BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE | CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen

D E C I S I O N
of 10 June 1997

Case Number: T 0530/95 - 3.3.4

Application Number: 90304413.9

Publication Number: 0395367

IPC: C12N 15/55

Language of the proceedings: EN

Title of invention:
Method for producing the XmaI restriction endonuclease and methylase

Applicant:
NEW ENGLAND BIOLABS, INC.

Opponent:
-

Headword:
XmaI/NEW ENGLAND BIOLABS

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (yes) - after amendment"

Decisions cited:
T 0032/82, T 0068/85, T 0500/91, T 0886/91, T 0223/92, T 0296/93

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0530/95 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 10 June 1997

Appellant: NEW ENGLAND BIOLABS, INC.
32, Tozer Road
Beverly
Massachusetts 01915 (US)

Representative: Davies, Jonathan Mark
Reddie & Grose
16 Theobalds Road
London WC1X 8PL (GB)

Decision under appeal: Decision of the Examining Division of the European Patent Office posted 6 February 1995 refusing European patent application No. 90 304 413.9 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: L. Galligani
J.-C. Saisset

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division issued on 6 February 1995 by which the patent application was refused pursuant to Article 97(1) EPC on the ground that the subject-matter of claims 1 to 7 then on file did not involve an inventive step (Article 56 EPC).

Claims 1 and 3 read as follows:

"1. Isolated DNA segment coding for the XmaI restriction endonuclease, wherein the isolated DNA segment is obtainable from *Xanthomonas malvacaerum* ATCC No. 9924.

3. Isolated DNA segment coding for the XmaI restriction endonuclease and methylase, wherein the isolated DNA segment is obtainable from *X. malvacaerum* ATCC No. 9924."

II. The examining division took the following prior art documents into consideration:

(1) J. Mol. Biol., 1977, Vol. 112, pages 521 to 529;

(2) EP-A-0 193 413;

(3) Gene, 1988, Vol. 74, pages 25 to 32.

The examining division considered that document (1), which described the isolation of the XmaI restriction endonuclease enzyme from Xanthomonas malvacaerum ATCC No. 9924, represented the closest prior art, and defined the problem to be solved as the provision of a DNA segment encoding the XmaI restriction endonuclease. In its view, the proposed solution, which was claimed

as a result to be achieved, did not involve an inventive step because, in order to solve the stated technical problem, the skilled person would have readily taken the known strain ATCC 9924 as a starting material and would have arrived at the claimed DNA by means of a straightforward application of techniques well known from documents (2) and (3). As a matter of fact, the procedure described in the patent application was essentially identical to the one described in document (2) ("Wilson procedure"), the only differences being **i)** that the initial plasmid library was not digested with XmaI, but with its isoschizomer SmaI, and **ii)** that an extra XmaI/SmaI site was introduced into the cloning vector. The latter changes were suggested to the skilled person by document (3), which, while stating that the XmaI system was refractory to cloning, indicated how obstacles could be overcome eg by introducing selection sites [see, in the present case, measure ii)] and using an isoschizomer [see, in the present case, measure i)]. Thus, the changes to the known procedure which were adopted in order to solve the technical problem were obvious for the skilled person in the light of document (3). For these reasons, there was no basis for claims broadly drafted in the form of an obviously desirable objective.

III. In the official communication dated 8 July 1996, the board expressed the provisional opinion that favourable consideration could be given to the appellants' arguments in support of inventive step. However, the board noted that certain claims were not in compliance with the requirements of Article 84 EPC. Furthermore, a formal objection under Article 123(2) EPC was raised against claim 6 on file.

IV. After further letter exchanges between the board and the appellants, on 27 May 1997 the appellants filed four new claim requests, of which the main request contained claims identical to those rejected by the examining division, exception made for an amendment introduced in claim 6 in response to the board's objection.

V. Oral proceedings took place on 10 June 1997. All previous requests were withdrawn and only one new request (claims 1 to 7) was filed. Independent claims 1 and 3 thereof read as follows:

"1. Isolated DNA segment coding for the XmaI restriction endonuclease, an enzyme which recognizes the DNA sequence 5'-CCCGGG-3' and cleaves between C_1 and C_2 leaving a four nucleotide 5' overhang, wherein the isolated DNA segment is obtainable from a 10.3Kb *HindIII* fragment of *Xanthomonas malvacaerum* ATCC No. 9924.

3. Isolated DNA segment coding for the XmaI restriction endonuclease an enzyme which recognizes the DNA sequence 5'-CCCGGG-3' and cleaves between C_1 and C_2 leaving a four nucleotide 5' overhang, and methylase, wherein the isolated DNA segment is obtainable from a 10.3Kb *HindIII* fragment of *X. malvacearum* ATCC No. 9924."

