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# D E C I S I O N
## of 30 September 2004

**Case Number:** T 0626/00 - 3.3.4

**Application Number:** 91907669.5

**Publication Number:** 0549581

**IPC:** C12P 21/08

**Language of the proceedings:** EN

**Title of invention:**
Framework mutated antibodies and their preparation

**Patentee:**
THE WELLCOME FOUNDATION LIMITED

**Opponents:**
Protein Design Labs, Inc.
Athena Neurosciences, Inc.
Genentech, Inc.

**Headword:**
Framework-mutated antibodies/WELLCOME

**Relevant legal provisions:**
EPC Art. 54, 56, 83, 84, 123(2)(3)

**Keyword:**
"Main Request, Auxiliary Request 1 - added matter (yes)"
"Auxiliary Request 2 - sufficiency of disclosure (yes)"
"Novelty (yes)"
"Inventive step (yes)"

**Decisions cited:**
T 0435/91

**Catchword:**
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 0626/00 - 3.3.4

# D E C I S I O N
**of the Technical Board of Appeal 3.3.4**
**of 30 September 2004**

**Appellant:** (Proprietor of the patent)
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**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office posted 11 February 2000 revoking European patent No. 0549581 pursuant to Article 102(1) EPC.**

**Composition of the Board:**

**Chairwoman:** U. M. Kinkeldey
**Members:** G. L. Alt
G. E. Weiss

## Summary of Facts and Submissions

I. European patent No. 0 549 581 with the title "Framework mutated antibodies and their preparation" is based on European patent application No. 91 907 669.5 and was granted with a set of claims for the Designated Contracting States AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL and SE and with a corresponding set of claims for the Designated Contracting States ES and GR.

II. The patent was opposed by three parties. Article 100(a) EPC - lack of novelty and inventive step - , Articles 100(b) EPC and 100(c) EPC were invoked as grounds of opposition. The opposition division revoked the patent. It found that the subject-matter of claim 1 of the main request contravened the requirements of Article 123(2) EPC, that the subject-matter of auxiliary requests 1 and 2 did not meet the requirements of Article 83 EPC and that the subject-matter of claim 1 of auxiliary requests 3 and 4 did not meet the requirements of Article 56 EPC.

III. The patentee lodged an appeal against the decision of the opposition division. Together with the statement of grounds of appeal he filed a new main request, corresponding to auxiliary request 1 before the opposition division and an auxiliary request corresponding to auxiliary request 3 before the opposition division.

IV. Respondents I, II and III (opponents 1, 2 and 3) filed a response to the appellant's submission.

V. The parties were summoned to oral proceedings. In a communication annexed to the summons the board indicated its preliminary opinion on some of the issues.

VI. The appellant and respondent III replied to the board's communication. The appellant filed a new main request and two new auxiliary requests.

VII. Respondents II and III commented on the claims of the new requests. The appellant answered by submitting a new main request which contained a modified claim 1 and in which claim 7 was deleted and a new auxiliary request 2 was made. The former auxiliary request 2 was renumbered as auxiliary request 3.

VIII. The new main request comprised two sets of claims, one for the Designated Contracting States AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE and one for the Designated Contracting States ES and GR.

Independent claims 1, 9 and 17 of the new main request in the version for the Designated Contracting States AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE read:

"1. A process for the preparation of an antibody chain in which complementarity determining regions (CDRs) of the variable domain of the antibody chain are derived from a first mammalian species and the framework of the variable domain and, if present, the or each constant domain of the antibody chain are derived from a second different mammalian species, which process comprises:

(i) mutating the framework-encoding regions of DNA encoding a variable domain of an antibody chain of the

said first species such that the mutated framework-encoding regions encode the said framework derived from the said second species; and

(ii) expressing the said antibody chain utilising the mutated DNA from step (i);

the mutation of step (i) being such that an antibody incorporating the antibody chain expressed in step (ii) retains the antigen binding capability of the antibody of the first mammalian species, and wherein the variable domain framework of the second species is that of the variable domain of an antibody of the second species selected as having a variable domain sequence with about the most overall homology to the sequence of the variable domain of the antibody of the first species."

"9. An antibody which is capable of binding to human CD4 antigen, in which the CDRs of the light chain of the antibody have the amino acid sequences:
CDR1: LASEDIYSDLA
CDR2: NTDTLQN
CDR3: QQYNNYPWT

in which the CDRs of the heavy chain of the antibody have the amino acid sequences:
CDR1: NYGMA
CDR2: TISHDGSDTYFRDSVKG
CDR3: QGTIAGIRH, and

in which the framework of the variable domain and, if present, the or each constant domain of each chain are derived from a mammalian non-rat species."

