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Datasheet for the decision of 3 November 2009

Case Number: T 1338/06 - 3.3.08

Application Number: 95923921.1

Publication Number: 0804731

IPC: G01N 33/543

Language of the proceedings: EN

Title of invention:
Method and apparatus for fabricating microarrays of biological samples

Patentee:
The Board of Trustees of the Leland Stanford Junior University

Opponents:
Abbott Molecular Inc.
Sheard, Andrew Gregory
Glaxo Group Limited

Headword:
Microarray/LELAND STANFORD JUNIOR UNIVERSITY

Relevant legal provisions:
RPBA Art. 15(3)

Relevant legal provisions (EPC 1973):
EPC Art. 54, 56, 87, 123(2)(3)
EPC R. 57a

Keyword:
"Documents (33) to (36) - not admitted"
"Added matter - no"
"Priority - no (claims 13 and 14)"
"Novelty - yes"
"Inventive step - yes"

Decisions cited:
G 0002/98

Catchword:
-

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Case Number: T 1338/06 **-** 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 3 November 2010

Appellant I: (Patent Proprietor)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 29 March 2006 concerning maintenance of the European patent No. 0804731 in amended form.

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
C. Rennie-Smith

Summary of Facts and Submissions

I. European patent No. 0 804 731 with the title "Method and apparatus for fabricating microarrays of biological samples" was granted on European patent application No. 95 923 921.1 (published as WO 95/35505), which was filed as PCT/US95/07659 on 16 June 1995 claiming the priority of two earlier US applications filed on 17 June 1994 and 7 June 1995, respectively.

II. Five oppositions were filed on the grounds of Article 100(a) in conjunction with Article 54 (lack of novelty) or Article 56 EPC 1973 (lack of inventive step), as well as on the grounds of Article 100(b) and (c) EPC 1973. Opponents 01 and 03 withdrew their oppositions during the opposition proceedings.

III. In an interlocutory decision of the opposition division posted on 29 March 2006, the amended claims according to the auxiliary request then on file (claims 1 to 6 as granted and claims 7 to 17 filed on 6 December 2005) and the invention to which they related, were found to meet the requirements of the EPC 1973, the claims as granted being found to offend against Article 123(2) EPC 1973 in view of claim 8. The opposition division, thus, decided that the patent could be maintained on the basis of the amended claims of the auxiliary request, the description as granted save for the adapted pages 4 and 4a filed on 6 December 2005, and the figures of the patent as granted.

IV. The patent proprietor (appellant I) and opponent 02 (appellant II) each lodged an appeal against the interlocutory decision of the opposition division.

V. Together with its statement of grounds of appeal, appellant I filed five sets of amended claims as auxiliary requests 1 to 5, while maintaining the granted claims as its main request. As a subsidiary request, oral proceedings under Article 116 EPC 1973 were requested.

VI. Appellant II submitted its statement of grounds of appeal together with fresh evidence in the form of two scientific publications (documents (35) and (36); see section XVI *infra*). A copy of document (21), which had already been filed in opposition proceedings, was also submitted. Oral proceedings were requested if the board intended to reach any decision other than revocation of the patent.

VII. On 26 September 2006, opponent 05 withdrew its opposition.

VIII. Each appellant submitted comments on the grounds of appeal of the other appellant. In its submission, appellant I requested that documents (33) and (34) (see section XVI *infra*) filed at a late stage of the opposition proceedings and documents (35) and (36) filed by appellant II together with its statement of grounds of appeal (see section VI above) be disregarded.

IX. Opponent 04 (party as of right) did not submit any comments.

X. The parties were summoned 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 drew the attention of the parties to some of the issues to be discussed during the oral proceedings, in particular issues in connection with Articles 100(c), 87, 54 and 56 EPC 1973.

XI. Appellant I requested that the oral proceedings be postponed on the grounds that its representatives were unable to attend on the fixed dates. The board re-scheduled the oral proceedings to ensure that at least one of the two representatives of appellant I was able to attend.

XII. Together with its reply to the board's communication, appellant I filed four new first to fourth auxiliary requests which replaced the auxiliary requests previously on file.

XIII. Both appellant II and the party as of right informed the board that they did not intend to attend the oral proceedings.

