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D E C I S I O N
of 26 February 1999

Case Number: T 0034/95 - 3.3.4

Application Number: 86903731.7

Publication Number: 0221173

IPC: G01N 33/53

Language of the proceedings: EN

Title of invention:
Diagnostic reagents based on unique sequences within the variable region of the T cell receptor and uses thereof

Applicant:
California Institute of Technology

Opponent:
-

Headword:
Diagnostic reagents/CALIFORNIA INSTITUTE OF TECHNOLOGY

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
"Main request: Admissibility of a generalization of a feature in claims (yes)"

Decisions cited:
T 0157/90, T 0397/89, T 0770/90, T 0133/85

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0034/95 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 26 February 1999

Appellant: California Institute of Technology
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 11 July 1994 refusing European patent application No. 86 903 731.7 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
C. Holtz

Summary of Facts and Submissions

I. European patent application No. 86 903 731.7, filed as International Application No. PCT/US86/00882 with the title "Diagnostic reagents based on unique sequences within the variable region of the T cell receptor and uses thereof" was published under the International Publication number WO 86/06413.

II. The application was refused by a decision of the Examining Division. That decision was based on a set of 42 claims submitted during the oral proceedings and on the description and drawings as originally filed, except for pages 4 and 15, which were filed with the letter of 21 January 1993.

Claims 1, 2, 33 and 34, comprising in bold the amendments objected to by the Examining Division under Article 123(2) EPC, read as follows:

"1. A method of testing for a specific disease in a human or animal subject, which disease has an immunological involvement, which comprises:

a. contacting a T cell-containing sample obtained from the subject with an immunological reagent capable of binding to T cells and having specificity for an amino acid sequence within **the variable region of a chain of the T cell antigen receptor** of T cells associated with the specific disease, under conditions that permit the formation of a detectable complex between the immunological reagent and T cells that contain the

amino acid sequence; and

b. comparing the extent of formation of the detectable complex in the sample with that in a sample from a normal subject, thereby enabling diagnosis of the disease of interest or monitoring of its progress."

"2. A method of testing for a specific disease in a human or animal subject, which disease has an immunological involvement, which comprises:

a. contacting a T cell nucleic acid-containing sample obtained from the subject with a nucleic acid reagent capable of binding specifically to a nucleic acid sequence encoding an amino acid sequence within **the variable region of a chain of the T cell antigen receptor** of T cells associated with the specific disease, under conditions that permit the formation of a detectable complex between the nucleic acid reagent and a T cell nucleic acid sequence encoding the amino acid sequence; and

b. comparing the extent of formation of the detectable complex in the sample with that in a sample from a normal subject, thereby enabling diagnosis of the disease of interest or monitoring of its progress."

"33. A method for detecting organ transplant rejection in a human or animal subject into whom or which an organ from a different subject has been transplanted which comprises:

a. contacting a T cell-containing sample obtained from the host subject with an immunological reagent capable of binding to T cells and having specificity for an amino acid sequence within **the variable region of a chain of the T cell antigen receptor** of T cells associated with organ transplant rejection, under conditions that permit the formation of a detectable complex between the immunological reagent and T cells that contain the amino acid sequence; and

b. comparing the extent of formation of the detectable complex in the sample with that in a sample from a normal subject, thereby enabling diagnosis of the rejection of the transplanted organ."

"34. A method for detecting organ transplant rejection in a human or animal subject into whom or which an organ from a different subject has been transplanted, which comprises:

a. contacting a T cell nucleic acid-containing sample obtained from the subject with a nucleic acid reagent capable of binding specifically to a nucleic acid sequence encoding an amino acid sequence within **the variable region of a chain of the T cell antigen receptor** of T cells associated with organ transplant rejection, under conditions that permit the formation of a detectable complex between the nucleic acid reagent and a T cell nucleic acid sequence encoding the amino acid sequence; and

b. comparing the extent of formation of the detectable complex in the sample with that in a sample from a normal subject, thereby enabling diagnosis of rejection of the transplanted organ."

III. The only reason for the refusal was that the subject-matter of claims 1, 2, 33 and 34 did not meet the requirements of Article 123(2) EPC because the expression in the claims as filed "**variable region of the ß chain of the T cell receptor**" had been generalized to read "**variable region of a chain of the T cell receptor**". Owing to this new wording, the Examining Division held that claims 1, 2, 33 and 34 had been broadened to cover diagnostic methods involving reagents capable of binding not only to the variable ß chain of the T cell receptor ($V_ß$), but also to the variable á chain of the T cell receptor ($V_á$). However, the diagnostic use of $V_á$ binding reagents was not derivable in a direct and unambiguous manner from the application as filed. Thus, although there was "formal support" for the above generalization in the application as filed, this could not be allowed following the rationale emerging from decisions T 157/90 of 12 September 1991, T 397/89 of 8 March 1991 and T 770/90 of 17 April 1991, according to which formal support in an application as filed is insufficient for the generalization of a feature if the feature's general applicability was not evident to the skilled person.