"17. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, an antibody as claimed in any one of claims 9 to 16."

The set of claims contained 7 further claims dependent on claim 1 and 7 further claims dependent on claim 9.

In the version for the Designated Contracting States ES and GR the process-claims were identical to those of the first set of claims. The product-claims were filed as corresponding process-claims.

IX. Claim 1 of auxiliary request 1 in the versions for the Designated Contracting States AT, BE,CH, LI, DE, DK, FR, GB, IT, LU, NL, SE and ES and GR read:

"1. A process for the preparation of an antibody chain having a variable domain comprising three complementarity determining regions (CDRs) designated CDR1, CDR2 and CDR3 and a framework in which the CDRs are derived from a rodent species and the framework and, if present, the or each constant domain of the antibody chain are human, which process comprises;
(i) mutating the framework-encoding regions of DNA encoding a variable domain of an antibody chain of the rodent species such that the mutated framework-encoding regions encode the said framework derived from the rodent species; and
(ii) expressing the said antibody chain utilising the mutated DNA from step (i);
the mutation of step (i) being such that an antibody incorporating the antibody chain expressed in step (ii)

retains the antigen binding capability of the antibody of the rodent species, and wherein the human variable domain framework is that of the variable domain of a human antibody selected as having a variable domain sequence with the most overall homology to the sequence of the variable domain of the antibody of the rodent species, overall humology being determined on the basis that priority is given to human antibodies in which CDR1 and CDR2 are the same length as in the rodent antibody and only if no human antibody exists in which CDR1 and CDR2 are the same length as in the rodent antibody can one or more differences in length of CDR1 and CDR2 be allowed."

X. Oral proceedings took place on 30. September 2004.

XI. During oral proceedings the board remarked that the definition of "overall homology" in claim 1 of auxiliary request 1 differed from that in the application documents as originally filed and that therefore the amendment appeared to contravene the requirement of Article 123(2) EPC.

The appellant filed a new auxiliary request 2. The claims of this request were further amended during the oral proceedings. This latter request consisting of a set of claims for the Designated Contracting States AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE and a set of claims for the Designated Contracting States ES and GR was called "Revised new auxiliary request 2".

Claim 1 of the "revised new auxiliary request 2" for the Designated Contracting States AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE and ES and GR read:

"1. A process for the preparation of an antibody chain having a variable domain comprising three complementarity determining regions (CDRs) designated CDR1, CDR2 and CDR3 and a framework in which the CDRs are derived from a rodent species and the framework and, if present, the or each constant domain antibody chain are human, which process comprises:

(i) determining the amino acid sequence of the variable domain of the rodent antibody chain;

(ii) selecting a human antibody variable domain by:

(1) using a computer program to search all available protein and DNA databases for those human antibody variable domain sequences that are most homologous to the rodent antibody variable domain;

(2) listing the human antibody variable domain sequences that have the most overall homology to the rodent antibody variable domain making no distinction between homology within the framework regions and CDRs but considering overall homology;

(3) eliminating from consideration those human sequences that have CDRs that are [of] a different length than those of the rodent except for CDR3 and except where there are no or very few human sequences that have the same CDR lengths as that of the rodent antibody in which case human sequences with one or more differences in CDR length can be allowed;

(4) from the remaining variable domains, selecting the one that is most homologous to that of the rodent antibody;

(iii) preparing from cDNA encoding the rodent variable domain a cDNA encoding a reshaped antibody containing CDRs derived from the rodent antibody and a variable domain framework from the human antibody by comparing the rodent variable domain amino acid sequence to that of the chosen human antibody variable domain sequence and adding or deleting residues in the rodent cDNA so that the rodent framework amino acid sequence is identical to the human framework sequence;

(iv) if appropriate, linking the cDNA encoding the reshaped antibody variable domain to appropriate DNA encoding a constant region, cloning the cDNA into an expression vector, transfecting the expression vector into mammalian or other suitable cells and culturing the transformed cell line to express the antibody chain;

the addition or deletion of step (iii) being such that an antibody incorporating the antibody chain expressed in step (iv) retains the antigen binding capability of the antibody of the rodent species."

The product-claims (claims 7 to 14) and the claim to the pharmaceutical composition (claim 15) of each of the versions of this request were identical to the corresponding claims of the versions of the main request.

