is a basis for this claim in the application as filed.

24. Respondents IV, V, VIII, X and XIV considered the deletion of a feature from point (c) of claim 1 to contravene Article 123(2) EPC. Claim 19(c) as originally filed read:

"(c) the amino acid is predicted to have a side chain atom within about 3Å of the CDRs in a three-dimensional immunoglobulin model and to be capable of interacting with the antigen or with the CDRs of the humanized immunoglobulin." (emphasis added by the board)

The underlined passage is no longer contained in claim 1(c) of auxiliary request II.

Respondents X moreover argued that the deletion of the feature whereby the distance between the side chain atom and the CDRs is measured in a three dimensional immunoglobulin model constitutes a violation of the requirements of Article 123(3) EPC.

However, the description as originally filed on page 14, lines 21 to 25 shows that the technical feature omitted from original claim 19, point (c) is of non-obligatory nature. The relevant passage reads:

"Amino acids according to this criterion will **generally** have a side chain atom within about 3 angstrom units of some site in the CDRs and **must contain atoms that could interact with the CDR atoms ...**" (emphases added by the board).

The deletion of a this feature is not regarded as a violation of the requirements of Article 123(2) EPC.

No violation of Article 123(3) EPC can be seen either, as point 1(c) of auxiliary request II was identically contained in claim 7 as granted.

25. Respondent XII argued that claim 6, referring to an immunoglobulin heavy chain whose sequence is **homologous** to the one in figure 3, has no basis in the original application.

Page 16, lines 12 to 26 of the original description refers to the humanised anti-Tac antibody whose heavy and light chain variable region nucleotide and amino acid sequence is depicted in figures 3 and 4. It is stated that due to codon degeneracy and non-critical amino acid substitutions, the invention is not restricted to these exact sequences, which allows the "homology" wording without a violation of Article 123(2) EPC.

26. Respondent VIII's argument that the provision of only a light chain did not solve the technical problem underlying the invention - it being common knowledge that the heavy chain played a more important role in antigen binding - is not considered as an objection under Article 123(2) EPC.

Finally, Respondent XVII's comment, according to which the wording of claim 1 includes grafting of a heavy chain CDR into a light chain framework and thus contravenes Article 123(2) EPC, does not seem to be technically realistic and would require reading the

claim with a mind desirous of misunderstanding (cf T 190/99 *supra*).

Article 84 EPC

27. Claims 1 to 4 correspond to claims 7 to 10 as granted, but are restricted to the production of immunoglobulin light chains. Claims 5 to 15 correspond to claims 11 to 21 as granted, but are restricted to the specific immunoglobulin light and heavy chain variable region protein sequences of figures 3 and 4.
28. Respondents X argued that claim 1 lacks clarity as it refers in the introductory part to the production of a humanized immunoglobulin light chain, while in point (c) it refers to a humanized immunoglobulin.

The board notes that the description as originally filed on page 10, lines 10 to 24 states that an immunoglobulin according to the invention may also be present as a single chain. Thus, when claim 1 is read in the light of the description, it is clear.

29. As a consequence the board is convinced that claims 1 to 15 of the second auxiliary request meet the requirements of Articles 123(2), 123(3) and 84 EPC.

Remittal to the first instance - Article 111 EPC

30. Claim 1 refers to a generally applicable method for producing an immunoglobulin light chain. Examination of the substantive issues novelty, inventive step and sufficiency of disclosure was carried out by the opposition division with regard to claims restricted to

the production of only one specific immunoglobulin, which is explicitly described in the experimental part of the patent.

In the present case substantial amendments to the claims were proposed in the appeal. These proposals require further examination.

31. Remittal to the department of first instance is at the discretion of the board (cf decision T 249/93, 27 May 1998).

In the present case the board considered it procedurally adequate to examine the claims of this request with regard to the formal requirements (Articles 123(2) and (3) and Article 84 EPC). However, in the light of the substantive amendments made to the claims, the board considers it to be justified and appropriate to allow this set of claims to be examined by two instances for further issues.

32. Thus, the board at its discretion under Article 111(1) EPC remits the case to the Opposition Division for further prosecution.

Requests by Respondents IV, V and XI in case of remittal

33. As regards the requested restriction for new sets of claims in case of remittal, the board states that under Article 111(2) EPC the EPO department of first instance is bound by the *ratio decidendi* of the board of appeal if the case is remitted to the department whose decision was appealed in so far as the facts are the same.

However, first-instance proceedings are separate from appeal proceedings, the function of the latter being to give a judicial decision on the correctness of a separate earlier decision taken by a first instance department (G 9/91, OJ EPO 1993, 408 and G 10/91 OJ EPO 1993, 420). There is no provision in the EPC under which a board upon remittal can limit in advance the patentee's right to file a new set of claims. The Board has no competence to refuse a request which is up to now not on file. Therefore, if the Patentee files new requests, the first instance has to decide on them on its own, in application of the provisions of the EPC and the jurisprudence with respect to late-filed requests.

The request to order the first instance to expedite the proceedings is a request for accelerated proceedings. Generally, the manner of proceeding lies within the competence and is at the discretion of the instance which has to decide on the case before it.

As the request in question was not the subject of the decision under appeal, the board has no competence to decide on it, since the requested remittal for further prosecution under Article 111(1) EPC, second sentence, second alternative, presupposes that the board does not exercise its power within the competence of the first instance under the second sentence, first alternative of this provision.

Therefore, the requests of Respondents IV, V and XI are rejected.

Order

For these reasons it is decided that:

1. The appeal of Opponents 18 is rejected as inadmissible.
2. The decision under appeal is set aside.
3. The matter is remitted to the first instance for further prosecution on the basis of claims 1 to 15 of auxiliary request II filed on 22 June 2001.

The Registrar:

The Chairwoman:

P. Cremona

U. Kinkeldey