IV. An Appeal was filed, the fees paid and the written statement setting out the grounds of appeal comprised a main request and a first and second auxiliary requests. The claims of the main request were the same as the

claims refused by the Examining Division.

V. The Appellant essentially argued as follows:

- The application as filed contained all the technical information to find diseases associated with the variable regions of both the á and ß chains ($V_{á}$ and $V_{ß}$) of the T cell receptor and to apply the claimed diagnostic method. In support of this line of argument, the Applicant submitted a series of post published documents (document (5): Urban et al., Cell, Vol. 54, pages 577 to 592, (1988); document (6): Moller et al., J. Clin. Invest., Vol. 82, pages 1183 to 1191 (1988); document (7): Posnett et al., J. Clin. Invest., Vol. 85, pages 1770 to 1776 (1990); document (8): Arden et al., Nature, Vol. 316, pages 783 to 787 (1985)) giving evidence of the generalized application of the claimed diagnostic method. Therefore, the generalization of claims 1, 2, 33 and 34 did not contravene the requirements of Article 123(2) EPC.

- The passages on page 11, lines 3 to 5 and 27 to 31 related explicitly in general terms to the use of the variable regions of T cell receptors for the diagnosis of any disease having immunological association. On pages 57 and 58 the application as filed details were given relating to the isolation and identification of the variable region of both the á and ß chains of the T cell receptor.

VI. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis

of the claims rejected by the Examining Division (main request) or one of the first and second auxiliary requests submitted with the grounds of appeal, or the third auxiliary request submitted on 21 November 1994. Oral proceedings were also requested.

Reasons for the Decision

1. The appeal is admissible

Main request

2. The only point at issue is whether the generalization in claims 1, 2, 33 and 34 of the expression "variable region the ß chain of the T cell receptor" to "variable region of a chain of the T cell receptor" meets the requirements of Article 123(2) EPC.

3. Article 123(2) EPC needs to be considered when an amendment is proposed during the course of prosecution of an application, either to the claims or to the description and the drawings. The function of Article 123(2) EPC is to prevent the addition of subject-matter to a patent application after the date of filing. However, from the wording of Article 123(2) EPC it is also to be understood that amendments of claims - also a broadening of the scope of the claims as originally filed - can be allowable, but only when the application after the amendment does not "contain subject-matter which extends beyond the content of the application as filed". As is said in decision T 133/85 (OJ EPO 1988, 441), the original application may be

said to represent a "reservoir" upon which the applicant may draw to amend the application, but it must be observed that "in accordance with Article 123(2) EPC, the original application should be considered as a reservoir which cannot be expanded after the date of filing".

4. The T cell receptor is a membrane protein comprising á and ß chains, each in turn divided in variable and constant regions (see the application as filed, page 23, lines 28 to 32). The á and ß chains comprise variable (V), diversity (D) and junctional (J) domains (see page 58, lines 6 to 8, interpreted in the light of document (6), page 1183, under the heading "Introduction").

5. In order to decide whether the expression "variable region of a chain of the T cell receptor" in claims 1, 2, 33 and 34 represents subject-matter which extends beyond the content of the application as filed, it is necessary to find out whether this expression finds a basis in the original application. Thus, it is necessary to identify the content of the said "reservoir", i.e., the originally filed description and the originally filed claims.

6. The Board observes that claim 1 as filed has been split into present claims 1 and 2, each specifying that "the reagent binding to T cells" of claim 1 as filed should be an "immunological reagent" (claim 1) or "a nucleic acid reagent" (claim 2). Claim 33 represents a specific embodiment of claim 53 as filed, in which "the reagent binding to T cells" of claim 53 has been further defined as being an "immunological reagent". Claim 34

is also a specific embodiment of claim 53 as filed, in which "the reagent binding to T cells" of claim 53 has been further characterized as being "a nucleic acid sequence". The Examining Division raised no objections under Article 123(2) EPC to these amendments and the Board agrees as well. It is also noted that claim 53 as filed comprised the expression "variable region of the chain of the T cell receptor", whose meaning seems not to be clear because the T cell receptor was known to comprise two chains (the á and ß chains). Thus, the only meaningful wording would have been either "variable region of the chains of the T cell receptor" or "variable region of a chain of the T cell receptor" (emphasis added). The latter wording has been adopted in present claims 1, 2, 33 and 34.