XII. The documents referred to in the present decision are the following:

D1: EP-A-0 239 400

D2: EP-A-0 328 404

D3: WO-A-90/07861

D6: Nature, 1988, vol. 332, pages 323-327, Riechmann et al., "Reshaping human antibodies for therapy"

D8: PNAS, vol. 86, 1989, pages 10029-10033, Queen et al., "A humanized antibody that binds to the interleukin 2 receptor"

D16: Immunology, vol. 88, 1991, pages 4181-4185, Gorman et al.; "Reshaping a therapeutic CD4 antibody"

D23: Extracts from US-A-5 530 101

D28: WO-A-88/09344

D31: Reshaping antibodies for therapy, Routledge, Gorman and Clark in "Protein engineering of antibody molecules for prophylactic and therapeutic applications in Man", Ed. Mike Clark, Academic Titles, Nottingham 1993

Declaration of Herman Waldmann dated 1 March 2001

Declaration Michael R. Clark dated 19 June 2002

XIII. The Appellant's arguments in writing and during the oral proceedings, insofar as they are relevant to the present decision, may be summarized as follows:

*Main Request*
*Amendments - Article 123(2) EPC*

Basis for the added passage in claim 1 was to be found in claim 7 of the application as filed specifying that about the most homologous framework of an antibody chain of a different species is selected in combination with page 7 explaining that the framework is determined by listing human antibody variable domain sequences that have the most overall homology to the rodent antibody variable domain sequences.

*Auxiliary request 1*
*Amendments - Article 123(2) EPC*

The amendment was based on page 7, point 3. Although the wording in the claim was not exactly the same as in the application, the meaning was not changed.

*Revised new auxiliary request 2*

*Claims 1 to 6 - Process for the preparation of an antibody chain*
*Amendments and scope of protection - Article 123(2)(3) EPC*

The amendments to claims 1, 2 and 3 were based on pages 6 to 8 of the application documents as originally filed. Moreover, they did not extend the scope of protection because the claim was now limited to a specific embodiment.

*Sufficiency of disclosure - Article 83 EPC*

The process could reliably be carried out without undue burden. Not only did the patent describe a successful example, but also three further antibodies were prepared in accordance with the claimed process. This was mentioned in the declaration by Herman Waldman.

There was the possibility that a search in the available computer databases at the priority date of the patent in suit would find germline sequences. If a germline sequence was found in the first step, it could be treated by the process like any antibody sequence. No further information was necessary.

*Novelty - Article 54 EPC*

The method disclosed in document D3 differed from that of the patent at least in the way in which the humanised antibody was prepared.

*Inventive step - Article 56 EPC*

Document D3 was the closest prior art document. The problem to be solved in view of this document was the provision of an alternative, simple method with which antibodies could be produced retaining binding specificity.

At the priority date of the patent the few existing humanised antibodies had been made by CDR-grafting or by total synthesis. These approaches did not however render obvious the approach as claimed. Evidence for

this view came from document D6 where a mouse antibody was available, but where nevertheless the authors choose to change CDRs in a human antibody.

Document D28 put the emphasis on putting restriction sites between the framework and CDR regions in order to render the exchange process easier. If a person skilled in the art had combined the teachings of D3 and D28, this would possibly have lead to an improvement of the existing methods, but it would not have rendered obvious the claimed subject-matter.

XIV. The Respondents' arguments in writing and during the oral proceedings, insofar as they are relevant to the present decision, may be summarized as follows:

*Main request*
*Amendments - Article 123(2) EPC*

The passage added to the end of claim 1 recited step 2 of a 4-step process for the selection of a suitable human antibody variable domain sequence. It was evident that the steps of the 4-step process were linked. If they were separated, the process would give different results. Consequently, carrying out the process of the patent with only step 2 added new matter.

*Auxiliary Request 1*
*Amendments - Article 123(2) EPC*

No objections were raised by the respondents.

*Revised new auxiliary request 2*

*Claims 1 to 6 - Process for the preparation of an antibody chain*
*Sufficiency of disclosure - Article 83 EPC*

Antibodies fulfilling the functional definition at the end of claim 1 could only be prepared with undue burden.

Document D23 disclosed an antibody having a sequence selected according to the criteria of the patent. Nevertheless it had lost its binding capability. This showed that the process of the patent did not always work. Therefore, one example in the patent was not enough to show that antigen binding capability was generally retained when framework sequences were selected according to the process of the patent.

Statements Prof. Clark had made in his declaration suggested that un-rearranged germline gene sequences coding for antibody molecules were among the sequences to be screened for the determination of a suitable human framework region. However, according to document D31 the homology search with germline genes required a modified method which was not described in the patent. Therefore, to the extent that germline genes were an embodiment of the claim 1, it lacked sufficient disclosure.