Claim 2 relates to a recombinant DNA vector comprising a DNA segment according to claim 1. Claims 4 and 5 concern a cloning vector comprising the isolated DNA segment according to claims 1 and 3, respectively. Claim 6 relates to a host cell transformed by the vector according to either claim 4 or 5. Claim 7 is directed to a method of producing XmaI restriction endonuclease by culturing the said host cell.

VI. The appellants submitted essentially that only with the benefit of hindsight it could be seen which particular combination of modifications of the available general Wilson method (cf eg document (3)) had to be chosen in order to achieve the claimed subject-matter. The skilled person did not clearly know at which stage or for what reason the method did not readily produce the XmaI restriction-methylase (R-M) system. In the absence of any guidance, the skilled person could not make any predictions about the cloning of this difficult R-M system. For these reasons, the subject-matter of claims 1 to 7 involved an inventive step.

VII. The appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of the only request filed at oral proceedings on 10 June 1997.

Reasons for the Decision

Article 123(2) EPC

1. All the amendments introduced in the present claims are fairly based on the application as filed. The feature "an enzyme which recognizes the DNA sequence 5'-CCCGGG-3' and cleaves between C_1 and C_2 leaving a four nucleotide 5' overhang" with reference to the XmaI restriction endonuclease is found on page 5, first paragraph thereof, while the feature "obtainable from a 10.3Kb *HindIII* fragment of *Xanthomonas malvacaerum* ATCC No. 9924" with reference to the isolated DNA segment is found inter alia on page 5, last paragraph and Figure 3. Thus, no objection under Article 123(2) EPC is seen by the board.

Article 84 EPC

2. No clarity objections under Article 84 EPC is seen by the board in respect of the claims at issue. The indication of the size and restriction end of the relevant fragment in claims 1 and 3 constitutes a concrete technical feature which characterises in an appropriate manner the actual achievement by the patent application, ie the identification and isolation of a DNA segment from *X. malvacaerum* ATCC No. 9924, and which enables the skilled person to perform the invention (cf. eg decisions T 32/82 OJ EPO 1984, 354,in particular point 15 of the reasons, and T 68/85 OJ EPO 1987, 228, in particular point 8.4.1. of the reasons).

Novelty (Article 54 EPC)

3. No novelty objection has been raised by the examining division against the broader claims previously on file. No novelty objection against present narrower claims 1 to 7 is seen by the board having regard to the documents on file.

Inventive step (Article 56 EPC)

4. In the board's judgement, document (3) constitutes the most appropriate starting point for the evaluation of inventive step. This document outlines a method of general applicability (known as the "Wilson method") for cloning type-II restriction and modification (R-M) genes, including the XmaI R-M system . Cloning of these genes is said to be useful inter alia for simplifying the purification of restriction endonucleases and methylases. The method is carried out essentially in three steps and is based on the fact that often R-M genes tend to be closely linked and thus clones containing both genes can be isolated by selecting for just one of the genes (the so-called "Hungarian

trick"). Document (3), which describes also the precautions to take in order to overcome the several obstacles encountered in the cloning of R-M genes, reports that about 80% of the cloning attempts yielded clones that carried at least the modification gene, ie the gene encoding the methylase (cf. page 27, left column). However, at the same time, document (3) states:" Among the 20% of M genes we have failed to obtain, some could probably be cloned were we to repeat or extend the experiments. Others, including ... XmaI R-M systems, have proven refractory to multiple cloning attempts" (loc.cit., emphasis added).

5. In the light of this document, the **technical problem** to be solved can be defined as the cloning and expression of the XmaI R-M system, ie the identification and isolation of a DNA sequence encoding the XmaI restriction endonuclease and methylase to be used for simplifying (eg easier purification, production of greater quantities) the production of the enzymes in a recombinant system.

6. As a **solution** thereto, the patent application proposes a DNA segment coding for the XmaI restriction endonuclease (claim 1) and for the XmaI restriction endonuclease-methylase (claim 3) as obtainable from a 10.3kb *HindIII* fragment of X. malvacearum ATCC 9924 as well as vectors (claims 2, 4-5), host cells transformed therewith (claim 6) and their use in a method for producing XmaI restriction endonuclease (claim 7). As shown by the description such a segment was indeed cloned, characterised and expressed at detectable levels in a transformed host cell (E.coli). Thus, the board is satisfied that the technical problem underlying the application is solved.

