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Datasheet for the decision of 19 January 2016

Case Number: T 1252/11 - 3.3.08

Application Number: 00926204.9

Publication Number: 1196630

IPC: C12Q1/68

Language of the proceedings: EN

Title of invention:
DETECTION OF NUCLEIC ACID REACTIONS ON BEAD ARRAYS

Patent Proprietor:
Illumina, Inc.

Opponents:
Roche Diagnostics GmbH
BioArray Solutions Ltd

Headword:
Bead arrays/ILLUMINA

Relevant legal provisions:
EPC Art. 56, 83, 84, 111, 123(2)
EPC R. 80
RPBA Art. 13

Keyword:
New main request - admitted into the proceedings
Amendment occasioned by a ground for opposition (yes)
Clarity (yes)
Added matter (no)
Sufficiency of disclosure (yes)
Inventive step (yes)
Remittal for adaptation of the description

Decisions cited:
T 1808/06

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

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Case Number: T 1252/11 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 19 January 2016

Appellant: (Opponent 01)	Roche Diagnostics GmbH Sandhofer Strasse 116 68305 Mannheim (DE)
Representative:	Bösl, Raphael Konrad Isenbruck Bösl Hörschler LLP Patentanwälte Prinzregentenstraße 68 81675 München (DE)
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Party as of right: (Opponent 02)	BioArray Solutions Ltd 35 Technology Drive Suite 100 Warren NJ 07059 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 4 April 2011 concerning maintenance of the European Patent No. 1196630 in amended form.**

Composition of the Board:

Chairman	M. Wieser
Members:	M. R. Vega Laso
	D. Rogers

Summary of Facts and Submissions

I. European patent No. 1 196 630 with the title "Detection of nucleic acid reactions on bead arrays" was granted on European patent application No. 00926204.9, which had been filed as international application under the PCT and published as WO 00/63437 (in the following "the application as filed"). The patent was granted with 26 claims.

II. Two oppositions to the grant of the patent were filed relying on the grounds for opposition under Article 100(a) in conjunction with Articles 54 and 56; and Article 100(c) EPC. Opponent 01 relied also on the ground for opposition under Article 100(b) EPC.

III. In an interlocutory decision under Article 101(3)(a) and 106(2) EPC posted on 4 April 2011, an opposition division of the European Patent Office found that, account being taken of the amendments introduced into claims 1 to 24 according to the main request then on file and the amended description filed during the oral proceedings, the patent and the invention to which it relates met the requirements of the EPC.

IV. Opponent 01 (appellant) lodged an appeal against the interlocutory decision of the opposition division and submitted a statement setting out the grounds of appeal. The patent proprietor (respondent) replied to the statement of grounds of appeal. Both parties requested oral proceedings as a subsidiary request. Opponent 02 (party as of right) did not make any submissions.

V. The board summoned the parties to oral proceedings. In a communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) attached to the

summons, the board expressed a provisional opinion on some substantive issues to be discussed at the oral proceedings, in particular issues relating to Articles 123(2), 83 and 56 EPC and the adaptation of the description.

VI. Under cover of a letter dated 7 January 2016 in response to the board's communication, the respondent submitted amended claims 1 to 24 as auxiliary request. Neither the appellant nor the party as of right made substantive submissions.

VII. Oral proceedings were held on 19 January 2016 in the presence of the appellant and the respondent. Although duly summoned, the party as of right was not represented. During the oral proceedings, the respondent withdrew the set of claims filed together with the statement of grounds of appeal and re-filed the claims according to the auxiliary request as its new main request.

VIII. Claim 1 of the main request reads now as follows:

"1. A method of sequencing a plurality of target nucleic acids each comprising a first domain and an adjacent second domain, said second domain comprising a plurality of detection positions, said method comprising:

a) providing a plurality of hybridization complexes each comprising a target sequence and a sequencing primer that hybridizes to the first domain of said target sequence wherein said hybridization complexes are attached to sites on an array, said array comprising at least a first substrate with a surface comprising individual sites;

b) extending each of said primers by the addition of a first nucleotide to the first detection position using a first enzyme to form an extended primer; and

c) detecting the release of pyrophosphate (PPi) to determine the type of said first nucleotide added onto said primers, wherein said release of PPi is detected by secondary enzymes, said second enzymes being attached to said sites on said array,

wherein said hybridization complexes are attached to microspheres, said microspheres being associated with discrete individual sites on said surface of said substrate."