*Novelty - Article 54 EPC*

One of the two possible alternatives to determine a suitable human acceptor antibody disclosed in document

D3 was to compare complete variable domains. The practical part of the process of the patent, i.e. the physical production of the designed antibody was implicitly disclosed in document D3.

*Inventive step - Article 56 EPC*

There was no example in the patent demonstrating the reshaping of a rodent antibody according to the claimed process. Therefore the patent did not show that the problem was solved and therefore lacked an inventive step.

Moreover, once the skilled person had the idea of grafting CDR regions on human antibodies in mind, it was obvious that the same antibody could as well be prepared by grafting framework regions on a rodent antibody.

Finally, the concept of framework-grafting had been explicitly disclosed by document D28.

*Revised new auxiliary request 2*

*Claims 7 to 15 - Antibody and pharmaceutical composition*

No objections were raised with regard to these claims.

XV. *Requests*

The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis either of his main request submitted with the letter dated 30 July 2004 and

amended with letter dated 22 September 2004; his first auxiliary request submitted with the letter dated 30 July 2004; his revised second auxiliary request filed at the oral proceedings of 30 September 2004.

Respondents I, II and III (opponents 01, 02 and 03) requested that the appeal be dismissed.

## Reasons for the Decision

1. *Field of the invention*

An antibody molecule is composed of two protein chains, the heavy and the light chain, forming a Y-shaped molecule. The antigen binding site is situated towards the end of each chain. It is composed of three complementarity determining regions (CDR) determining the antigen specificity of the molecule and of four framework regions (FR) which hold the CDRs in the correct conformation.

For therapeutic purposes in humans, for example cancer treatment, human monoclonal antibodies are preferred, since non-human molecules are recognised as foreign by the human body provoking an immune response leading to elimination of the antibody.

Human monoclonal antibodies are however difficult to obtain since the standard hybridoma procedure for producing monoclonal antibodies yields rodent monoclonal antibodies. Consequently, there is a large choice of rodent antibodies binding to desired antigens

whereas the number of available human antibodies is limited.

To overcome this problem various approaches have been developed aiming at reducing the immunogenicity of a rodent antibody but nonetheless taking advantage of their easy availability. The strategy underlying the patent in suit is the so-called "reshaping" of antibodies. It consists in the combination of the CDRs from a rodent antibody with the framework regions from a human antibody. Ideally, such a mixed antibody retains the binding capability of the rodent antibody, but is less immunogenic than it.

The process claimed in the patent in suit comprises the selection of a human-rodent antibody pair such as to minimize the necessary sequence modifications, the theoretical design of a reshaped antibody based on the selected pair whereby the framework region of the rodent antibody is adapted to the one of the selected human antibody and the production of the reshaped antibody.

*Main request (versions for the Designated Contracting States AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE and ES and GR)*

*Amendments - Article 123(2) EPC*

2. The application documents as originally filed disclose on pages 6 to 7 a 4-step process for determining a human framework region suitable for combination with selected rodent CDRs:

"1.Using a computer program, search all available protein(and DNA) databases for those human antibody variable domain sequences that are most homologous to the rodent antibody variable domains. (...)

2. List the human antibody variable domain sequences that have the most overall homology to the rodent antibody variable domain (from above). Do not make a distinction between homology within the framework regions and CDRs. Consider the overall homology.

3. Eliminate from consideration those human sequences that have CDRs that are of a different length than those of the rodent CDRs. This rule does not apply to CDR3, because the length of this CDR is normally quite variable. Also, there are sometimes no or very few human sequences that have the same CDR lengths as that of the rodent antibody. If this is the case, this rule can be loosened, and human sequences with one or more differences in CDR length can be allowed.

4. From the remaining human variable domains, the one is selected that is most homologous to that of the rodent."

3. Claim 1 is directed to a process for the preparation of an antibody chain in which the CDRS of the variable domain of the antibody chain are derived from a first mammalian species and the framework of the variable domain are derived from a second different mammalian species. The passage added to the end of claim 1 of the main request defines the framework to be used by reference to the process by which it is obtained, namely that it is "selected as having a variable domain

sequence with about the most overall homology to the sequence of the variable domain of the antibody of the first species." Thus, according to the claim 1 the suitable framework is one which is selected by carrying out step 2 of the process recited in point 2 above.

