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D E C I S I O N
of 6 March 1998

Case Number: T 0902/94 - 3.3.4

Application Number: 89310424.0

Publication Number: 0364255

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:
Multiplex genomic DNA amplification for deletion detection

Applicant:
Baylor College of Medicine

Opponent:
-

Headword:
DNA amplification/Baylor College of Medicine

Relevant legal provisions:
EPC Art. 123(2), 54, 69(1)

Keyword:
"Formal allowability - (yes)"
"Novelty - (yes)"

Decisions cited:
T 0286/83, T 0026/85

Catchword:
-

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Case Number: T 0902/94 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 6 March 1998

Appellant: Baylor College of Medicine
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 6 June 1994 refusing European patent application No. 89 310 424.0 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
J.-C. Saisset

Summary of Facts and Submissions

I. European patent application No. 89 310 424.0 published under No. 0 364 255 with the title " Multiplex genomic DNA amplification for deletion detection" was refused by the Examining Division in a decision dated 12 April 1994 and posted on 6 June 1994.

Originally filed claim 1 read as follows:

"1. A method for simultaneously detecting deletions at a plurality of DNA sequences, comprising the steps of:

treating DNA to form single-stranded complementary strands;

adding a plurality of paired oligonucleotide primers, each pair specific for a different sequence, one primer of each pair substantially complementary to a part of the sequence in the sense-strand and the other primer of each pair substantially complementary to a different part of the same sequence in the complementary anti-sense strand;

annealing the plurality of primers to their complementary sequences;

simultaneously extending said plurality of annealed primers from each primer's 3' terminus to synthesize an extension product complementary to the strands annealed to each primer, said extension products, after separation from their complement, serving as templates for the synthesis of an extension product from the other primer of each pair;

separating said extension products from said templates to produce single-stranded molecules;

amplifying said single stranded molecules by repeating, at least once, said annealing, extending and separating steps; and

identifying said amplified extension products from each different sequence."

Dependent claims 2 to 4 related to further specific features of the plurality of genomic DNA sequences to be detected. Dependent claims 5 and 6 related to the properties and sequences of the plurality of paired primers to be used in the case of X-linked muscular dystrophy. Dependent claim 7 related to the nature of the tissue, the sequences to be tested should be derived from. Dependent claim 8 related to a plurality of specific paired primers to be used in the simultaneous detection of a plurality of genomic DNA sequences. Dependent claims 9 to 17 related to specific DNA sequences from the gene responsible for muscular dystrophy.

II. The decision of the Examining Division was taken on the basis of a set of claims 1 to 18 filed on 12 April 1994. Claim 1 differed from originally filed claim 1 in that the wording "plurality" was replaced by "at least three" and the expression "all primers being subjected to the same conditions" was added to the second characterising feature of the claim. A new claim 9 was introduced which related to further possible embodiements of the method of claim 1. Claims 9 to 17 were renumbered claims 10 to 18.

III. The grounds for refusal were that "the subject-matter of claims 1 to 5 does not meet the requirements of Article 54 EPC. The subject-matter of claim 9 lacks an inventive step under Article 56 EPC. The subject-matter

of claims 10 to 18 does not meet the requirements of Article 84 EPC." A further ground for refusal was lack of unity a posteriori (Article 82 EPC),(see point 3 of the decision).

IV. The reasons given for the decision were as follows:

The method of claims 1 to 5 was not new because it was already disclosed in

Document (3) American Journal of Human Genetics, vol. 43, no. 3 suppl. (1988) Abstract no. (0711) 3.2

where the detection of multiple deletions at the Duchenne muscular dystrophy locus via multiplex genomic DNA amplification (PCR) was performed by combining several sets of primers in a single reaction.

Claim 9 related to the same method as in claim 1, specifying the technical parameters of the extension step, its subject-matter being thus novel over the teachings of document (3). These technical parameters were, however, known from the skilled person at the filing date. Inventive step was, thus, lacking.

Claims 10 to 18 lacked clarity in that they related to DNA sequences which only partly included but were not defined primers to be used in the claimed method.

There was lack of unity a posteriori between the claims relating to the method of claim 1 being performed on different genes, as this method which constituted the link between these claims was not novel.

V. The Appellant lodged an appeal against this decision, paid the appeal fee and submitted a statement of grounds for the appeal.

VI. A communication was sent by the Board according to Article 11(2) of the Rules of Procedure of the Boards of Appeal, setting out the Board's provisional, non binding opinion.

VII. The Appellant sent some further submissions together with affidavits.

VIII. In the course of oral proceedings, the Appellant filed a new set of eight claims as new only request.

Claim 1 of this last set of claims 1 to 8 read:

"1. A method for simultaneously detecting in a sample target DNA sequences, comprising the steps of:

providing in a common reaction vessel the sample in single-stranded form and pairs of oligonucleotide primers, each pair specific for a different sequence, one primer of each pair substantially complementary to a part of the sequence in the sense-strand and the other primer of each pair substantially complementary to a different part of the same sequence in a complementary anti-sense strand;

annealing the pairs of primers to their complementary sequences;

simultaneously extending said pairs of annealed primers from each primer's 3' terminus to synthesize an extension product complementary to the strands annealed to each primer, said extension products, after separating from their complement, serving as templates for the synthesis of an extension product from the other primer of each pair;

separating said extension products from said templates to produce single-stranded molecules of the target sequences;

amplifying said single stranded target sequences by repeating, at least once, said annealing, extending and separating steps; and

identifying whether said amplified extension products have been synthesized from each different sequence, as a measure of the presence or absence of each target sequence, characterized in that:-

the method is adapted to detect simultaneously more than two target sequences by utilising more than two pairs of oligonucleotide primers."