Dependent claims 2 to 13 are directed to variants of the method according to claim 1. Claims 14 to 23 relate to kits for nucleic acid sequencing. Dependent claim 24 relates to a specific embodiment of the method or the kit as defined in the previous claims.

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

(5): US 4,971,903, published on 20 November 1990;

(6): E. D. Hyman, 1988, Analytical Biochemistry, Vol. 174, pages 423 to 436;

(7): WO 98/40726, published on 17 September 1998;

(8): WO 98/13523, published on 2 April 1998; and

(18): B. A. Barshop et al., 1991, Analytical Biochemistry, Vol. 197, pages 266 to 272.

X. The submissions made by the appellant concerning issues relevant to this decision, were essentially as follows:

Admission of the set of claims according to the main request into the proceedings

There was no doubt that the claims according to the main request had been filed late. Since they were not clearly allowable, in particular with regard to Rule 80 and Article 84 EPC, the board should not admit them into the proceedings.

Rule 80 EPC

The introduction of the word "*said*" in step c) of the method of claim 1 was not occasioned by any ground for opposition, contrary to the requirement of Rule 80 EPC.

Article 123(2) EPC

The opposition division erred in finding that there was a basis in the application as filed for a method of sequencing a plurality of target nucleic acids which does not involve the use of a capture probe. In the section "Attachment of Target Sequences to Arrays" starting on page 91 of the application as filed, several methods for the attachment of target sequences to microspheres distributed on a surface of a substrate were disclosed, in particular a direct attachment using a capture probe and an indirect attachment using a so-called capture extender probe. It was stated in the passage on page 93, lines 19 to 20 that, in one embodiment, capture probes were not used and the target sequences were attached directly to the sites on the array. The term "directly" was used with respect to two

different embodiments, and had no clear and unambiguous meaning. As regards a method of sequencing nucleic acids, only the attachment of the target sequences by means of adapters (see page 91, lines 13 to 15 and Figure 1C), or the use of a capture probe comprising a sequencing primer (see page 93, lines 17 to 19) were disclosed in the application as filed.

There was no basis in the application as filed for hybridization complexes attached to sites of an array. The description clearly discriminated between the terms "hybridization complex" and "target sequence". Attachment to the surface of an array or to microspheres distributed on the surface of the array was disclosed in the application only in connection with the target sequences. Thus, Article 123(2) EPC was contravened.

Article 84 EPC

It was unclear to which of the sites recited in claim 1, step a) the amended feature "*... second enzymes being attached to said sites on said array, ...*" referred. Due to this ambiguity, claim 1 offended against Article 84 EPC.

Article 83 EPC

The requirements of Article 83 EPC were not fulfilled. The patent did not disclose how a support comprising microspheres having attached both hybridization complexes and secondary enzymes could be produced. Moreover, the problem of sequencing a plurality of target nucleic acids was not solved in case of randomly distributed microspheres because claim 1 did not specify that a coding/decoding process had to be used. This was an essential feature.

Article 56 EPC

Document (8) as the closest state of the art

Document (8) disclosed an array-based DNA pyrosequencing method for real-time sequencing of a plurality of samples in parallel. The target nucleic acids were bound to discrete individual sites on the surface of a solid support which could comprise also particles or microspheres.

Starting from document (8), the objective technical problem was the provision of an alternative method of sequencing a plurality of target nucleic acids using the PPi-base sequencing-by-synthesis method. The solution proposed in the claims was obvious in view of document (18) which described luminescent immobilised enzyme test systems for inorganic pyrophosphate. A person skilled in the art would have combined the teachings of documents (8) and (18) because both documents concerned the detection of pyrophosphate with the help of a pyrophosphatase and a luciferase in a continuous process, and both referred to automated systems.