7. The key question in the present case is whether the skilled person, starting from the disclosure of document (3), would have readily expected to succeed in cloning the XmaI restriction and modification genes. This is because if in a given technical situation it is found that the skilled person for the purpose of Article 56 EPC would have had no confidence or strong doubts about the possibility of readily attaining a desired result by application of a known technique, then the actual achievement of the result, expressed in terms of the concrete technical features which contributed to such achievement, may be regarded as involving an inventive step, as this implies an element of surprise (cf. eg decision T 296/93 OJ EPO 1995, 627).

8. The problem of the cloning of the XmaI R-M system had already been tackled in document (3) where - as stated above, cf point 4 - a method of general applicability for cloning type-II restriction and modifications (R-M) genes (the "Wilson method") had been proposed. When faced with the stated technical problem, the skilled person would inevitably have taken into account the statement made in relation to the XmaI R-M system, namely that that it had proven refractory to multiple cloning attempts. The skilled person would have noted that document (3), while stating that among the 20% of M genes which were not obtained **some could probably** be cloned by repeating the experiments, dashed the hopes in respect of other systems, including the XmaI R-M system, by qualifying them as "**refractory** to **multiple** cloning attempts" (emphasis added). This statement would have negatively influenced the degree of confidence of the skilled person in the possibility of successfully achieving the cloning and expression of XmaI. The skilled person would not have readily derived from document (3) or from any other prior art document

any useful specific hints as to the strategy to follow in order to succeed where others had failed. While it is true that document (3) suggested, among the measures to be taken to overcome possible obstacles, two measures which were indeed adopted in the experimental protocol according to the present application (cf Section II supra, measures i) and ii)), it should be taken into account that:

- the suggestions made in document (3) are quite general, ie not directed to any specific technical difficulty in the cloning of the XmaI R-M system;

- the skilled person reading document (3) would have noted that the same authors who had provided also a general description of precautions to take in order to overcome obstacles in cloning of R-M genes had repeatedly failed in their attempts to clone the XmaI R-M system. From this, the skilled person would have concluded that the task was difficult and that its successful conclusion, if ever possible, would have depended not much on the technical skill in putting into practice the sequence of precise steps of the theoretical experimental "Wilson" protocol, this being possibly a matter of routine, but more importantly on the ability of devising and performing appropriate modifications in the said protocol or even of taking a different approach.

Under these circumstances, it cannot be said that the skilled person would have readily expected to achieve the cloning and expression of the XmaI system. As a matter of fact, the skilled person would not have been able to predict which of the wealth of possible technical measures would have ensured success. Only with the foreknowledge of the invention, is now possible to trace back the way that led to

identification and isolation of a DNA coding for the XmaI restriction endonuclease-methylase from a 10.3kb *HindIII* fragment of X. malvacearum ATCC 9924.

9. As regards the analysis of the technical situation made by the examining division which led it to reject the present application (see Section II supra), the board observes that it was made in respect of a different set of claims, wherein independent claims 1 and 3 were broadly formulated in terms of the result to be achieved. Furthermore, it presupposed a too high level of skill for the skilled person for the purpose of Article 56 EPC. As stated eg in decision T 500/91 of 21 October 1992 relating to the field of genetic engineering (cf in particular point 2.2 of the reasons), the skill of the notional skilled person for the purpose of Article 56 EPC does not include solving technical problems by performing scientific research in areas not yet explored or problematic. Although it has to be accepted that at the priority date of the present application (1989) the average skill in genetic engineering had developed already to a considerable degree, in the present case account should be taken of the fact that only one year before the invention was made, ie in 1988, the authors of document (3), dealing with the cloning of type-II R-M systems, were not successful in achieving the claimed result, ie cloning of the XmaI system. Thus, further research was necessary. However, from the the notional skilled person for the purpose of Article 56 EPC nothing more can be expected than the carrying out of experimental work by routine means within the framework of the normal practice of filling gaps in knowledge by application of the existing knowledge (see eg decisions T 886/91 of 16 June 1994, in particular point 8.2.4, last sentence of the reasons, and T 223/92 of 20 July 1992, in particular point 5.5. of the reasons). In the board's view, in the present case the finding of a

solution to the technical problem underlying the application involved more than the said routine activities. In fact, it required the ability to choose the appropriate measures in tackling a known difficult task in which others had repeatedly failed.

10. For these reasons, in the board's judgement, the subject-matter of claims 1 to 7 involved an inventive step and, consequently, the appellants' request is allowable.

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 only request (set of claims 1 to 7) filed at the oral proceedings on 10 June 1997 and of a description to be adapted.

The Registrar: The Chairperson:

A. Townend U. Kinkeldey

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE ★ CHAMBRES DE RECOURS DE L'OFFICE EUROPÉEN DES BREVETS ★ BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

Beglaubigt/Certified Certifiée conforme: München/Munich

Geschäftsstelle Registry/Greffe

11. JULI 1997

1726.D