4. Article 123(2) stipulates that "a European patent may not amended in such a way that it contains subject-matter which extends beyond the content of the application as filed." In evaluating whether this requirement is fulfilled, it is firstly noted that there is no explicit disclosure in the application documents as originally filed suggesting the possibility of separating step 2 from the remaining steps of the 4-step process. The appellant's reference to claim 7 as originally filed cannot change this view since this claim relates to a process which is different from the one now claimed in that the selection of the framework is made on the basis of the framework sequence alone: "...in which about the most homologous framework of an antibody chain of a different species is selected in step (b) as the framework to which the framework of the said variable domain is to be altered". Secondly, there is also no implicit disclosure. In the board's opinion, implicitly, the application is pointing away at least from separating the two most important steps of the method disclosed on pages 6 to 7, namely steps 2 and 3 (see point 2 above), because in situations referred to in step 3 of the 4-step process, the selected frameworks are different depending on whether they are obtained solely by performing step 2 or additionally step 3. Thus, recognizing the evident possibility of obtaining different results, the skilled person would have

considered that at least steps 2 and 3 of the 4-step process are linked and cannot be separated. Consequently, by limiting the structure of suitable framework regions by a functional definition corresponding to step 2 only, antibodies are produced that would not have been produced if the complete process had been carried out, thus giving rise to subject-matter which was not disclosed in the application documents as originally filed. Hence, this amendment contravenes the requirements of Article 123(2) EPC.

5. Therefore, the main request is rejected.

*Auxiliary Request 1 (versions for the Designated Contracting States AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE and ES and GR)*

*Amendments - Article 123(2) EPC*

6. Claim 1 defines suitable framework sequences as in claim 1 of the main request: "wherein the variable domain framework of the second species is that of the variable domain of an antibody of the second species selected as having a variable domain sequence with the most overall homology to the sequence of the variable domain of the antibody of the first species". Additionally, a definition of the term "overall homology" is given: "overall homology being determined on the basis that priority is given to human antibodies in which CDR1 and CDR2 are of the same length as in the rodent antibody and only if no human antibody exists in which CDR1 and CDR2 are the same length as in the rodent antibody can one or more differences in length

of CDR1 and CDR2 be allowed". This definition corresponds to step 3 of the process recited above in point 2. Thus, at first glance the claim defines the suitable framework region by reference to steps 2 and 3 of the 4-step process. However, step 3 does not describe variable domain sequences with the most "overall homology". Rather, they are described in step 1 and 2 of the process. These sequences are found by a search in a computer database and then listed according to their homology. The criteria now recited in claim 1 as a definition for "overall homology" are applied only to the so-found sequences. Thus, the way in which the steps 2 and 3 are combined in the claim results in a definition for suitable framework regions which is not disclosed in the application documents as originally filed. Consequently, when following the instructions given by this definition frameworks are selected and antibodies produced that were not disclosed in the application documents as originally filed. Consequently, this amendment contravenes the requirements of Article 123(2) EPC.

7. Therefore, auxiliary request 1 is rejected.

*"Revised new auxiliary request 2" for the Designated Contracting States AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE*

*Claims 1 to 6 - Process for the preparation of an antibody chain*

*Amendments, scope of protection - Article 123(2)(3) EPC; definition of subject-matter, clarity, support - Article 84 EPC*

8. The respondents did not raise objections under Articles 84, 123(2) and (3) EPC nor does the board.

*Sufficiency of disclosure - Article 83 EPC*

9. Three separate lines of attack were formulated under Article 83 EPC.

(a) Firstly, the respondents argue that a skilled person cannot without undue burden obtain antibodies fulfilling the functional definition of retaining the binding capability. Therefore, in view of decision T 435/91 (OJ EPO 1995, 188) having established that a skilled person must be able to achieve essentially all alternatives falling under a claim without undue burden, the requirements of Article 83 EPC are not met.

(b) Moreover, the respondents argue that document D23 discloses an antibody which, despite fulfilling the homology-criteria of the patent in suit, has lost its original binding capability. This shows that the claimed process does not always lead to the desired result, i.e. the retention of the antigen binding capability in each and every case. Therefore, the one example of a reshaped antibody in the patent in suit, even in combination with common general knowledge, is not enough to provide the skilled person with sufficient information as to how a failure could be turned into success.

(c) Finally, it is argued that the disclosure of the patent is not enabling when antibodies are to be

prepared starting from germline sequences because document D31 teaches that these sequences need a modified type of homology search, i.e. basically the mouse antibody variable region has to be broken into sections corresponding to the germline variable region gene elements and the sections have to be compared separately. This information is however not contained in the patent in suit.

10. As far as objection (a) above is concerned, the board observes the following:

The de facto production of the antibody chain is described by claim 1 as follows:

"...preparing from cDNA encoding the rodent variable domain a cDNA encoding a reshaped antibody containing CDRs derived from the rodent antibody and a variable domain framework from the human antibody by comparing the rodent variable domain amino acid sequence to that of the chosen human antibody variable domain sequence and **adding or deleting residues in the rodent cDNA so that the rodent framework amino acid sequence is identical to the human framework sequence..."** (emphasis added).