XIV. At the oral proceedings, which were held on 3 November 2009, only appellant I was represented. In the course of the oral proceedings, appellant I filed a set of amended claims (claims 1 to 14) which replaced its previous main request.

XV. Claims 1 to 3, 8, 10 and 11 of the set of claims filed during the oral proceedings (main request) read as follows:

"1. A method of forming a microarray of analyte-specific assay regions on one or a plurality of solid support(s), comprising:

(a) loading a solution of an analyte-specific assay reagent in a reagent-dispensing device having an elongate capillary channel (i) formed by spaced-apart, coextensive elongate members, (ii) adapted to hold a selected quantity of the reagent solution, and (iii) having a tip region at which the reagent solution in the channel forms a meniscus,

(b) tapping the tip of the dispensing device against the solid support at a defined position on the solid support, with an impulse effective to break the meniscus in the capillary channel and deposit a selected volume of the reagent solution on the solid support(s), and

(c) repeating steps (a) and (b) with different analyte-specific assay reagents, deposited at different defined positions on the solid support(s), until the microarray(s) is formed.

2. The method according to claim 1, wherein the microarray has discrete analyte-specific assay regions and each assay region in the microarray has a selected, analyte-specific assay reagent.

3. The method according to claim 2, wherein the selected volume is between 0.002 and 2 nl.

8. An apparatus useful for forming a microarray of analyte-assay regions on a plurality of solid supports, wherein each region has a selected, analyte-specific reagent comprising

(a) a holder for holding, at known positions, a plurality of planar supports,
(b) a reagent dispensing device having an elongate open capillary channel adapted to hold a quantity of the reagent solution and having a tip region at which the reagent solution in the channel forms a meniscus,
(c) positioning means for positioning the dispensing device at a selected array position with respect to a support in said holder,
(d) dispensing means for moving the device into tapping engagement against a support with a selected impulse, when the dispensing device is positioned with respect to that support, with an impulse effective to break the meniscus of liquid in the capillary channel and deposit a selected volume of solution on the surface, and
(e) control means for controlling and positioning the dispensing means.

10. A substrate with a surface comprising a microarray of distinct polynucleotides, wherein (i) the microarray has at least about 1000 discrete regions of polynucleotides per cm^2 of substrate surface, (ii) each distinct polynucleotide is located at a separate region of the microarray, and (iii) each distinct polynucleotide is at least 50 subunits in length.

11. A substrate with a surface comprising a microarray of distinct polynucleotides that are at least 50 subunits in length, obtainable by the method of any one of claims 1 to 7, wherein the microarray has at least about 1000 discrete regions of distinct polynucleotides per cm^2 of substrate surface."

Dependent claims 4 to 7 concern specific embodiments of the method of forming a microarray, and dependent claim 9 relates to a particular embodiment of the apparatus of claim 8. Dependent claims 12 to 14 concern various embodiments of the substrate according to claim 10 or 11.

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

(1): WO 93/09668, published on 27 May 1993;

(5): WO 92/10588, published on 25 June 1992;

(6): US 4,378,333, published on 29 March 1983;

(7): K. R. Khrapko et al., 1991, DNA Sequence, Vol. 1, pages 375 to 388;

(18): EP-A1-0 063 810, published on 3 November 1982;

(19): WO 96/17958, published on 13 June 1996;

(21): US 4,981,783, published on 1 January 1991;

(24): E. Maier et al., 1994, Journal of Biotechnology, Vol. 35, pages 191 to 203;

(33): Declaration by Dr Julian Gordon of 24 May 2005;

(34): L. H. Augenlicht, 1988, Basic and Clinical Perspectives of Colorectal Polyps and Cancer,

eds. G. Steele et al., Alan R. Liss, Inc., New York, pages 195 to 202;

(35): T. D. Wilkins et al., 1975, Applied Microbiology, Vol. 30, No. 5, pages 831 to 837;

(36): A. G. Craig et al., 1990, Nucleic Acids Research, Vol. 18, No. 9, pages 2653 to 2660.