Document (5) or (6) as the closest state of the art

Documents (5) and (6) described a pyrosequencing method using a column instead of an array. Confronted with the problem of providing an alternative method of sequencing a plurality of nucleic acids using a PPi-based sequencing method, a person skilled in the art would combine the method of document (5) or (6) with the teaching of document (8) in view of document (18). The technical effect underlying the claimed invention,

i.e. the sequencing of a plurality of nucleic acids with an increased reaction rate, was already known to the skilled person from documents (8) and (18). There was no additional technical effect associated with the use of microspheres for binding the target nucleic acids. Microsphere-based fibre optic sensors were anyway known from document (7). Thus, the subject-matter of claim 1 did not involve an inventive step.

XI. The respondent's submissions, insofar as they are relevant to the present decision, may be summarised as follows:

Admission of the set of claims according to the main request into the proceedings

The new main request differed from the request considered allowable by the opposition division in that it included the word "*said*" in step c) of claim 1, so as to clarify the location of the sites occupied by the secondary enzymes. This amendment was introduced not only in order to overcome an objection under Article 123(2) EPC, but also in view of an issue raised by the board in the context of inventive step. The amendment was clear and straightforward and did not give rise to any new objections. No issues of lack of procedural fairness could arise by admitting the new main request.

Article 123(2) EPC

Claim 1 was entirely consistent with the content of the application as filed and therefore compliant with the provisions of Article 123(2) EPC. The passage on page 91 of the application clearly emphasized that most (but not all) of the described methods relied on capture probes.

An unambiguous disclosure that a capture probe need not be used for attaching the target nucleic acid to an array site was provided in the passage on page 93, lines 19 and 20. Attachment via a capture probe was only a preferred embodiment. It was stated in the passage on page 91, line 5 of the specification that the attachment may be direct or indirect. Direct attachment included those situations wherein an endogenous portion of the target sequence hybridized to the capture probe, or where the target sequence had been manipulated to contain exogenous adapter sequences that were added to the target sequence, e.g., during an amplification reaction.

In the passage on page 82, paragraph 2 of the application as filed, there was a clear reference to the target sequences including the first and second domains. Since the sequencing primer hybridized to the target sequence forming a hybridization complex with the first domain, there could be no doubt that the hybridization complexes had to be attached to the sites of an array.

Article 83 EPC

Detailed explanation of how both the random and non-random distribution of microspheres would be implemented in the method of the invention was given in the specification on pages 97 and 101, whilst the way in which the secondary enzymes may be attached to sites on the array in a manner which enabled the claimed invention to operate was set out at page 88, lines 1 to 15. The description of how the hybridization complexes were attached was set out on pages 99 and 100. In the absence of any data indicating that these teachings did not work, allegations of lack of sufficient disclosure were unconvincing.

Article 56 EPC

Document (8) as the closest state of the art

Starting from document (8), the technical problem to be solved was the provision of an improved sequencing method for a plurality of nucleic acid sequences. The solution proposed in claim 1 was not obvious to a person skilled in the art in view of the teaching of document (18). The technology described in this document was based on a continuous flow of substrate through the immobilised enzymes in a column. No reference was made to using this technology in conjunction with DNA sequencing, let alone on arrays for DNA sequencing. It was only with hindsight that the teaching of documents (8) and (18) would have been combined. But even if it were to be considered that the skilled person would have done so, it would not have resulted in the claimed invention. Thus, the objection of lack of inventive step was not justified.

Document (5) or (6) as the closest state of the art

Document (5) taught the provision of a series of columns in which a nucleic acid template was extended in one of the initial columns, whilst detection of the sequence occurred in the final column. Document (6) disclosed a method in which the hybridization complex and all secondary enzymes were bound in columns. Neither of these documents disclosed an array or a system that could be used to sequence a plurality of nucleic acids. Thus, documents (5) and (6) could not constitute the closest state of the art.

Nevertheless, if either of these documents were to be used as the starting point for assessing inventive step, the technology described therein was so fundamentally different from that of the present invention that the skilled practitioner would have never considered altering the precisely ordered capillaries and columns by replacing them with arrays. Document (18) provided no motivation to do so. A combination of the teachings of document (5) or (6) with those of document (8) clearly relied upon hindsight analysis. Thus, the claimed subject-matter was indeed inventive.