These instructions are complemented by the following functional feature at the end of claim 1:

"...the addition or deletion of step (iii) being such that an antibody incorporating the antibody chain expressed in step (iv) retains the antigen binding capability of the antibody of the rodent species."

Functional definitions are used to define a plurality of structural alternatives having a common effect or property. In the present case however, the step, the result of which is defined by the functional definition is carried out such "that the rodent framework amino acid sequence is identical to the human framework sequence". This is an instruction that leaves no room for alternatives. Therefore, the functional definition at the end of claims 1 is regarded merely as the statement of the consequence of carrying out step (iii). Consequently, the respondents' argument along the line of decision T 435/91 (supra) that a skilled person must be able to achieve all alternatives falling under a functional definition without undue burden is not applicable here.

11. The respondents' objection (b) above is related to the question whether the disclosure of the invention in the patent in suit is sufficient to enable the skilled person to reliably achieve the desired result when carrying out the claimed process.

The process of claim 1 of the patent in suit requires in part (ii) to select a human antibody variable domain that is most homologous to a rodent antibody variable domain based on the overall homology of the two domains. The patent in suit discloses at the top of page 11 that of all known antibody variable heavy domain regions, the overall amino acid sequence of the variable heavy domain region of the human antibody KOL is most homologous to that of the rat CD4 antibody variable heavy domain region. The experimental data on page 11 of the patent in suit show that an antibody having the rat CD4 antibody variable heavy domain

reshaped to contain the variable heavy region framework sequences of the human antibody KOL has a greater binding affinity to CD4 antigen-expressing cells than an antibody having a combination of the CDRs of the CD4-antibody and the framework regions of the less homologous variable heavy chain domain sequence of the human NEW antibody. Since both antibodies have identically reshaped light chains, the difference in affinity can be ascribed to the reshaped heavy chains. Thus, the patent in suit discloses one antibody successfully reshaped according to the criteria of the process of claim 1 of the patent in suit.

12. Document D23 discloses in column 41, last paragraph, the humanization of the mouse anti-Tac monoclonal antibody which is known (for example document D8) to bind to the p55 chain of the human interleukin 2 (IL-2) receptor. Document D23 states that the reshaped antibody is designed as follows: "..., only mouse anti-Tac amino acids in category (I), i.e. in the CDRs themselves, were used, with all other amino acids coming from the human Eu framework". According to document D23, column 42 the antibody with this sequence neither detectably binds the IL-2 receptor in a binding nor in a competition assay. In other words, it has lost its binding capability.

13. Nevertheless, in the board's view, document D23 is not suitable to challenge the reliability of the claimed process for the following reasons. There is no detailed disclosure in document D23 about the strategy underlying the selection of the anti-Tac - Eu antibody-pair. For example, information is lacking as to whether it involved the comparison of whole variable regions as

required by claim 1 or whether at the time when the homology search was performed, the variable regions of the mouse anti-Tac antibody and the human Eu antibody were indeed those with the most overall homology as also required by the claim 1.

14. The reliability of a process may only be successfully called into doubt by evidence relying on the same process. As shown above, prima facie, document D23 does not fulfil this requirement. Thus, it is not a suitable piece of evidence to substantiate the respondents' argument of lack of sufficiency of disclosure due to unreliability of the process.

15. Additionally, the board notes that even if the variable domain regions in document D23 had been selected in the way as claimed in the patent in suit, the disclosure of the lack of binding of the reshaped antibody in this document would nevertheless not convince the board about the unreliability of the claimed process. The skilled person knows that when attempting to reshape an antibody a balance must be found between the necessary "humanizing" modifications of the sequence and the wish to retain the binding capability. However, based on its common general knowledge about the influence of modifications in the primary structure on the three-dimensional structure of a protein, the skilled person would not be surprised to encounter cases where a satisfactory compromise may not possible. This view is confirmed by document D16, published eight month after the priority date of the patent in suit, stating on page 4181 that "reshaping antibodies is a relatively new procedure where success cannot necessarily be guaranteed for any individual antibody". Thus, at the

priority date of the patent in suit, it lay in the very nature of the process of reshaping antibodies that occasional failures could not be excluded. The board is of the opinion that in this case a single example of non-reproducibility cannot be sufficient to prove unreliability of the claimed process.

16. Finally, it is noted that in the present case the possibility of occasional failure is counterbalanced not only by an example of a successfully reshaped antibody in the patent in suit, but in addition by three other antibodies (referred to in the Waldmann declaration) which were designed according to he claimed process and which retained the desired binding capability.