XVII. The submissions made by appellant I orally or in writing, as far as they are relevant to this decision, may be summarized as follows:

Admission of documents (33) to (36) into the proceedings

Documents (35) and (36) had been filed only upon appeal, ie. after the expiry of the opposition period, and moreover they were not, ***prima facie***, highly relevant. The same applied to the declaration of Dr. Gordon (document (33)) and the publication by Augenlicht (document (34)) filed at a late stage during the opposition proceedings. These documents failed to build a case of high likelihood to prejudice maintenance. They should, therefore, be rejected as belated.

Article 87 EPC 1973 - Priority

A density of 10,000 regions per in^2, which corresponded to 1,550 regions per cm^2, could be derived from page 13, lines 14 to 16 of the first priority document. Since the value of 10,000 regions per in^2 lay within the range of 1550 regions per cm^2, a person skilled in the art

could derive this feature directly and unambiguously from the priority document.

Article 54(2) and (3) EPC 1973 - Novelty

Claim 1

Capillary tubes were described in document (18) as examples of manual transfer of antigens or immunoglobulins to a support. However, release of the solution of antigens or immunoglobulins as envisaged in document (18) did not involve contact of the dispensing device with the solid support, but instead it was the liquid to be dispensed which made direct contact with the support.

The argument that "a simple capillary tube" would fall under the terms of claim 1 ignored the structural differences between the reagent dispensing device as defined in claim 1 on the one hand, and capillary tubes on the other hand. In particular, the elongate capillary channel of the reagent-dispensing device of the invention was formed by spaced-apart, coextensive elongate members which gave rise to an open capillary channel.

The method of claim 1 did not only make use of a reagent-dispensing device which was structurally distinct from what was disclosed in the prior art, but also involved method steps which were not anticipated in the prior art. In particular, dispensing occurred by tapping the tip of the dispensing device against the solid support with an impulse effective to break the meniscus in the capillary channel. Means for achieving

this effect were described in paragraph [0055] of the patent as granted and illustrated in Figures 2A to 2C in an exemplary manner.

Claim 8

The objection of lack of novelty based on document (21) was not justified, because the apparatus described in this document did not comprise a dispensing device having an elongate open capillary channel, but rather stainless steel prongs embedded in an aluminium base. Document (35) could not be used to construe the term "prong" in document (21) as something else than a simple metal pin. The assertion that in document (21) use was made of an apparatus as described in document (35) was mere speculation.

Claims 10 and 11

Document (5) disclosed the uses of the VLSIPS array for DNA sequencing, fingerprinting and genetic mapping. The VLSIPS technology described in this document was not suitable for the manufacture of a microarray of polynucleotides each having more than 50 monomeric units. Moreover, document (5) failed to provide an achieved density of at least about 1000 discrete regions of polynucleotides per cm^2.

Documents (19) and (24) did not disclose the feature which relates to a microarray of polynucleotides of greater than 50 subunits in length on a solid support, wherein the microarray had at least about 1000 discrete regions per cm^2 of solid support.

Article 56 EPC 1973 - Inventive step
Claims 1 and 8

The opposition division was correct in deciding that the method and the apparatus of claims 1 and 8 involved an inventive step.

Claims 10 and 11

None of the documents on file suggested and also enabled a substrate as claimed.

Article 83 EPC 1973 - Sufficiency of disclosure

The opposition division correctly acknowledged that forming a microarray of distinct polynucleotides on a substrate applying the method as claimed was clearly described in the specification and enabled a person skilled in the art to carry out the invention.

XVIII. The submissions made by appellant II in writing, as far as they are relevant to this decision, may be summarized as follows (N.B. Appellant II did not attend the oral proceedings during which the new main request was filed. Thus, the objections made in writing to corresponding subject-matter of the previous requests are reported hereinafter):

Articles 54(2),(3) EPC 1973 - Novelty

Claim 1

Claim 1 related to a method of forming a microarray of analyte-specific reagents. The claim was not limited by

any features relating to the number or density of analyte-specific reagents on the array, nor were the analyte-specific reagents limited to nucleic acid reagents.

Document (18) disclosed a method in which multiple microdots of analyte-specific reagents, for example, antigens, were deposited using capillary tubes on to the substrate. The feature that the capillary tube was tapped so as to release the meniscus (the "tapping feature") was clearly inherent in the use of a capillary tube to apply dots to a matrix. Thus, claim 1 could not be considered to be new.

