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Datasheet for the decision of 22 September 2005

Case Number: T 0914/04 - 3.3.04

Application Number: 87304433.3

Publication Number: 0246864

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:
Hybridisation probes

Patentee:
BIO-RAD LABORATORIES, INC.

Opponent:
Perkin Elmer Corp.

Headword:
Hybridisation probes/BIO-RAD

Relevant legal provisions:
EPC Art. 54, 111(2), 113(1), 123(2)(3)
EPC R. 57a

Keyword:
"Added subject-matter (no)"
"Broadening of scope of protection (no)"
"Novelty (yes)"

Decisions cited:
G 0004/92, T 0822/98

Catchword:
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Case Number: T 0914/04 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 22 September 2005

Appellant: (Opponent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 11 May 2004 concerning maintenance of European patent No. 0246864 in amended form.

Composition of the Board:

Chairman: R. Gramaglia
Members: G. Alt
R. Moufang

Summary of Facts and Submissions

I. The decision concerns the second appeal proceedings relating to the opposition against European patent No. 0 246 864, which had been granted on the basis of 13 claims and opposed on the grounds of Article 100(a) EPC. Claim 1 as granted read:

"1. A method for discriminating between alternative nucleotide sequences, which method comprises subjecting adjacent segments of a target base sequence to hybridisation with a detectable first nucleotide probe and with a second nucleotide probe, to form a hybrid, the nucleotide sequence of the first and second probe being such that where they form a split probe hybrid with a complementary target sequence they may subsequently be linked, subjecting any hybrid obtained to linkage, and detection of any hybrid obtained;
the DNA sequence of the detectable first nucleotide probe and of the second nucleotide probe being such that a potential mismatch in the target sequence lies either between the said probes or at the terminal end of one of said probes which is contiguous with the other of the said probes;
the method being effected such that a complementary target sequence is discriminated from a target sequence with one or more non-complementary nucleotides."

II. This board of appeal in a different composition had set aside, with decision T 0822/98 of 11 October 2001, the earlier decision of the opposition division revoking the patent and had remitted the case to the department of first instance for further prosecution on the basis

of the then second auxiliary request (claims 1 to 11) filed during appeal oral proceedings before the board.

III. After remittal, the opposition division issued the decision now under appeal, i.e., an interlocutory decision according to which the patent can be maintained on the basis of the third auxiliary request consisting of claims 1 to 10, pages 2 to 13 of an amended description and Figures 1 to 4. This request had been submitted as "Fourth Auxiliary Request" during the oral proceedings on 30 March 2004 and was renumbered in the decision in view of the withdrawal of a higher ranking request.

Independent claims 1, 8 and 9 of this request read as follows:

"1. A method for discriminating between alternative nucleotide sequences, which method comprises subjecting adjacent segments of a target base sequence to hybridisation with a detectable first nucleotide probe and with a second nucleotide probe, to form a hybrid, the nucleotide sequence of the first and second probe being such that where they form a split probe hybrid with a complementary target sequence they may subsequently be linked, subjecting any hybrid obtained to linkage, and detection of any hybrid obtained;
the DNA sequence of the detectable first nucleotide probe and of the second nucleotide probe being such that a potential mismatch in the target sequence lies between said probes;
the method being effected such that a complementary target sequence is discriminated from a target sequence with one or more non-complementary nucleotides.

8. A split probe hybrid comprising a detectable first nucleotide probe and a second nucleotide probe hybridised to adjacent segments of a target base sequence, the detectable first nucleotide probe being capable of linkage to the second nucleotide probe, characterised in that the detectable first nucleotide probe and the second nucleotide probe are hybridised to either side of a variant sequence associated with a disease state or to the corresponding normal sequence.

9. A kit for discriminating between alternative nucleotide sequences according to the method of claim 1, which comprises a detectable first nucleotide probe and a second nucleotide probe, each probe having a nucleotide sequence homologous to adjacent segments of a target sequence, a potential variant sequence being present between said segments; the detectable first nucleotide probe and the second nucleotide probe being such that a potential variant sequence is present between said probes, the kit additionally containing a reagent(s) for linking said probes."

Dependent claims 2 to 7 and 10 related to specific embodiments of the method of claim 1 or the kit of claim 9.

IV. The appellant (opponent) lodged an appeal against this decision of the opposition division.

V. Oral proceedings were held on 22 September 2005 in the absence of the appellant who had informed the board with a letter dated 20 September 2005 that he would not attend. During the oral proceedings the respondent

(patentee) filed a new request (claims 1 to 10; description pages 2 to 13 and Figures 1 to 4), only differing in that the description according to the new request, compared to the revised description as maintained by the opposition division included the re-instatement on page 6, lines 12-13, of the original wording "whereby to denature any oligonucleotide probe hybridised to the target sequence across a base pair mismatch".