XII. The appellant (opponent 01) requested that the decision under appeal be set aside and the patent be revoked.

XIII. The respondent (patent proprietor) requested that the decision under appeal be set aside and the patent be maintained on the basis of claims 1 to 24 of the main request filed at the oral proceedings before the board on 19 January 2016.

Reasons for the Decision

Admission of the set of claims according to the main request into the proceedings (Article 13 RPBA)

1. The set of claims according to the respondent's main request is identical to the claims filed as an auxiliary request in response to the board's communication under Article 15(1) RPBA. Since these claims must be regarded as an amendment to the respondent's case after it had filed its reply to the grounds of appeal, it is at the board's discretion to admit and consider them (see Article 13(1) RPBA).

2. The board, exercising its discretion taking into account the criteria specified in Article 13(1) and (3) RPBA, decides to admit and consider the amended claims of the main request. While the appellant is right when saying that these claims could have been filed at an earlier stage of the proceedings, the board holds that the sole amendment introduced into the feature "*... said secondary enzymes being attached to said sites on said* array" in step c) of the method of claim 1, neither increases the complexity of the case nor raises any issues which the board or the other parties cannot reasonably be expected to deal with without adjournment of the oral proceedings. Thus, the admission of the amended claims into the appeal proceedings does not run contrary to the need for procedural efficiency.

Rule 80 EPC and Article 84 EPC

3. The findings in the decision under appeal concerning amendments introduced into the claims during opposition proceedings (see section 3.1 of the decision) have not been contested by the appellant.

4. As regards the objection under Rule 80 EPC to the amendment introduced into claim 1 of the present main request, the board does not share appellant's view that the insertion of the wording "*said* [sites]" in step c) of the claimed method has not been occasioned by a ground for opposition.

5. In its statement of grounds of appeal (see page 5, section (c) of the statement), the appellant raised an objection under Article 123(2) EPC arguing that, while the passage on page 87, lines 24 to 34 of the application on file read "*... said secondary enzymes being attached to* ***the*** *sites on said array*" (emphasis

added by the board), the article "*the*" had been omitted in step c) of the method claimed in claim 1 of the main request then on file.

6. Moreover, in its communication under Article 15(1) RPBA the board indicated that the feature in step c) lacked a clear reference to the sites to which the hybridization complexes are attached. In the board's provisional view, this issue could be relevant to the assessment of inventive step (Article 56 EPC), in particular with regard to the question whether or not the technical effect purported to be achieved ("... *increased concentration of the required enzymes is obtained in the immediate vicinity of the reaction ...*"; see column 76, lines 43 and 44 of the patent in suit) would be in fact achieved if the secondary enzymes were not attached to the substrate at sites in the immediate vicinity of the hybridization complexes (see section 17 of the communication).

7. In view of the above, the board holds that the amendment introduced into claim 1 of the present main request has been occasioned by either, or both, of the objection(s). These objections are grounds for opposition under Article 100 EPC.

8. As regards the appellant's further objection that, as a result of the introduction of the wording "*said*" in step c), claim 1 does not meet the clarity requirement of Article 84 EPC, the board disagrees. The wording "*... attached to said sites on said array*" in step c) of the method of present claim 1 clearly refers to the wording "*... said hybridization complexes are attached to sites on an array*" in step a). Contrary to appellant's view, the board cannot see any ambiguity in

this respect. Hence, the objection under Article 84 EPC is not justified.

Article 123(2)(3) EPC

9. In the decision under appeal, the opposition division found that the subject-matter of the amended claims according to the main request did not extend beyond the content of the application as filed, and that the scope of the claims as granted had not been extended (see section 3.2.4 of the decision).

10. In appeal proceedings, the appellant contested the findings of the opposition division concerning the alleged omission of the feature "capture probe" in step a) of claim 1.