In the decision under appeal, the opposition division had overlooked the technical reality of how capillary tubes were used to release their contents. The contents would not touch the support before the tube; rather, there would be contact between the tube and the support and a breaking of the meniscus so as to release the contents.

Document (21) described a replicating device consisting of 96 stainless steel prongs embedded in an aluminium base. Ejector means were not provided. This device was used to produce arrays by replicating a set of clones onto nitrocellulose filters. The contact with the substrate was by "imprinting" of the prongs onto the surface. Since three filters could be imprinted before the replicating tool must be recharged, it was clear that the prongs had to be filled with analyte-specific reagent, as described in document (35). The release of the contents had to involve contact ("tapping") of the

prong to the substrate. Thus, also document (21) affected the novelty of the subject-matter of claim 1.

Claim 8

Claim 8 was not limited to an apparatus for forming a nucleic acid based microarray, because analyte-specific reagents were referred to in a general sense. Neither was the array defined in terms of a particular density of "discrete regions". Thus, the additional features over claims 1 to 3 seemed to be merely the means to mechanize the positioning and tapping of the dispensing device. These features were inherent in the robot device described in document (36) or as referred to in document (24). Thus, in view of these documents the subject-matter of claim 8 lacked novelty.

Claims 10 and 11

Document (18) described microarrays having the features specified in these claims. The "obtainable by" language was not capable of imparting novelty to the claimed microarrays. Also documents (5), (24) and (19) were novelty-destroying, the latter being part of the state of the art under Article 54(3) EPC 1973.

Article 56 EPC 1973 - Inventive step
Claims 1 and 8

The whole content of document (18) related to the provision of microarrays containing analyte-specific reagents. While in Example 1 of this document a microsyringe was used to deposit the analyte-specific reagents, capillary tubes were explicitly mentioned in

the document and, in any event, were part of routinely-used laboratory equipment. The choice of laboratory equipment to administer the analyte-specific reagent to the array was simply part of the routine activities of a person skilled in the art and could not involve any inventive step.

The technical problem as set up by the opposition division had a number of failings: (i) it referred to "mass fabrication", which was not required by claim 1; (ii) it referred to "high density" arrays, whereas there was absolutely no density requirement in claim 1; (iii) it referred to polynucleotide arrays, whereas claim 1 referred to arrays of "analyte-specific reagents"; and (iv) it referred to polynucleotides of a particular length. It was therefore apparent that the technical problem was not set up on the basis of the features of the claims.

As it was believed that claim 1 lacked novelty over document (18), it was difficult to formulate a technical problem. It appeared that, in comparison with document (18), the method of claim 1 was nothing more than an alternative method of producing a microarray. Such a mere alternative method could not be seen to involve an inventive step.

If document (21) was not considered prejudicial to the novelty of claim 1, the closeness of its teaching to the claims of the patent meant that the claims would nevertheless lack an inventive step. For example, an alternate dispensing means would be a mere obvious alternative.

Compared to claim 1, claim 8 included as additional feature means to mechanize the positioning and tapping of the dispensing device. These features were inherent in the robot device described in document (36). In any event, the mere mechanization of a process could not provide an inventive step to a non-inventive process; providing the "means for" tapping a capillary could not, of itself, make the tapping of that capillary inventive.

Claims 10 and 11

The claims related to microarrays themselves, and defined those microarrays without reference to the "tapping feature". The opposition division erred in the formulation of the problem to be solved. According to the opposition division, the problem was how to provide by mass fabrication a microarray by depositing, at high density, a solution of polynucleotides having a length of at least 50 subunit bases onto the solid support(s). However, the claims in question did not require mass fabrication, neither did they require that the arrays were formed by deposition of a "solution of" polynucleotides. Thus, the claimed microarrays could be produced by any method.

The claimed subject-matter lacked an inventive step in view of documents (18) and (24). The latter document was prior art within the meaning of Article 54(2) EPC 1973 because claim 10 was not entitled to the first priority date.

Although the density of the probes on the arrays was not stated in documents (21) and (34), it was clear from both the declaration of Dr. Gordon (document (33))

and document (18) that a density of probes greater than 1000 per square centimetre was readily achievable at the priority date of the patent in suit. Consequently, in view of these documents the claimed microarrays did not involve an inventive step.