17. Concerning the respondents' objection (c) above, it means in other words that, if germline sequences were selected after having carried out the steps encompassed by part (ii) of claim 1, the antibody reshaped by using these sequences would not retain binding capability because successful reshaping would only be achieved if the germline sequences were selected according to the strategy disclosed in document D31.

18. The board is not convinced of this argument either. It has been noted above that sufficiency of disclosure of a process can only be successfully challenged with data obtained by reproduction of the same process. Thus, what would be needed to support the respondents' argument was evidence that germline sequences were selected according to steps one to four of part (ii) of the process of claim 1, but that nevertheless the combination of their framework with the CDRs of the

corresponding rodent antibody gave rise to a non-functional reshaped antibody. However, this evidence is not present in document D31 and therefore no case of lack of enablement of the claimed process for germline sequences has been made out. In the board's view, document D31 rather appears to suggest that the probability of pulling out a germline sequence by a homology search according to the claimed process is low because germline sequences need a special search strategy.

19. Thus, sufficiency of disclosure is acknowledged.

*Novelty - Article 54 EPC*

20. Document D3 is the only document cited against the novelty of the subject-matter of claim 1 of this request. The document discloses the preparation of an antibody consisting of framework sequences derived from the human antibody Eu and CDR sequences derived from the mouse antibody Tac. In its general introductory part document D3 discloses on page 18 how the antibody is produced: "The nucleic acid sequences of the present invention capable of ultimately expressing the desired human-like antibodies can be formed from a variety of different polynucleotides (genomic or cDNA, RNA, synthetic oligonucleotides and components (e.g. V, J, D and C regions) as well as by a variety of different techniques. Joining appropriate genomic sequences is presently the most common method of production, but cDNA sequences may also be utilized." This passage is followed by a reference to two documents, being documents D1 and D6 in these appeal proceedings. Both deal with a human antibody as acceptor of rodent CDRs.

In the specific example of document D3, DNA for expression of the antibody heavy chain is synthesized from four different oligonucleotides. Thus, as far as the actual production of the antibody is concerned, document D3 is limited to the general statement that a variety of different techniques may be used and to the more specific disclosure of grafting of rodent CDRs region to human antibodies and complete synthesis.

21. Step (iii) of the process of claim 1 characterizes the production of the antibody as follows: "(iii) preparing from cDNA encoding the rodent variable domain a cDNA encoding a reshaped antibody containing CDRs derived from the rodent antibody and a variable domain framework from the human antibody by comparing the rodent variable domain amino acid sequence to that of the chosen human antibody variable domain sequence and adding or deleting residues in the rodent cDNA so that the rodent framework amino acid sequence is identical to the human framework sequence".

A comparison with the teaching of document D3 (see above in point 20) shows that these steps cannot be derived directly and unambiguously from this document. Consequently, since the method of document D3 and that of claim 1 differ in at least this step, the process of claim 1 is novel over that of document D3.

*Inventive step - Article 56 EPC*

22. There is agreement among the parties and the board that document D3 is the closest prior art. It relates, as the patent in suit, to a method for preparing reshaped, human antibodies. Essentially, the method disclosed in

document D3 differs from the method disclosed in the patent by the way in which the antibody is produced, a difference which was discussed in detail in relation to the requirement of novelty.

23. Having regard to the teaching of the closest prior art document D3 the problem to be solved by the patent can be formulated as the provision of an alternative process for the production of an antibody having CDR regions from a rodent antibody and framework regions from a human antibody.

24. The solution to this problem as claimed is to add or delete residues in the framework sequence of rodent cDNA so that the corresponding amino acid sequence becomes identical to the previously selected human framework sequence.

25. The patent in suit does not disclose a worked example where the whole process as claimed has been carried out. Thus the question arises whether the claimed solution has indeed been achieved. In view of the findings of the board in relation to sufficiency of disclosure, especially in point 11 above, this question can be answered in the affirmative.

26. For the assessment of inventive step the question needs to be answered whether at the priority date of the patent in suit it was obvious or not for a skilled person seeking to produce an antibody containing CDRs derived from a rodent antibody and framework regions derived from a human antibody to modify the framework region of a given rodent antibody.

27. Firstly, the respondents argue that a combination of the teachings of documents D3 and D28 would have rendered the claimed method obvious because document D28 states on page 45 under the heading of "Principle of exchange" that "three CDRs (**or alternatively, four FRs**) can be replaced per VH or VL"(emphasis added by the board).