VI. The submissions in writing by the appellant, insofar as they are relevant to the present decision, can be summarized as follows:

Article 123(2)(3) EPC

– In the application as filed and the patent as granted, any embodiment which involved the hybridisation of a probe across a mismatch would have been interpreted by the skilled person to encompass a situation in which the mismatch was at the terminal end of the probe.

– The deletion of this embodiment of claim 1 without adequate amendment of the description or clarification of the way in which the gap might be filled had effectively added subject matter and broadened the scope of claim 1 (similar comments applied to independent claims 8 and 9), contravening Article 123(2) and (3) EPC, since the description and claim 1, when read in the light of the description, encompassed embodiments in which a probe hybridised across a mismatch, in which the mismatch was present anywhere within that probe,

not at the terminal end of the probe (see points 7 and 11 below for more details).

Novelty

– Document Dl (EP-A-0 185 494) disclosed on page 6, lines 7-25, a method for diagnosis of genetic abnormalities by the detection of specific sequences in nucleic acids. On page 24, lines 11 to 14 of document Dl it was stated that "similarly a series of probes each adjacent the next could be used to demonstrate the proximity of specific sequences or to increase the size of the ligated probes". This passage disclosed a situation wherein the diagnostic probe hybridised to a portion of a target nucleotide sequence containing a potential mismatch and the contiguous probe bound to a nucleotide sequence contiguous with this DNA stretch containing a potential mismatch, and a further probe bound to a nucleotide sequence on the other side of this mismatch-containing DNA portion (see points 14-16 below for more details). Therefore the above passage led to a lack of novelty of the subject matter of present claim 1.

VII. The submissions in writing and at the oral proceedings by the respondent (patentee), insofar as they are relevant to the present decision, can be summarized as follows:

Article 123(2)(3) EPC

– In decision T 0822/98 (see point 13 of the reasons) it has been ruled that the set of claims of the Second Auxiliary Request then on file (which comprised claims identical to claims 1, 8 and 9 now objected to) fulfilled the requirements of Article 123(2) and (3) EPC. This issue could not be taken up again ("res judicata"), as the facts were identical.

Novelty

– Document D1 did not disclose the presence of a mismatch between the probes.

VIII. The appellant (opponent) has requested in writing that the patent be revoked.

The respondent (patentee) requested that the decision under appeal be set aside and the patent be maintained in amended form on the basis of the new documents (claims: 1 to 10; description: pages 2 to 13; Figures: 1 to 4) filed at the oral proceedings before the board of appeal on 22 September 2005.

Reasons for the Decision

Procedural consequences of the absence of the appellant

1. According to Article 11(3) RPBA, the board shall not be obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral

proceedings of any party duly summoned who may then be treated as relying only on its written case. Furthermore, in the board's judgement, the present decision to maintain the patent on the basis of, inter alia, a description which has been further amended during oral proceedings (see paragraph V supra) in the absence of the appellant does not conflict with the principles laid down in the decision of the Enlarged Board of Appeal G 4/92 (OJ EPO 1994, 149), whereby a decision against a party who has been duly summoned but who failed to appear at oral proceedings may not be based on facts put forward for the first time during those oral proceedings. This is because the re-instated passage on page 6 pertains to the embodiment still claimed. Therefore, the board does not regard this amendment a new fact which would require to delay the proceedings according to the above decision. Moreover, the appellant had reasonably to expect that the respondent would try to bring the description into line with the claims as finally set out in order to comply with the requirements of the EPC, including Rule 57a and Article 84 EPC. Consequently, the absence of the appellant at the oral proceedings did not prevent the board from reaching a decision.

The issues of the appeal

2. The only objections raised by the appellant in the appeal proceedings are those under Article 123(2)(3) EPC and lack of novelty over document D1 (EP-A-0 185 494), as clarity objections against some of the claims on file were not pursued and the board also sees none.

Article 123(2)(3) EPC

3. Claim 1 as granted included two separate embodiments of the claimed method of detection of a potential mismatch in a target sequence with adjacently hybridizing oligonucleotides, namely (i) a method wherein the detectable first nucleotide probe and the second nucleotide probe were such that a potential mismatch in the target sequence lay between said probes and (ii) a method wherein a potential mismatch in the target sequence lay at the terminal end of one of said probes which was contiguous with the other of said probes (see the wording "the DNA sequence of the detectable first nucleotide probe and of the second nucleotide probe being such that a potential mismatch in the target sequence lies either between said probes or at the terminal end of one of said probes which is contiguous with the other of said probes").