XIX. Appellant I requested that the decision under appeal be set aside and the patent be maintained on the basis of claims 1 to 14 of the main request filed during the oral proceedings.

XX. Appellant II requested in writing that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Documents (33) to (36) are not admitted into the proceedings

1. Appellant I requested that documents (33) to (36) be disregarded, on the grounds that these documents had been filed late and were, ***prima facie***, not highly relevant. In its communication under Article 15(1) RPBA in preparation for the oral proceedings, the board expressed its intention to discuss this issue with the parties. However, appellant II neither submitted in writing any counter-arguments in this respect nor attended the oral proceedings.

2. Documents (33) and (34) were filed, in fact, at a rather late stage of the opposition proceedings, well after the expiry of the opposition period. Neither of the two documents was discussed in the decision under appeal, possibly because the opposition division did

not consider their content to be material to the decision on the issues raised by the opponent. Nor does the board.

3. Document (33) is a declaration of Dr Julian Gordon, one of the inventors named in the European patent application No. 0 063 810, which is document (18) in the present proceedings. In his declaration, which was made in connection with different proceedings before the European Patent Office, Dr Gordon comments on the content of document (18) in relation to the provision of an array having a density of 1000 different probes per square centimetre, and provides some calculations on the density of spots based on numerical data from the document.

4. In the board's view, document (33) does not represent evidence which could be regarded as highly relevant to the present decision. As concerns the spot density calculations, the board considers itself technically competent to assess the numerical data provided in document (18) without recourse to expertise of Dr. Gordon. As regards the further comments on the content of document (18), the board notes that, while undoubtedly an expert in his field, Dr. Gordon's appreciation of the content of his own patent application could not be regarded as an objective expert opinion.

5. Document (34) is a scientific publication authored by Augenblick, the inventor named in the US patent No. 4,981,783, which is document (21) in the present proceedings. ***Prima facie***, the content of document (34) that could be relevant to the assessment of novelty

and/or inventive step in the present case, does not go beyond the content of document (21) which was filed together with the notice of opposition. As a matter of fact, in its submissions appellant II relied on both documents indistinctively. The board sees, thus, no reason to admit and examine in depth a fresh document which, apart from having been filed late, does not appear to add anything to the proceedings.

6. Documents (35) and (36) were filed by appellant II together with its statement of grounds of appeal. Document (35) was submitted as evidence in support of appellant II's argument that the term "prong" used in document (21) described not a simple pin, but rather a tubular structure capable of retaining liquid therein. However, since there is no link or reference whatsoever in document (21) pointing to document (35), there was, in the board's view, no reason for a person skilled in the art reading document (21) to give the term "prong" used in this document the meaning arguably suggested in document (35), instead of the usual meaning in the art ("metal pin"). Moreover, document (35), which is a scientific publication dealing with a specific technical matter rather than a general textbook, cannot be regarded as suitable evidence for a different meaning of the term "prong" in the field of microarrays.

7. Document (36) was submitted as evidence for "***Another dispensing device for the accurate replication of arrays of clones onto filters***" (see footnote 8 on page 6 of the statement of grounds of appeal; emphasis added by the board) in connection with appellant II's line of argument on lack of novelty with regard to document (21). However, appellant II failed to identify

any piece of information in document (36) which could be, ***prima facie,*** more relevant to the assessment of novelty - or inventive step - than the content of document (21) itself, a document that has been on file from the outset of the opposition proceedings.

8. For the reasons given above, the board decides not to admit documents (33) to (36) into the proceedings, as requested by appellant I.

Main request (claims 1 to 14 filed during the oral proceedings)

9. During the oral proceedings before the board, appellant I filed a new main request (claims 1 to 14) which replaced the previous main request. This request was essentially based on the second auxiliary request then on file (claims 1 to 18), on which appellant II had commented in writing, with the deletion of claims 8 to 10 and 18, re-wording of claims 2 and 3 which were made dependent on claim 1, and renumbering of the claims and dependencies. Notwithstanding the absence of appellant II at the oral proceedings, the board could decide on these amended claims, as they did not raise any new issues on which appellant II had not had the opportunity to comment. At any rate, by deciding not to attend the oral proceedings, appellant II chose to not exercise its right to be heard (see also Article 15(3) RPBA).