Dependent claims 2 to 8 corresponded to originally filed claims 2 to 8, except for the fact that the expression "a plurality of" was deleted from claims 2, 5, 6 and 8.

IX. The Appellant argued as follows:

With regard to Article 123(2) EPC:

New claim 1 differed from originally filed claim 1 in that the term "plurality" had been replaced by the term "more than two". Although this last expression was not to be found expressis verbis in the application as originally filed, the content of the application left the person skilled in the art in no doubt that the claimed method was to be performed on more than two genomic sequences, with more than two pairs of primers. Evidence for this was to be found, for example, on page 1, line 29, on page 3, line 25 to 32, on page 14, line 24 to 26. In example 8, three different primer pairs were used to screen three different genetic loci. On page 13 line 30, it was contemplated to simultaneously screen four deficiencies. The requirements of Article 123(2) EPC were, thus, fulfilled.

With regard to Article 54 EPC:

Document (3) which was considered by the Examining Division as detrimental to novelty was not enabling and, thus, should not be taken into consideration. Indeed, although it disclosed that the PCR reaction could be carried out starting from a multiplicity of pairs of primers, it did not provide any instructions on how to proceed. In particular, the necessity to use primers with about the same melting temperature, as well as the need to use a high amount of enzyme and to increase the time of reaction were not mentioned. The subject-matter of claims 1 to 8 was, thus, novel.

X. The Appellant requested that the decision under appeal be set aside, and that a patent be granted on the basis of the new set of claims 1 to 8 filed as new only request at the oral proceedings.

Reasons for the Decision

Article 123(2) EPC:

1. The differences between Claim 1 of the request and claim 1 as originally filed which are at issue here are that the terms "a plurality of DNA sequences" and "plurality of paired oligonucleotide primers" have been replaced by the terms "more than two target sequences" and "more than two pairs of oligonucleotide primers". There is no expressis verbis basis in the application as originally filed for these latter expressions.

2. From a purely linguistic point of view, it cannot be doubted that the meaning of the term "plurality" includes the value of "more than two". There, thus, remains to assess whether on a strictly technical

basis, it could be directly and unambiguously derived from the application as filed that the claimed method was to be carried out on more than two genomic sequences, i.e. with more than two primers, although the number of target sequences and pairs of primers was never explicitly defined as being "more than two".

3. On page 1, lines 28 to 30, the invention is defined as the simultaneous analysis of multiple genomic sequences. On page 3, lines 26 to 30, the prior art is discussed in the following terms: "Adding primers for a second sequence is usually possible, but when primers for more than two sequences are added the procedure falls apart. The present application is an improvement on the PCR method and solves the problem encountered when primers for multiple sequences are reacted simultaneously". On page 15, lines 15 to 16: "The number of analysis which can be run simultaneously is unlimited." In example 8, three genetic loci are simultaneously screened with the help of many primers for the presence of deletions.

4. Thus, the Board is satisfied that, in the light of the description, the skilled person would expect that the method of claim 1 relates to simultaneously detecting more than two target sequences by utilising more than two pairs of oligonucleotide primers. Claim 1 has not been amended in such a way as to include subject-matter which is not derivable from the content of the application as filed.

5. The same reasoning applies to dependent claims 2, 4, 6 and 8 where the term "a plurality of" has been deleted.

6. The requirements of Article 123(2) EPC are, thus fulfilled.

Article 54 EPC

7. According to the case law of the European patent office (see for example, T 286/83, OJ EPO 1987,5 or T 26/85, OJ EPO 1990, 22), a prior art document destroys novelty if the subject-matter of the claims in question is disclosed in said document in a way that allows others to reproduce it.

8. The Examining Division decided that the disclosure of document (3) was detrimental to the novelty of the claims 1 to 5.

9. Document (3) is a pre-published abstract by the Appellant which discloses that "multiplex PCRs can be performed by combining several sets of primers, allowing deletion detection at multiple widely dispersed regions of the DMD gene in a single reaction". This abstract is, however, lacking in technical details. It refers to the polymerase chain reaction (PCR) as the basis for developing the multiplex genomic DNA amplification method but no technical instructions are given on how to carry out this last method. Mention is further made of a possible "slight modification of the reaction" and of "further modifications of this technique", but, yet again without specifying of which technical kind these modifications should be. Finally, it is suggested that the method "**should be** applicable to any hemizygous locus.."(emphasis added). In the Board's opinion, these statements are so general that the skilled person was not put in the position to reproduce the abstract's content. Thus, document (3) is not considered enabling.

10. The Board sees no reason to depart from the earlier case law of the Boards of Appeal mentioned in paragraph 8. Thus, in view of the findings in paragraph 9, the conclusion is reached that

document (3) must not be taken into account when assessing the novelty of claims 1 to 8. As no other document on file was considered to be novelty destroying by the Examining Division and the Board sees none either, novelty is acknowledged.

11. There being a new set of claims on file, the requirements for patentability other than formal allowability under Article 123(2) EPC and novelty under Article 54 EPC have not yet been examined by the first instance.

12. In the same manner, sufficiency of disclosure remains to be evaluated. At the present time, the Board does not feel in a position to decide that the technical disclosure in the patent application enables the skilled person to carry out the invention as claimed, in particular, in view of its finding (paragraph 9, above) that the disclosure of document (3) is not enabling.

13. Accordingly, it is considered suitable that the Appellant be given the chance to defend the application before two instances. In accordance to Article 111(1) EPC, the case is, thus, remitted to the first instance for further prosecution.

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 for further prosecution on the basis of the set of claims filed during oral proceedings.

The Registrar: The Chairwoman:

D. Spigarelli U. Kinkeldey