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D E C I S I O N
of 3 May 1999

Case Number: T 0966/98 - 3.3.4

Application Number: 92201245.5

Publication Number: 0502589

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:
Kit for use in amplifying and detecting nucleic acid sequences

Applicant:
F. Hoffmann-La Roche AG

Opponent:
-

Headword:
DNA detection/HOFFMANN-LA ROCHE AG

Relevant legal provisions:
EPC Art. 84, 56

Keyword:
"Clarity - yes"
"Inventive step - yes"

Decisions cited:
-

Catchword:
-

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Case Number: T 0966/98 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 3 May 1999

Appellant: F. Hoffmann-La Roche AG
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 22 April 1998 refusing European patent application No. 92 201 245.5 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
S. C. Perryman

Summary of Facts and Submissions

I. European patent application No. 92 201 245.5, publication No. 0 502 589 with the title: "Kit for use in amplifying and detecting nucleic acid sequences" was filed as a divisional application to the application published under No. 0 200 362. It was refused by the Examining Division.

II. The decision of the Examining Division was taken on the basis of the amended set of claims filed on 13 March 1998, as the sole request.

Claim 1 of this request read as follows:

"1. An exponential amplification and detection kit for the amplification and detection of (a) specific nucleic acid sequence(s) contained in a single- or double-stranded nucleic acid or in a mixture of such nucleic acids in a sample, which kit comprises in packaged form:

(a) at least a first and a second oligonucleotide primer different from each other, wherein

(aa) one of said primers is substantially complementary to said single-stranded nucleic acid or to one strand of said double-stranded nucleic acid;

(ab) the other primer of said primers is substantially complementary to a complement of said single-stranded nucleic acid or to the other strand of said double-stranded nucleic acid; and

wherein

(ac) said primers define the termini of the specific nucleic acid sequence to be amplified and detected;

(b) an agent for polymerisation; and

(c) means for detecting the amplified specific nucleic acid sequence."

Dependent claims 2 to 12 related to further features of the kit of claim 1 and claims 13 and 14 related to the use of a kit according to claims 1 to 12.

The Examining Division found that the subject-matter of claim 1 was unclear and lacked inventive step. Lack of clarity resulted from the fact that the oligonucleotides contained in the kit were characterized by their complementarity to a template which remained unspecified. Thus, it was impossible for the skilled person to know whether he/she was working inside or outside of the scope of the claim.

Document (2) was the closest prior art. It disclosed a kit for M13 sequencing which only differed from the kit of claim 1 in that it lacked means for detecting the amplified sequences (feature (c)). The addition of such means was self evident, seeing that the identification of the products obtained in the sequencing reactions carried out with the kit of document (2) equally required to be detected.

III. The Appellants (Applicants) lodged an appeal against

this decision, paid the appeal fee and submitted a statement of grounds for the appeal.

IV. The following documents are mentioned in the present decision:

(1) EP-A-0 138 242,

(2) Molecular Biologicals, Pharmacia Catalog, pages 48 and 49, 1984,

(3) New England Nuclear Catalog, pages 134 and 135, 1983.

(4) Kleppe, K. et al., J. Mol.Biol., No. 56, pages 341 to 361, 1971.

V. At oral proceedings, the Appellants submitted a new main request for consideration by the Board.

Claim 1 of this request differed from claim 1 of the request refused by the Examining Division by including in the first part of the claim the word "template", so that this part read:

"An exponential amplification and detection kit for the amplification and detection of (a) specific **template** nucleic acid sequence(s) contained in a single- or double-stranded nucleic acid or in a mixture of such nucleic acids in a sample..."(emphasis added by the Board).

The word "template" was also added in claims 2, 12 to 14 to qualify the specific nucleic acid sequence to be

amplified. All other claims remained unchanged.

VI. The Appellants argued essentially as follows:

Clarity:

To restrict the kit to one containing oligonucleotides able to anneal to a specifically mentioned template would amount to an unjustified restriction of the scope of protection, seeing that the amplification reaction, the kit was to be used for, could be carried out with any template.

The concern of the Examining Division that the skilled person would not know, when working with two oligonucleotides whether he/she was working inside or outside of the scope of the claim was unfounded. Indeed a situation where two oligonucleotides would happen to be useful for the amplification of a "template" DNA molecule, although their sequences had not been derived from the specific sequence of the termini of said DNA molecule, was theoretically conceivable, but had no likelihood to occur.

The functional limitation that the oligonucleotides can be used for amplification of a **specific** natural template taken together with the technical feature that they must anneal to the termini of said sequence provided the skilled person with an unambiguous characterisation of the claimed subject-matter.

Inventive step

Document (2) cited by the Examining Division as closest

prior art proposed kits for sale which were of use for DNA **sequencing** starting from M13 sequencing vectors. These kits were not suitable for the **amplification** of DNA sequences, since M13 was not amplified during the sequencing reaction. In contrast, the technical problem solved by the patent application was to provide means for the specific and precise amplification of a specific sequence. It was not possible to derive either this problem or its solution from document (2), even if combined with any of the other documents on file.

VII. The Appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 14 submitted at the oral proceedings on 3 May 1999.

Reasons for the Decision

1. The appeal is admissible

Article 123(2) EPC; amendments

2. The amendments of the claims (see section V above) are allowable in the light of the disclosure of the application as filed, e.g. page 10, lines 18 to 26.