Rule 57a and Article 123(2) EPC 1973

10. Claims 1 and 4 to 7 according to the present main request are identical to the corresponding claims of the auxiliary request on the basis of which the

opposition division decided that the patent could be maintained.

11. The opposition division found that the claimed subject-matter of these claims did not extend beyond the content of the application as filed. This finding was not contested by appellant II, and the board sees no reason to disagree with the opposition division's decision in this respect.

12. The board is also satisfied that, contrary to the opponents' objection to claim 1 as granted under Article 100(c) EPC 1973, the deletion of the language "*a known amount of* [a selected, analyte-specific reagent]" - which was included in claim 1 of the application as filed, but is missing in both the present claim 1 and claim 1 as granted - does not introduce any subject-matter which extends beyond the content of the original application. The requirement that each region in the array has a known amount of a selected, analyte-specific reagent is implicit in step (b) of the method according to present claim 1: if a selected volume of a reagent is deposited on a solid support at defined positions - as specified in step (b) -, each region of the formed array will necessarily have a known amount of the reagent, namely the amount of reagent which has been deposited.

13. As concerns claims 2 and 3, which are dependent from, respectively, claims 1 and 2, the board believes that the amendments introduced into these claims have been occasioned by the ground of opposition of Article 100(c) EPC 1973 and, thus, conform to Rule 57a EPC 1973.

14. The board is also convinced that the subject-matter of the amended claims does not extend beyond the content of the application as filed. The features specified in claim 2 are disclosed on page 13, lines 5 to 8 of the application as filed, and the claimed method has a basis in claim 1 of the application as filed. A basis of the feature "*the selected volume is between 0.002 and 2 nl*" in present claim 3 is found on page 16, lines 33 and 34, and in Table 1 of the application as filed.

15. The present amended claim 8 differs from claim 11 as granted in that the reagent-dispensing device is required to have an elongate **open** capillary channel, and that the feature "*the channel is open-sided*", which in the granted claim characterised solely the tip region of the channel, has been deleted. The amendments introduced into claim 8 have been occasioned by the ground of opposition of Article 100(c) EPC 1973 and, thus, conform to Rule 57a EPC 1973. Basis for the apparatus for forming a microarray defined in present claim 8 is found in claim 6 as originally filed.

16. Present claims 9 to 14 are identical to claims 12 to 17 as granted, except for the necessary adaptation of the numbering and dependencies after the deletion of claims 8 to 10 as granted. No objections were raised by appellant II in this respect, and the board has no concerns of its own.

17. Summarising the above: the amendments introduced into the present claims are in conformity with both Rule 57a EPC 1973 and Article 123(2) EPC 1973.

Article 123(3) EPC 1973

18. The board is also satisfied that the amendments introduced into claims 2, 3 and 8 do not extend the protection conferred by the patent as granted.

19. The method of forming a microarray according to independent claim 2 as granted comprised the step of loading a solution in a reagent-dispensing device characterised by, ***inter alia***, having an elongate capillary channel which was **open-sided at the tip region**, whilst in the method of independent claim 3 as granted the capillary channel of the reagent-dispensing device was not required to be open-sided, either at the tip region or elsewhere.

20. The amended claims 2 and 3 as presently on file are now dependent from claim 1, either directly (claim 2) or indirectly (claim 3) via the dependency from the preceding claim. Consequently, each of claims 2 and 3 includes the features of claim 1, in particular the feature which characterises the capillary channel of the reagent-dispensing device as "***formed by spaced-apart, coextensive elongate members***". A person skilled in the art derives from this feature that the capillary channel must be open-sided over the whole length of the elongate members, and not only at the tip region. Since this additional requirement introduces a limitation, the protection conferred by claims 2 and 3 has not been extended, compared to the corresponding claims as granted.

21. The same reasoning applies, ***mutatis mutandis***, to amended claim 8, which is directed to an apparatus

useful for forming a microarray. While in the corresponding claim of the set of claims as granted (ie. claim 11) only the tip region of the capillary channel was required to be open-sided, present claim 8 specifies that the elongate capillary channel of the dispensing device is open and formed by spaced-apart, coextensive elongate members, which implies that the capillary channel is open-sided over the whole length of the elongate members. Hence, compared to claim 11 as granted, the protection conferred by the present claim 8 is more limited.