4. Claim 1 presently before the board no longer includes embodiment (ii) above, i.e., the case wherein a potential mismatch in the target sequence lies at the terminal end of one of said probes which is contiguous with the other of said probes, so that the patent now only relates to embodiment (i) above, wherein the detectable first nucleotide probe and the second nucleotide probe are such that a potential mismatch in the target sequence lies between said probes.

5. There is no definition in present claim 1 of the size of the gap between the detectable first nucleotide probe and the second nucleotide probe, nor is there any limitation as to how the gap should be filled.

6. One way of filling the gap (see page 6, lines 1 to 29 of the filed patent application as published and page 6, lines 5 to 33 of the revised description) consists in adding a third (or further) probe(s) which hybridise(s) to the target sequence across the potential mismatch between the first detectable polynucleotide probe and the second polynucleotide probe. To distinguish between complementary and non-complementary sequences, the hybrid is subjected to selective denaturation. If one of the probes binds to the target sequence across a mismatch then this probe is selectively denatured. The three or more adjacently hybridized oligonucleotides are then subjected to a linkage reaction. If one of the probes has been denatured then the first and second probes will not be linked. This allows the discrimination between a target sequence containing a mismatch and a target sequence which does not contain a mismatch.

7. The appellant maintains that in the application as filed (see page 3, lines 10-14; page 3, line 25; page 4, lines 21-24) and in claim 1 as granted (c.f. "at the terminal end of one of said probes") any embodiment relating to hybridisation of an oligonucleotide probe across a mismatch, such as the embodiment described in the preceding point, would have been considered by the skilled person to relate to a situation wherein the potential mismatch was **at the terminal end of the probe**. Therefore, in the appellant's view, in the absence of further adequate amendments to the description (e.g. deletion of the passage on page 6, lines 5 to 33 of the description presently on file), present claim 1 may now be interpreted to encompass a situation in which a probe is provided which hybridises across a potential

mismatch which does not need to be at the terminal end of the probe. Hence, the present revised description adds subject matter over the application as filed and claim 1 (similar comments apply to independent claims 8 and 9), when interpreted in the light of said revised description, broadens the scope of the claim 1 as granted.

8. The respondent argues that the "Second Auxiliary Request" then before the board in the first appeal proceedings (T 0822/98), comprising claims identical to claims 1, 8 and 9 now objected to has been found by the then competent board to fulfil the requirements of Article 123(2) and (3) EPC. Thus the issue of whether or not these claims satisfy the requirements of Article 123(2) and (3) EPC could not be taken up again ("res judicata"), as the facts were identical.

9. In decision T 0822/98 (see point 13 of the reasons) it is indeed stated that "No objections under Article 123(2) and (3) EPC were raised by the [then] respondents" (now appellant) against the claims of the Second Auxiliary Request then on file and that "Nor does the board have any such objections".

10. Under Article 111(2) EPC, the department of first instance is bound by the ratio decidendi of the board of appeal if the case is remitted to the department whose decision was appealed insofar as the facts are the same. This binding effect also exists in the framework of subsequent appeal proceedings (see Case Law of the Boards of Appeal of the EPO, 4th edition 2001, page 536 with references to the established case law). However, this binding effect (res judicata)

merely applies to present claims 1, 8 and 9, not to the amended description, which may be used to interpret the above claims, an issue which the previous board did not deal with.

11. It is the appellant's view that the present revised description adds subject matter over the application as filed and claims 1, 8 and 9, when interpreted in the light of said revised description, broaden the scope of the corresponding granted claims. To buttress the above view, the appellant has selected a series of passages from the application as filed (page 3, lines 10-14; page 3, line 25; page 4, lines 21-24) and from claim 1 as granted (c.f. "at the terminal end of one of said probes") for showing that any embodiment relating to hybridisation of an oligonucleotide probe across a mismatch, such as the embodiment described on page 6, lines 5-23 of the patent, would have been considered by the skilled person to relate to a situation wherein the potential mismatch was at the terminal end of the probe.

12. However, the board notes that the above passages have been taken out of longer sentences relating to two **distinct** and **independent** embodiments connected by the term "or" (see page 3, lines 10-14: "the DNA sequence of the detectable first nucleotide probe and of the second nucleotide probe being such that a potential mismatch in the target sequence lies either between the said probes **or** at the terminal end of one of said probes which terminal end is contiguous with the other of said probes"; page 3, lines 22-26: "In the present invention the probes are designed to hybridise to the target sequence on either side of a potential mismatch, there being a gap, preferably a single nucleotide gap,

between the probes **or** the probes may be designed to hybridise to contiguous sequences in the target sequence any potential mismatch being present at the terminal end of one of said probes which terminal end is contiguous with the other probes"; see also page 4, lines 23-24: "the potential variant sequence will be at the terminal end of one of said probes, which terminal end is contiguous with the other of the said probes" in connection with page 4, lines 20-21: "**or** it may be present between the said segments"; see granted claim 1: "the DNA sequence of the detectable first nucleotide probe and of the second nucleotide probe being such that a potential mismatch in the target sequence lies either between the said probes **or** at the terminal end of one of said probes which is contiguous with the other of said probes"; emphasis by the board).

13. Therefore, the board does not adhere to the appellant's view that the skilled person would derive from the application as filed and granted claim 1 the obligatory equation "hybridisation of an oligonucleotide probe across a mismatch = potential mismatch at the terminal end of the probe". Hence, there is no addition under Article 123(2) EPC or broadening under Article 123(3) EPC by deleting one embodiment from the description and from granted claim 1 (which had comprised two separate embodiments connected by the word "or"), resulting in the claims and in the amended description presently before the board.

Novelty

14. Document D1, a document pursuant to Article 54(3) EPC, discloses on page 6, lines 7-25 a method for diagnosis

of genetic abnormalities or other genetic conditions by the detection of specific sequences in nucleic acids. This is done by hybridising a DNA sample with a probe ("the diagnostic probe") complementary to a portion of a target sequence containing the nucleotide mismatch ("the diagnostic portion"; see page 8, line 34 to page 9, line 2), and another probe ("the contiguous probe") complementary to a nucleotide sequence contiguous with the diagnostic portion. The diagnostic probe only remains bound to the sample nucleic acid when it contains a target sequence. The diagnostic and contiguous probes are then covalently attached to yield a target probe which is complementary to the target sequence and the probes which are not attached are removed.

15. On page 24, lines 11 to 14 of document D1 it is stated that "similarly a series of probes each adjacent the next could be used to demonstrate the proximity of specific sequences or to increase the size of the ligated probes".

16. The appellant maintains that the above passage in document D1 discloses a situation wherein the diagnostic probe hybridises to a diagnostic portion of a target nucleotide sequence containing a potential mismatch, the contiguous probe binds to a nucleotide sequence contiguous with the diagnostic portion and a further probe binds to a nucleotide sequence on the other side of the diagnostic portion, i.e., a situation identical to the embodiment set out on page 6, lines 5-27 of the revised description, wherein a probe hybridised to the target sequence across a mismatch, in between a first detectable polynucleotide probe and a

second polynucleotide probe. It is thus the appellant's view that the passage on page 24, lines 11 to 14 of document Dl leads to a lack of novelty of the subject matter of present claim 1.

17. In the board's judgement, however, the above passage of document D1 relates to further aspects of the detection method according to document D1, namely to see if a specific sequence is close to another (if they are, they will ligate, otherwise not) or to increase the size of the ligated probes.

18. But even assuming in the appellant's favour that the skilled person would derive from the above passage that a mismatch is implicitly present in one of the DNA sequences involved, there is no pointer in the above passage in document D1 to the mismatch being between the "detectable first nucleotide probe" and "the second nucleotide probe" as required by claim 1 at issue. On the contrary, the skilled person reading this passage would reasonably assume that the "series of probes each adjacent the next" may be positioned 5'- , 3'- or both to the system represented by the "diagnostic probe"/"second probe" (the latters being in turn possibly situated 5'- or 3'- to each other). Therefore, the above passage conceptually discloses more than the claimed specific embodiment, which remains "hidden", in the sense that it is not directly and unambiguously derivable therefrom.

19. In conclusion, no case of lack of novelty has been made out.

Reformatio in peius

20. The re-instatement by the respondent of the original wording on page 6, lines 12-13 ("whereby to denature any oligonucleotide probe hybridised to the target sequence across a base pair mismatch"; ibidem), is irrelevant for a possible reformatio in peius. This passage in fact merely illustrates the implicit result of subjecting the hybrid obtained to denaturation for discriminating between a complementary target sequence and a complementary target sequence comprising a mismatch (see page 6, line 12). That this discrimination method works via the denaturation of any oligonucleotide probe hybridised to the target sequence across a base pair mismatch is implicit to the skilled person in the light of the patent in suit taken as a whole (see page 3, lines 20-21; page 5, lines 25-30 and claim 6: "no denaturation is effected for a perfectly complementary ...sequence"). Since the deletion of this passage could raise concerns in view of Rule 57a EPC, the passage was re-introduced into the description.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent in amended form on the basis of the following documents:

Claims: 1 to 10 as filed during oral proceedings

Description: pages 2 to 13 as filed during oral proceedings

Figures: 1 to 4 as filed during oral proceedings.

The Registrar: The Chairman:

P. Cremona R. Gramaglia