11. The board shares the opposition division's view that a person skilled in the art would not derive from the application as filed that the use of capture probes in the sequencing method disclosed therein was compulsory. For instance, claims 9 and 10 of the application as filed do not require a capture probe for the attachment of the hybridization complexes to a surface of a substrate. Moreover, in the description of the application as filed various possibilities for the attachment of the target sequences to the surface of an array are disclosed. In particular, in the passage starting on page 93, line 19 it is disclosed that the target sequences (and, consequently, the hybridization complexes) are attached directly to the sites of the array. It is apparent from the passage bridging pages 93 and 94 that the attachment can be effected by, e.g., incorporating biotinylated nucleotides into the nucleic acids and coating the microspheres with streptavidin. Chemical crosslinking is also contemplated (see page 94,

line 15). In view of this disclosure, the board cannot accept the appellant's argument that the use of the term "directly" must be restricted to the attachment via a capture probe.

12. Nor can the board accept the appellant's argument that the attachment of the hybridization complexes to sites on an array as specified in claim 1 has no basis in the application as filed. Attachment of the target sequences to the sites of an array is – undisputedly – disclosed in the application as filed (see section "Attachment of Target Sequences to Arrays" starting on page 91). Since the hybridization complexes are formed by hybridization of the sequencing primer to the target sequence, this implies that also the hybridization complexes must be attached to those sites.

13. In view of the above, the board concludes that appellant's objections under Article 123(2) EPC are not justified.

14. The opposition division's findings on Article 123(3) EPC were not contested in appeal proceedings.

Article 83 EPC

15. In its statement of grounds of appeal, the appellant contested the opposition division's findings on Article 83 EPC (see section 3.3 of the decision under appeal) relying on essentially the same arguments as in opposition proceedings.

16. As regards the appellant's argument concerning the allegedly insufficient disclosure of an attachment of the hybridization complexes and the secondary enzymes to one and the same bead, the opposition division referred

to the passage on page 88, lines 2 to 15 of the application as filed describing the attachment of enzymes to array sites either directly or using flexible linkers. Attachment of the target sequences to the array is described in the passage from page 91, line 1 to page 94, line 17. The appellant has not brought forward any verifiable facts that would preclude attachment of hybridization complexes and secondary enzymes to the same bead using the methods disclosed in the application as filed.

17. It is, in the board's view, doubtful whether the appellant's further objection based on the absence in the claims of an - allegedly essential - feature requiring an encoding/decoding process may be regarded as an objection of lack of sufficient disclosure in the application as filed. But even if so, the board observes that encoding/decoding systems which can be used for random arrays are disclosed in the passage starting on page 101, line 14 of the application as filed.

18. The board therefore concludes that appellant's objections under Article 83 EPC are not justified.

Article 54 EPC

19. The findings in the decision under appeal on the issue of novelty were not contested by the appellant, and the board has no reason to doubt that these findings are correct.

Article 56 EPC

Document (8) as the closest state of the art

20. Document (8) describes a "real time" method of sequencing DNA, based on the detection of base incorporation by the release of pyrophosphate (PPi) which is detected enzymically, e.g. by the generation of light in the luciferase-luciferin reaction. The method allows rapid detection and provision of sequence information. This is achieved by using, in place of dATP, a dATP analogue which does not interfere with the luciferase reaction, and by performing the chain extension and detection, or signal-generation, reactions substantially simultaneously, by including the PPi-detection enzymes in the polymerase reaction step (see page 3, first full paragraph, and page 4, second and third full paragraphs). The DNA may be attached, directly or indirectly, to a solid support which may take the form of microtitre wells or comprise particles, fibres or capillaries (see paragraph bridging pages 8 and 9).

21. In a particular embodiment of the sequencing method, an array format is used. Samples are distributed over a surface, for example a microfabricated chip, allowing analysis of many samples in parallel. The solution containing the enzymes and one nucleotide flows over the surface and the signal produced by each sample is detected (see paragraph bridging pages 14 and 15).

22. In the decision under appeal, the opposition division found that the method of claim 1 as then on file differed from that described in document (8) in that (i) the secondary enzymes, i.e. the enzymes required for detecting PPi, are attached to sites on the array and

(ii) the hybridization complex is attached to microspheres associated with discrete individual sites on said array (see section 3.5.4.4 of the decision). According to present claim 1, the secondary enzymes are attached to the sites on the array where the hybridization complexes are attached.