22. It follows from the above that the amendments introduced into the claims conform to Article 123(3) EPC 1973.

Article 87 EPC 1973 - Priority

23. The opposition division found that a range of "***at least about 1000 discrete regions of polynucleotides per cm^2***" as specified in claims 13 and 14 according to the auxiliary request then on file could not be derived, directly and unambiguously, from a value of 10,000 regions per in^2 (1550 regions per cm^2) as specified on page 13, lines 14 to 16 of the US application Serial No. 08/261,388, the priority of which is claimed as first priority for the present patent.

24. This finding applies equally - ***mutatis mutandis*** - to claims 10 and 11 according to the present request, which are identical to claims 13 and 14 as granted. Even if it is true that, as appellant I argued, a density value of 1550 regions per cm^2 falls within the

range specified in claims 10 and 11 ("at least about 1000 regions per cm^2"), neither the range as such, nor any substrates comprising a microarray with at least about 1000 regions of polynucleotides per cm^2, other than substrates containing - specifically - 1550 regions per cm^2, are directly and unambiguously derivable from the priority application (see opinion G 2/98, OJ EPO 2001, 413).

25. Consequently, the first priority date claimed in the patent cannot be acknowledged for the present claims 10 and 11. Thus, for the purpose of assessing whether or not a document is comprised in the state of the art to be considered under Articles 54(1) and 56 EPC 1973, the relevant date is, as concerns claims 10 and 11, the second priority date of the European application on which the present patent is based, ie. 7 June 1995, where their subject-matter is explicitly described.

26. In the decision under appeal, the opposition division did not decide on the priority issue with respect to the remaining claims of the auxiliary request then on file. On appeal, appellant II approved of the opposition division's adverse decision in respect of the priority of the claims corresponding to present claims 10 and 11, but did not raise any objections to the validity of the first priority as regards the remaining claims. Also the board sees no reason to raise any objections of its own motion.

27. Consequently, as concerns the present claims 1 to 9 and 12 to 14, the relevant date for the purpose of determining the state of the art under Articles 54(1)

and 56 EPC 1973 is considered to be the first priority date, ie. 17 June 1994.

Article 54(2) and (3) EPC 1973 - Novelty

28. The decision of the opposition division to reject the claims as granted for reasons of lack of novelty was taken in respect of subject-matter which is no longer claimed. However, the reasons given by the opposition division for acknowledging novelty in respect of claims 1, 11, 13 and 14 of the auxiliary request, which were identical to present claims 1, 8, 10 and 11, may also apply, ***mutatis mutandis***, to the present request.

Claim 1

Documents (1), (6), (7), (18), (19) and (24)

29. In the decision under appeal, the opposition division found that none of documents (1), (6), (7), (18), (19) and (24) described a method of forming a microarray as defined in present claim 1. This finding was questioned by appellant II only as concerns document (18).

30. In the view of the opposition division, document (18) failed to disclose a method of forming a microarray in which the release and deposition of the assay reagent was initiated by tapping the tip of the dispensing device at a defined position of the substrate on which the microarray was to be formed. Relying on, ***inter alia***, the passage on page 10, third paragraph of document (18), the opposition division found that, in the method described in document (18) the antigen or

immunoglobulin solution was deposited on the substrate only by direct contact.

31. The passage of document (18) on which the opposition division relied reads:

> *"The antigens or immunoglobulins are applied to the described solid support by direct contact, by which term mechanical transfer, either manual, e.g. with capillary tubes or pipettes or syringes or by the aid of liquid or gaseous propellants, such as sprays, e.g. by a suitably directed stream of air or gas or some template or applicator miniaturized by means of procedures such as are in common practice in micro-electronics, with the use of lithographic or similar procedures, or by "charged drop" propulsion as in high-speed electronic printing, is understood."* (see page 10, third paragraph of document (18))

32. Like the opposition division, the board is satisfied that, from the statements in that passage a person skilled in the art could not derive, directly and unambiguously, the "tapping feature" which characterises the method of claim 1, ie. the step of depositing a selected volume of the reagent solution by tapping the tip of the dispensing device with an impulse effective to break the meniscus in the capillary channel.