7. In the Board's view, there is an *expressis verbis* statement in the application as filed that the diagnostic method of the invention may rely on **any** amino acid sequence present in the T cell receptor (or the respective nucleic acid sequence which encode it) for the diagnosis of diseases having immunological association. The relevant passages are the following:

- "This invention utilizes the presence of unique amino acid sequences (or the unique nucleic acid sequences which encode them) within the T cell receptor" (page 11, lines 3 to 5)

- "...it is contemplated that any unique amino acid sequence present in the T cell receptor in increased copies in a disease state may be used in the practices of the subject invention..." (page 11, lines 27 to 30)

8. Further, the application as filed also states on page 58, lines 6 to 8 that "The amino acid sequence of the **V**, J and D domains of the **alpha** and **beta** polypeptide is determined..." and at lines 13 to 15 that "The nucleotide sequence of the **variable region** of the **alpha** or **beta** gene mRNA is determined by the primer extension method..." (emphasis added). Thus, in the Board's judgement, these passages are not only in line with the statement made on page 11 (see point 7 supra) that the diagnostic method of the invention may rely on any amino acid sequence present in the T cell receptor, but also imply that the said amino acid sequence may be taken from the variable region of the á chain of the T cell receptor. Therefore, the expression "variable region of a chain of the T cell receptor" can be derived directly and unambiguously by a skilled reader from the "reservoir" represented by these four passages cited above. Consequently, the Board acknowledges that the subject-matter of claims 1, 2, 33 and 34 of the main request satisfy the requirements of Article 123(2).

9. The Examining Division relied on decisions T 157/90 (supra), T 397/89 (supra) and T 770/90 (supra). However, the present situation, where there is **verbal support** in the application as filed for a generalization should be distinguished from situations where no such explicit or implicit verbal support can be found, as in the cases dealt with in decisions T 157/90 (see point 2.4 of the reasons: "The application as originally filed does not contain any further information about apparent variations or

equivalents and, therefore, the explicit disclosure relates to the glycine as the additional amino acid at the carboxy-terminal end of human calcitonin for the purpose of an amidation either of proline or glycine by means of carboxypeptidase Y, and nothing more"), T 397/89 (see point 2.4 of the reasons: "The feature of Claim 1 ("means for transmitting torsional and longitudinal forces") is therefore a generalisation of the teaching disclosed in the application as originally filed which is not supported in that application even when read by a skilled person") and T 770/90 (see point 2.5 of the reasons: "Also no other indications in the description which explicitly or implicitly would propose other factors can be found").

10. As regards sufficiency of disclosure, the Examining Division accepted that the amended claims satisfied the requirements of Article 83 EPC (see end of paragraph 2 of the decision under appeal). The Board agrees with this conclusion. Further, the Board observes that the only objections under Article 54 EPC and Article 56 EPC raised by the Examining Division were against the "immunological reagents". The Applicant reformulated the claims objected to in the form of a first and second diagnostic use of immunological reagents or nucleic acids capable of binding to the variable region of the ß-chain of the T cell antigen receptor. In paragraph 4.2 of the communication of 22 March 1993, the Examining Division accepted that the claims in the form of a first and second diagnostic use of immunological reagents or nucleic acids met the requirements of Article 54 EPC and Article 56 EPC. The Examining Division accepted the Applicant's arguments that this use as diagnostic agents was only possible in

the light of the two technical teachings disclosed by the present application, namely (i) there is a limited number of amino acid sequences present in the variable region of the T cell receptor and (ii) these sequences are associated with a disease. These technical teachings were neither disclosed nor rendered obvious by any document of the prior art (see paragraph 3 of the Applicant's submission of 21 January 1993). The Board agrees as well. On the same grounds, it must be acknowledged that the diagnostic use of present claims 37 to 40, the diagnostic methods of claims 1 to 34, 41 and 42 satisfy the requirements of Article 54 EPC and Article 56 EPC. These requirements are also met by the polypeptide of independent claim 35 and the polydeoxyribonucleotide of claim 36 since they are specific amino acid or DNA sequences associated with the T cell lymphoma MOLT-3 (see application, page 51, lines 21 to 22) and they are not disclosed or rendered obvious by any prior art document. In conclusion, the subject-matter of the claims of the main request satisfy the requirements of the EPC. The Appellant's main request can be accepted by the Board. In view of this, it is superfluous to examine the first, second and the third auxiliary requests, or to summon to oral proceedings.

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 grant a patent on the basis of the claims of the main request submitted before the Examining Division at the oral proceedings on 4 May 1994.

The Registrar: The Chairwoman:

U. Bultmann U. Kinkeldey