23. As indicated in the passage on page 87, lines 28 to 30 of the application as filed, the technical effect associated with this feature is a faster reaction rate for detection, and the use of less enzyme. This is to be regarded as an improvement over the method of document (8). Hence, the objective problem to be solved is not to provide an alternative sequencing method - as the appellant argued -, but rather to provide an improved sequencing method for a plurality of nucleic acid sequences, as the opposition division stated in the decision under appeal (see page 20, second paragraph).

24. Even though the application as filed does not include experimental data showing that this technical problem is in fact solved by the method of claim 1, it is, in the board's view, credible that co-immobilization of the hybridization complexes and the secondary enzymes at the same sites results in a faster reaction rate for detection of PPi, and evidence to the contrary has not been brought forward, either in opposition or appeal proceedings.

25. In the appellant's view, the solution proposed in claim 1 was obvious in view of document (18). This document describes a luminescent immobilized enzyme test system for the detection of PPi using a column filled with Sepharose beads on which a pyrophosphatase (e.g. ATP sulfurylase) and firefly luciferase are co-immobilised, and a continuous flow of saturating

concentrations of substrate through the column. The sample containing PPi is injected in the system and luminescence is detected using a luminometer (see Figure 2). The system is said to allow for automation (see lines 10 to 12 of the abstract). It is stated on page 271, right-hand column:

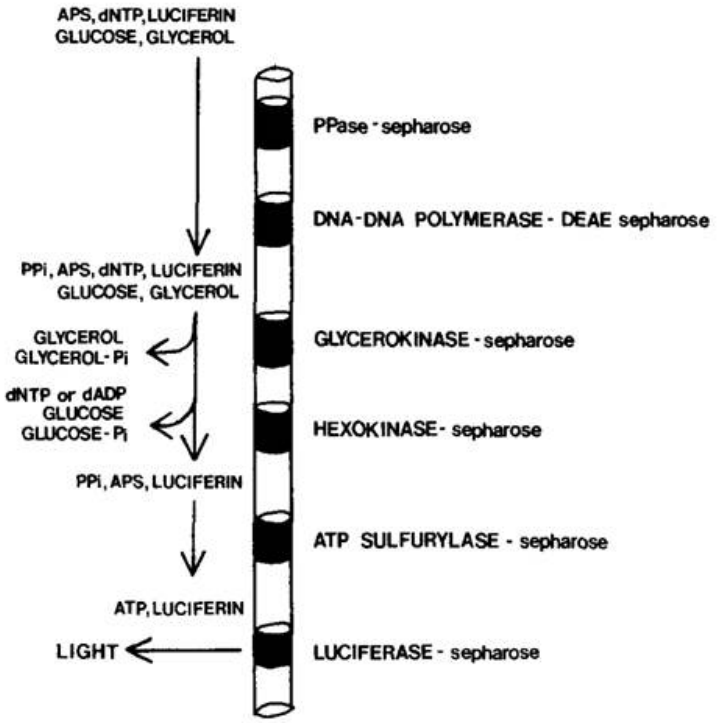
"*The catalytic responsiveness of a system of enzymes that carry out consecutive reactions is significantly greater when they are coimmobilized than when they are free in solution, as reflected in the rapidity with which the steady-state rate is attained (21) and in the overall reaction rate when the first reaction is reversible (22). This is assumed to be due to the spatial proximity of the coimmobilized enzymes and the high local concentration of the intermediate that arises because of the diffusional resistances within the unstirred solvent layers (23).*"

26. It should be noted that the statements in this passage of document (8) are of a general nature and do not specifically relate to the enzymes involved in PPi detection. A person skilled in the art could possibly derive from this passage that co-immobilisation of the two enzymes involved in the PPi detection reaction onto Sepharose beads may result in a greater catalytic responsiveness and a faster reaction rate. However, neither in this passage nor anywhere in document (8) is it suggested to immobilise the enzymes on an array at the sites where the hybridization complexes are attached, i.e. where PPi is released during the sequencing reaction. Thus, even if the skilled person had combined the teachings of documents (8) and (18), he/she would have not arrived at the method of present claim 1 without applying inventive skills. Hence, in view of these two documents the subject-matter of

claim 1 is considered to involve an inventive step within the meaning of Article 56 EPC.