28. The board is not convinced by this argument. The core technical teaching of document D28 is a concept about how a nucleic acid sequence encoding an antibody variable region can be modified in order to facilitate the insertion of CDRs or framework regions of choice. To this end, as disclosed for example on pages 11, 34 or 39, restriction sites are inserted at the framework-CDR or CDR-framework borders. Thus, document D28 contemplates the exchange of framework regions in case the DNA molecule has been modified by insertion of restriction sites. Thus, as far as the factual production of the antibody is concerned, a combination of the teachings of D3 and D28 would have resulted in the additional inclusion of restriction sites at the borders of CDR and framework regions during the design of the antibody and followed by synthesis of the antibody from oligonucleotides and not in the idea of modifying residues in the framework of a rodent antibody in order to match with the framework region of a previously selected human antibody which is, in the board's view, quite a different approach.

29. Secondly, the respondents argue that the addition or deletion of framework residues of a mouse antibody cDNA was an obvious, a, so to speak, "complementary"

alternative to CDR-grafting in view of the alternatives already existing in the prior art.

30. However, now that the invention disclosed in the patent in suit is made available, mutating the framework of a rodent antibody instead of mutating a human antibody or synthesising it from scratch seems to be a simple and convenient method, especially in view of the fact that a great number of rodent antibodies are available. But the board considers that the idea underlying the claimed process was not in the skilled person's mind before the priority date of the patent. Having regard to the documents on file the scientific situation in the field of reshaping antibodies was the following at the priority date of the patent in suit:

(a) The earliest document D1, published in 1987, suggests to replace CDRs of a human antibody by analogous parts form CDRs of an antibody of different specificity based on the knowledge that CDRs determine the binding specificity. This is achieved by oligonucleotide synthesis as described on page 13, first paragraph of the document or by oligonucleotide directed mutagenesis described in the paragraph bridging pages 13 and 14.

(b) Document D1 on page 13, third paragraph, in principle also already foreshadows the teaching of D28, published in December 1988, namely making a synthetic gene with suitable restriction sites at the CDR-framework junctions.

(c) Mutagenic oligonucleotides were used in the scientific publication document D6, published in

July 1988 and in the related patent application, document D2, published in August 1989 in order to mount the CDRs of a mouse antibody to a human antibody.

(d) Finally, the focus of document D8, a scientific publication of December 1989 and the related patent application, document D3, published in July 1990, i.e. two month before the priority date of the patent in suit, is on the improvement of the method of determination of an advantageous combination of mouse and human sequence elements that would retain binding affinity (for example document D3, pages 5 and 6 and D8, last sentence of introduction). As mentioned above in point 20 when it comes to the production of the newly designed antibody, document D3, apart from a general suggestion that a variety of different techniques may be used, and also document D8, rely on whole synthesis from oligonucleotides.

Hence at the priority date of the patent in suit the scientific community working on "humanization" of antibodies, on the one hand concentrated on improving the process of selection of variable domain sequences in order to increase the chance of retaining binding specificity. On the other hand, it was a concern to facilitate the replacement of CDRs. Hence, the scientific community had chosen to develop established methods further, but there was no sign of a complete departure from them.

31. According to established case law, when answering the question whether a skilled person would have applied a

certain technical measure, it is necessary to show that there is a recognisable pointer in the state of the art to combine the known means for achieving the intended technical aim. In the light of the scientific situation depicted above, the board is convinced that this pointer is missing here. Thus, it is concluded that a skilled person would not have combined document D3 and the common general knowledge in order to solve the underlying problem in the claimed way.

32. Hence, an inventive step is acknowledged for the subject-matter of claim 1 of auxiliary request 2.

*Claims 7 to 15 - antibody and pharmaceutical composition*

33. Claims 7 to 15 correspond to claims 10 to 18 of the granted claims. No opinion was given on these claims by the opposition division because the patent was revoked for other reasons. No objections were raised against these claims by the respondents during the appeal proceedings and the board also sees none.

34. Hence, revised new auxiliary request 2 fulfils the requirements of the EPC.

*"Revised new auxiliary request 2" - claims for the Designated Contracting States ES and GR*

35. The claims of this request differ from those for the other Designated Contracting States in that the product-claims are formulated as process-claims. No objections were raised against them and the board sees none. Consequently, the conclusions reached above apply to this set of claims.

**Order**

**For these reasons it is decided that:**

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent with the following claims and a description to be adapted:

   - claims 1 to 15 for the Contracting States: AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE.

   - claims 1 to 15 for the Contracting States: ES, GR

   filed at the oral proceedings of 30 September 2004 as "revised new auxiliary request No. 2".

The Registrar: The Chairwoman:

P. Cremona U. M. Kinkeldey