Article 84 EPC; clarity

3. The reasoning of the Examining Division on Article 84 EPC (see section II above), while correct in theory, does not take into account how the sequences of oligonucleotides such as are parts of the claimed kit,

are obtained. It is readily apparent from the state of the art cited in the present case, that the sequence of oligonucleotides which are complementary to a specific template is derived from the **known** sequence of the template: in document (1), the sequence of the primers for hybridisation to the genome of the corona-virus MHV-A59 is defined starting from known sequences in said genome; in documents (2) and (3), the sequences of the primers to be used for M13 sequencing are derived from the known sequence of M13.

4. In the Board's judgment, these examples reflect the way in which oligonucleotides complementary to a specific template are in general obtained. The probability that two oligonucleotides happen to be substantially complementary to the termini of an unidentified template from which their sequences are not derived can be ignored as de minimis.

5. Claim 1 relates to a kit comprising amongst other elements, two oligonucleotides, the sequences of which are derived from the sequences of the termini of a specific, albeit undefined template. The skilled person, would have no difficulty in determining which oligonucleotides were comprised within the claimed kit.

Article 54 EPC: novelty

6. Lack of novelty was not an objection raised by the Examining Division on the basis of any of the documents cited in the file. The Board too can see no objection on the ground of lack of novelty over the documents cited.

Article 56 EPC: inventive step

7. In this case there is no document among the cited documents on file which immediately suggests itself as the closest prior art from which to consider the invention now claimed. To apply the problem/solution approach it is thus necessary first to consider what aims the invention now claimed allows the skilled person to achieve, and then to formulate these aims as the problem to be solved, taking care to do this in a way in which the problem might have presented itself at the priority date to the skilled person having no knowledge of the solution now claimed.

8. The achievement of the kit claimed is that it provides means for the detection of specific nucleic acid sequences in a sample. The kit as claimed comprising the two oligonucleotide primers, an agent for polymerisation and means for detecting the amplified nucleic acid sequence, plausibly, on the basis of the numerous examples which are given in the patent specification of the use of the elements of the kit, solves this problem.

9. The problem to be solved can thus fairly be stated as being to provide means for the detection of nucleic acid sequences in a sample.

10. The solution provided by the kit claimed involves the selective amplification in the sample of only the specific template nucleic acid sequence to be detected. This form of the solution is not to be found in the documents on file nor in the common knowledge before the priority date which disclosed that a specific

sequence should be physically separated from other DNA sequences i.e. cloned, before it could be detected, as evidenced in the reference book Maniatis et al., Molecular Cloning; A laboratory Manual, Cold Spring Harbor Laboratory, published in 1982 (cited in the patent application).

11. The Examining Division considered document (2) as the closest prior art. This document describes on page 48 kits for DNA sequencing which contain some but not all of the same ingredients as now claimed. Their use according to the classical method of M13 sequencing (reference 6 in document (2)) does not lead to detection of the template to be sequenced but to the elucidation of its primary structure. The Board can see no reason why a skilled person would consider or derive any help from document (2) when trying to solve the problem as above formulated.

12. Document (3) proposes for sale kits for M13 DNA sequencing which are not so precisely defined as the kits described in document (2). Document (1) discloses a method of preparing cDNAs for the determination of nucleotide sequences of corona viruses. These two documents are as little relevant to inventive step as document (2).

13. Mention should be also made of document (4) cited in the European Search Report which is concerned with repairing in vitro synthesized, incomplete duplex portions of the yeast alanine tRNA gene where one of the strands in the duplex is shorter than the other. The authors show that in the presence of a DNA polymerase, the longer strand acts as a template and

the shorter one acts as a primer so that the shorter one is elongated and the incomplete duplex becomes a fully double-stranded DNA molecule. Radioactive nucleotides are used as means to follow the elongation reaction. At the end of document (4), the following statement is made: "The principles for extensive synthesis of the duplexed tRNA genes which emerge from the present work are the following. The DNA duplex would be denatured to form single strands, This denaturation step would be carried out in the presence of a sufficiently large excess of the two appropriate primers. Upon cooling, one would hope to obtain two structures, each containing the full length of the template strand appropriately complexed with the primer. DNA polymerase will be added to complete the process of repair replication. Two molecules of the original duplex should result. The whole cycle could be repeated, there being added every time a fresh dose of the enzyme...".

14. To the Board it appears that this document (4) published in 1971, some fourteen years before the priority date of the present application, would neither have suggested selective amplification of only the specific sequence to be detected in a sample to a person who had not already thought of it, nor to someone who had thought of it would document (4) have given any reasonable expectation of success that the method there suggested could be adapted to the selective amplification of any specific template nucleic acid sequence to be detected.

15. The board thus concludes that none of the cited prior art renders claim 1, or any of the other claims

obvious.

Article 83 EPC: sufficiency of disclosure

16. Sufficiency of disclosure was not dealt with in the decision of the Examining Division. As the application is a divisional of a now granted parent application which was filed in 1984, any unnecessary lengthening of the procedure which would necessarily result from sending the case back to the first instance is to be avoided. It appears that the necessary information, to the extent that it will ever be present during examination proceedings, is before the Board. The Board in this case exercises the discretion it has under Article 111(1) EPC, to consider itself whether this requirement of the EPC are fulfilled.

17. The description of the patent application, Example 2, part 1 gives the necessary information for the synthesis and characterisation of oligonucleotides complementary to a specific template. Examples 4 and 8 are two of the examples describing the DNA amplification of specific templates using the claimed kit. Means for detecting the amplified sequences are disclosed, in particular in Examples 6 and 11. The requirements of Article 83 EPC are fulfilled.

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 claims 1 to 14 submitted at the oral proceedings on 3 May 1999.

The Registrar: The Chairwoman:

U. Bultmann U. Kinkeldey