Document (5) or (6) as the closest state of the art

27. Both documents (5) and (6) describe the same method of sequencing DNA which is based on measuring of the PPi generated by a polymerisation reaction and makes use of a series of precisely ordered capillary columns each containing an enzyme covalently attached to Sepharose 4B. Document (6) is a scientific publication published in 1988 and document (5) the corresponding US patent granted and published two years later. A schematic diagram of the DNA sequencer used in the method is shown in Figure 1 of either document (5) or (6):



28. In the decision under appeal (see section 3.5.4.2), the opposition division held that the method described in

documents (5) and (6) differs from the method of claim 1 as then on file in that (i) the hybridization complexes are not attached to microspheres associated with individual sites on a solid support, in particular an array and (ii) the secondary enzymes (e.g. ATP sulfurylase and luciferase) are not attached to sites on the same array, but to different solid supports, specifically columns. The opposition division observed that the technical effect underlying the method of the present invention, i.e. an increased reaction rate resulting from the secondary enzymes being attached in immediate vicinity of the polymerisation reaction, could not be achieved by applying the method of documents (5) and (6). Nor could this method be applied to the sequencing of a plurality of target nucleic acids in parallel. This applies, *mutatis mutandis*, also to claim 1 of the present main request.

29. In the view of the opposition division, starting from document (5) and/or (6) the problem to be solved was to provide a method of sequencing a plurality of target nucleic acids using the PPi-based sequencing-by-synthesis with an increased reaction rate. The board agrees. As stated in paragraph 24 above, from a technical point of view - and in the absence of any evidence to the contrary - it is credible that the method proposed in claim 1 solves this technical problem.

30. The sole issue that remains to be considered is whether or not the proposed solution was obvious to a person skilled in the art. The board notices that in the passage bridging pages 434 and 435 of document (6) various suggestions are made as to how to improve the method described therein. This passage reads:

"*Other areas of research can improve this method. Solid support matrixes such as silica gel or glass beads may allow faster flow rates that will decrease the sequencing time. An analog of dATP that is normally incorporated into the DNA by the polymerase but is unable to bind to luciferase or development of a luciferase that shows greater substrate specificity would clearly be useful. Another possible area of investigation is development of a solid support, coupled to a mixture of luciferase and ATP sulfurylase, which is also able to bind the DNA sample. The entire sequencing could be carried out in one column. The use of chain-terminating nucleotides to keep sequencing in phase for more complicated templates should be investigated.*"

31. This passage merely hints at a possible development of a single **column** to which a mixture of secondary enzymes as well as the DNA sample is attached. However, there is no suggestion whatsoever as regards the use of an array having individual sites to which the DNA samples and the secondary enzymes are attached. Even if, as the appellant contended, a person skilled in the art could have resorted to other pieces of prior art, such as documents (8) and/or (18), for the reasons given in paragraph 26 above he/she would not have arrived at the claimed invention without applying inventive skills. In the board's view, the appellant's line of argument on lack of inventive step relying on a combination of up to four different documents (documents (5)/(6), (8), (18) and (7) (see section X above) is clearly tainted with hindsight.

32. Summarising the above, the board concludes that, in view of the documents relied upon by the appellant in appeal proceedings, its objection of lack of inventive step is not justified.

Adaptation of the description – Remittal (Article 111 EPC)

33. Since the claims according to the main request on file have been found to meet the requirements of the EPC, the board decides to remit the case to the opposition division for adaptation of the description to the amended claims.

34. In accordance with the jurisprudence of the Boards of Appeal (see e.g. decision T 1808/06 of 14 February 2008; see section 2 of the Reasons), Article 84 EPC is to be taken into account for the adaptation of the description (see Article 84 EPC, second sentence: "[The claims] *shall ... be supported by the description*"). Inconsistencies between the claims and the description must be avoided, and references to embodiments which are not encompassed by the amended claims should normally be deleted.

Conclusion

35. In view of the findings above, the appellant's request to revoke the patent must fail.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent upon the basis of claims 1 to 24 of the main request filed at the oral proceedings before the board on 19 January 2016 and a description to be adapted.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated