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**Datasheet for the decision
of 7 June 2011**

Case Number: T 2186/08 - 3.3.08

Application Number: 01944578.2

Publication Number: 1294944

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:

Detection of nucleic acids by type-specific hybrid capture method

Applicant:

QIAGEN Gaithersburg, Inc.

Headword:

Hybrid capture/QIAGEN

Relevant legal provisions:

EPC Art. 56

Relevant legal provisions (EPC 1973):

-

Keyword:

"Main request: inventive step (yes)"

Decisions cited:

T 0650/01

Catchword:

-



Case Number: T 2186/08 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 7 June 2011

Appellant: QIAGEN Gaithersburg, Inc.
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 29 May 2008
refusing European patent application
No. 01944578.2 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: M. Wieser
Members: T. J. H. Mennessier
D. S. Rogers

Summary of Facts and Submissions

- I. The applicant (appellant) lodged an appeal against the decision of the examining division, whereby the European patent application No. 01 944 578.2 with publication number 1 294 944 was refused. The application, entitled "*Detection of nucleic acids by type-specific hybrid capture method*", originated from an international application published as WO 01/96608.
- II. The decision was based on claims 1 to 39 of the main request filed on 11 March 2008 and on the three auxiliary requests filed at the oral proceedings held on 11 April 2008. The requests were refused for reasons of lack of inventive step (Article 56 EPC) in view of document D3, which was considered to represent the closest state of the art, taken together with document D4 (see Section IX, *infra*).
- III. On 8 October 2008, the appellant filed a statement setting out the grounds of appeal which was accompanied by three new auxiliary requests to replace the auxiliary requests refused by the examining division. The main request corresponded to the main request of 11 March 2008. Oral proceedings were requested.
- IV. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal attached to the summons to the oral proceedings, the board expressed its preliminary and non-binding views.
- V. Under cover of a letter dated 4 May 2011, the appellant replied to the board's communication by filing a main

request and two auxiliary requests to replace all the previous requests.

VI. The main request consisted of 26 claims of which claims 1, 2 and 19 read as follows:

- "1. A method of detecting a target nucleic acid comprising:
- a) hybridizing a single-stranded or partially single-stranded target nucleic acid to a capture sequence probe and a signal sequence probe to form double-stranded hybrids between said probes and the target nucleic acid, wherein the capture sequence probe and the signal sequence probe are capable of hybridizing to non-overlapping regions within the target nucleic acid and not hybridizing to each other; wherein said hybridization forms a capture sequence probe and signal sequence probe: target nucleic acid hybrid; and wherein the capture sequence probe is modified with at least one ligand;
 - b) adding a blocker probe to the hybridization reaction, wherein said blocker probe hybridizes to excess non-hybridized capture sequence probes;
 - c) capturing the capture sequence probe and signal sequence probe: target nucleic acid hybrid to a solid phase to form a bound hybrid; and wherein the capturing of the hybrid to the solid phase occurs through capturing of the ligand attached to the capture sequence probe in the hybrid to the solid phase; and
 - d) detecting the bound hybrid."

- "2. A method of detecting a target nucleic acid comprising:
- a) hybridizing a single-stranded or partially single-stranded target nucleic acid to an immobilized capture sequence probe and a signal sequence probe to form double-stranded hybrids between said probes and the target nucleic acid, wherein the immobilized capture sequence probe and the signal sequence probe are capable of hybridizing to non-overlapping regions within the target nucleic acid and not hybridizing to each other; wherein said hybridization forms an immobilized capture sequence probe and signal sequence probe: target nucleic acid hybrid; wherein the capture sequence probe is modified with at least one ligand and wherein the capture sequence probe is immobilized through the ligand,
 - b) adding a blocker probe to the hybridization reaction, wherein said blocker probe hybridizes to excess non-hybridized immobilized capture sequence probes; and
 - c) detecting the immobilized capture sequence probe and signal sequence probe: target nucleic acid hybrid."

- "19. A method of detecting a target nucleic acid comprising:
- a) hybridizing a single-stranded or partially single-stranded target nucleic acid to a capture sequence probe and a bridge probe to form double-stranded hybrids between said probes and the target nucleic acid, wherein the

capture sequence probe and the bridge probe hybridize to non-overlapping regions within the target nucleic acid and not hybridizing to each other; and further wherein a signal sequence probe hybridizes to the bridge probe and not to the target nucleic acid and the capture sequence probe and wherein said hybridization forms a capture sequence probe: target nucleic acid: bridge probe: signal sequence probe hybrid; and wherein the capture sequence probe is modified with at least one ligand;

- b) adding a blocker probe to the hybridization reaction, wherein said blocker probe hybridizes to excess non-hybridized capture sequence probes;
- c) capturing the capture sequence probe: target nucleic acid: bridge probe: signal sequence probe hybrid to a solid phase to form a bound hybrid; and wherein the capturing of the hybrid to the solid phase occurs through capturing of the ligand attached to the capture sequence probe in the hybrid to the solid phase; and
- d) detecting the bound hybrid."

Claims 3 to 18 and 23 to 26 were dependent on claim 1, or claim 2 or both and were directed to particular embodiments thereof. Claims 20 to 22 were dependent on claim 19 and were directed to particular embodiments thereof.

VII. At the oral proceedings, the board informed the appellant that not document D3 but the international application WO 93/10263 (the priority document of which, USSN 07/792,585, was mentioned on page 1 of the

published application at issue), was considered to represent the closest state of the art. The appellant agreed to the introduction into the proceedings of this newly presented document (to be referred to as document B1 in the present decision; see Section VIII, *infra*).

VIII. The following documents are referred to in the present decision:

(B1) WO 93/10263 (published on 27 May 1993)

(D3) US A 5,641,630 (published on 24 June 1997)

(D4) US A 5,681,697 (published on 28 October 1997)

IX. The submissions made by the appellant, insofar as they are relevant to the present decision, may be summarised as follows:

The technical problem to be solved was the provision of a hybridisation assay with improved specificity without sacrificing sensitivity. Document D4 would not have provided any relevant guidance to the skilled person aware of document D3 on how to arrive at the method of claim 1.

The difference between claim 1 and claim 2 was that the capture sequence probe was immobilised in claim 2 prior to the hybridisation step with the effect that the method of claim 2 could be performed directly on the solid support. Said immobilisation of the capture sequence probe had no effect on specificity or sensitivity of the method itself. Specificity was increased by the addition of blocker probes in both

cases. The blocker probe competed with the hybridisation of false targets to the capture sequence probe. The outcome of the methods of claims 1 and 2 was that the hybrid bound to the solid surface via the capture sequence probe was detected by measuring the signal emitted by the signal sequence probe hybridised to the target nucleic acid.

- X. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of claims 1 to 26 of the main request filed under cover of the letter of 4 May 2011.

Reasons for the Decision

Compliance of the main request with the requirements of the EPC

Compliance with Article 123(2) EPC

1. The main request differs from the main request of 11 March 2008 which was considered in the decision under appeal to comply with Article 123(2) EPC in that (i) previous claims 6, 7, 15 to 17, 20, 22, 23, 27, 30, 36 and 37 have been deleted, (ii) the characterising part of claim 33 has been introduced in previous claim 32 (see new claim 22), and (iii) previous claims 4, 38 and 39 have been amended. In claim 4, it has been specified that the solid phase is coated with streptavidin or avidin (see present claim 4); in claim 38, the term "said" has been added before the terms "blocker probes" (see present claim 25); and in claim 39, the nucleic acid probes have been identified

by specifying their nature (capture sequence probes or blocker probes) and by indicating their respective SEQ ID NOs. (see present claim 26).

2. It is the board's view that support exists for each of these amendments in the application published as WO 01/96608, the content of which corresponds to the application as filed (see paragraphs No. 0043 as regards claim 4, 0040 (6 last lines) as regards claim 22, and 0060 (with Tables 3 to 8) as well as 0085 (with Table 27) as regards claim 26). Thus, it is concluded that the main request complies with the requirements of Article 123(2) EPC).

Compliance with Article 84 EPC

3. As a result of the amendments carried out in previous claims 38 and 39, present claims 22 and 23 are now clear. The board concludes that the main request as a whole complies with the requirements of Article 84 EPC.

Compliance with Articles 54 and 83 EPC

4. In respect of the issues of novelty and sufficiency of disclosure, the board sees no reason to depart from the positive conclusion reached by the examining division in point 3.1 of the decision under appeal.

Compliance with Article 56 EPC

5. The assessment of inventive step will be based on the problem-solution approach as developed in the case law of the Boards of Appeal. As a first step, the document considered to represent the closest state of the art is

selected and the technical problem faced by the skilled person starting from that document is defined. The examining division distinguished two different technical problems, each of which was associated with a particular technical feature. It seems that this inappropriate reasoning was made as a consequence of an inaccurate analysis of claim 1 leading to the observation that the signal sequence probe was unlabelled, whereas claim 1 is silent in respect of the presence or absence of a label pre-attached to the probe.

6. It is established case law that the closest state of the art for assessing inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common (see in particular, decision T 650/01, point 4.3 of the Reasons).

7. Document D3 is an American patent granted on a 'continuation application' filed on 27 April 1995 for the same invention claimed in a prior application [USSN 744,800] filed ten years earlier on 13 June 1985, which means that document D3 reflects the technology as it stood for this rapidly evolving technical field in the mid-eighties (note that a corresponding international application [WO 86/07387] claiming the priority of USSN 744,800 was published on 18 December 1986). This technology relies primarily on the use of beads (see all examples) and radioisotopic labels (see Examples 1 to 4).

8. Document B1 is an international patent application filed on behalf of the appellant. It claims the priority of the American application No. 07/792,585 filed on 15 November 1991, which is referred to in paragraph 0003 of the application at issue. One of the inventors of the application at issue, A. Lörincz, also contributed to document B1.
9. Document B1 relates to a more recent technology than document D3, namely the one underlying the "Hybrid Capture II (HC II) assay (Digene)" referred to - for comparison purpose - in the examples of the application at issue (see in document B1, the method of claim 1, pages 26 to 27 and Figure 1, using a microtiter plate as the solid support instead of a test tube as described on page 11, lines 21 to 23).
10. Furthermore, document B1 and the application at issue serve the same purpose, namely the development of methods for the detection of contaminant viral nucleic acids, such as human papillomavirus or human herpesvirus DNAs in clinical specimens, which are suitable for effective routine use in laboratories.
11. Therefore, the board is of the view that document B1 is a more appropriate document than document D3, the document selected by the examining division. Thus, document B1 qualifies as the closest state of the art.
12. The technical problem faced by the skilled person starting from document B1 may be seen in the provision of a method having improved specificity when compared with the method of document B1 - with a reduction of

cross-reactivity - without sacrificing sensitivity. The solution thereto is the method of claim 1.

13. A primary distinguishing feature between the method of claim 1 and the method of document B1 is that, for the capture on the solid support of the double-stranded hybrids formed between the target nucleic acid and the signal sequence probe, the method of claim 1 employs an oligonucleotide (capture sequence probe) whereas the method of document B1 uses an immobilised antibody prepared against the said hybrids. Another essential distinguishing feature is the use in the method of claim 1 of a blocker probe.

14. Both the blocker probe and the capture sequence probe contribute to the solution to the problem as defined above as illustrated by Examples 8 and 9 of the application at issue (see WO 01/96608). Example 9 (see page 32 to 33) shows that background effects which can produce false-positive are reduced, as target capture is exclusively a function of hybridisation to the capture sequence probes, Example 8 emphasizes the role of the blocker probes in preventing non-specific hybridisation of the capture sequence probes to non-targeted nucleic acids (see more particularly lines 17 to 19 on page 30, where the results of Table 14 are commented, and from lines 30 on page 31 to line 2 on page 31, where the results of Table 15 are commented). Thus, the board is satisfied that the technical problem is solved.

15. The question to be answered is whether the skilled person would have found in the state of the art any incitation to modify, without exercising any inventive

activity, the method of document B1 and would have arrived at the method of claim 1 in an obvious way. Document D3 is not relevant as it does not disclose any of the two distinguishing features noted at point 9 (see *supra*). Nor is document D4 (the other document cited by the examining division in the decision under appeal) relevant, as it relates to assays that used the branched chain DNA signal amplification technology. The method of claim 1 does not rely on this peculiar technology which is built on a series of hybridisation reactions resulting in a 'sandwich' complex of probes and target sequence (see Figures 1 to 8 of document D4). A review of the other documents cited during the written phase of the examination leads the board to the conclusion that they do not contain any teaching which would have suggested to the skilled person to modify the method of document B1 by replacing the capture antibody by a capture oligonucleotide and by adding a blocker probe.

16. Thus, the board reaches the conclusion that the method of claim 1 involves an inventive step. Although the methods of claims 2 and 19 are not exemplified in detail in the application at issue, the board sees no reason not to accept the concept that the blocker probes and the capture sequence probes as referred to in claims 2 and 19 would function in the same way as in the method of claim 1 and would allow the achievement of the same improvements as compared to those achieved with the method of claim 1. Thus, the board concludes that also the methods of claims 2 and 19 involve an inventive step and that, therefore, as the rest of claims are dependent claims, the main request as a whole complies with the requirements of Article 56 EPC.

Adaptation of the description

17. At the oral proceedings the appellant adapted the description to the main request. The board is satisfied that the description was satisfactorily amended in accordance with the EPC.

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 in the following version:

Description:

Pages 1 and 1a as submitted at the oral proceedings on
7 June 2011

Pages 2 to 49 of the application as published

Claims:

No. 1 to 26 of the main request filed under cover of
a letter dated 4 May 2011

Drawings:

Figures 1 to 7 of the application as published

Sequence listing:

Pages 1 to 42 filed under cover of a letter dated
19 April 2004

The Registrar

The Chairman

A. Wolinski

M. Wieser