33. The board cannot accept appellant II's argument that the "tapping feature" is inherent in the use of a capillary tube for applying dots to a matrix as described in document (18). Tapping the tip of a

capillary tube on a surface represents only one possible method of using a capillary tube for depositing liquid contained in a capillary channel onto a surface. Other possibilities are, for instance, piston-driven air displacement, or displacement of the liquid within the capillary tube with a plunger, as described in Example 1 of document (18). In the board's view, the mere disclosure of the use of a capillary tube for dispensing liquid does not make available, directly and unambiguously, to a person skilled in the art the particular approach of tapping the tip of the capillary tube on the surface, let alone doing it with an impulse effective to break the meniscus in the capillary channel and to deposit a selected volume (see decision G 2/98; ***supra***).

34. The board fails to see the relevance of the question whether or not the contents of a capillary tube, when released onto a support, touch the support before or after the tube, in the context of assessing novelty with regard to document (18). Even if it is assumed - for the sake of argument - that using a capillary tube as described in document (18) may necessarily involve a momentary contact of the tip of the capillary tube with the support before the contents of the tube are released, there is an essential difference between the method described in the document of the prior art and the method according to present claim 1, namely that the latter method comprises the step of tapping the capillary tube on the substrate **with a certain impulse**, and that it is precisely this impulse which causes the meniscus in the capillary channel to break so as to release a **selected** volume of the reagent solution. Neither this feature of the

method of claim 1, nor the further feature which characterises the capillary channel of the dispensing device as formed by spaced-apart, coextensive elongate members, are disclosed in document (18).

35. The board, thus, concludes that, having regard to the content of document (18), the subject-matter of claim 1 is new.

36. The opposition division's finding that the "tapping feature" was not derivable from any of the further documents (1), (6), (7), (19) and (24) discussed in the decision under appeal, has not been questioned by appellant II, and the board sees no reason to do so of its own motion.

Fresh objection of lack of novelty relying on document (21)

37. As no objection of lack of novelty relying on document (21) was raised by the opponents in opposition proceedings, in the decision under appeal the opposition division did not decide on the issue. The objection was raised by appellant II for the first time in its statement of grounds of appeal.

38. In its communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) sent in preparation for the oral proceedings, the board observed that appellant II had not put forward any reasons why the objection of lack of novelty based on document (21) - and document (34) - had not been raised in the proceedings before the opposition division. Appellant II neither replied to the board's communication nor attended the oral proceedings.

39. The board is not aware of any circumstances that may have prevented the objection of lack of novelty based on document (21) from being raised in the proceedings before the opposition division. Moreover, having considered the arguments put forward by appellant II and the contents of this document, which describes methods of analysing the level of expression of genes involved in pathological conditions, the board believes that the objection is, ***prima facie***, also not justified.

40. Reading document (21), in particular the passage on column 6, lines 17ff., it is immediately apparent that the replicating device described therein, which consists of stainless steel prongs embedded in an aluminium base, has no similarity at all with the dispensing device as defined in claim 1. Further, the method for imprinting filters with the replicating device described in document (21) (see column 6, lines 24 to 30) does not appear to rely on tapping the tip of a capillary tube against the solid support to break the meniscus in the capillary channel, as required by claim 1.

41. Thus, the objection of lack of novelty with regard to document (21) was not only belated but also, ***prima facie***, unfounded. Under these circumstances, the board, exercising its discretionary power, decides to disregard it.

Claim 8

42. Independent claim 8, which concerns an apparatus for forming a microarray (see section XV above), is

identical to claim 11, both as granted and according to the first auxiliary request in opposition proceedings. In the decision under appeal, the subject-matter of this claim was found to be novel with regard to documents (1), (6), (7), (18), (19) and (24).

43. In fact, none of these documents describes an apparatus with the features specified in present claim 8, in particular (i) a reagent dispensing device having an elongate open capillary channel formed by spaced-apart, coextensive elongate members, and (ii) dispensing means for moving the device into tapping engagement against a support with a selected impulse effective to break the meniscus of liquid in the capillary channel and deposit a selected volume of solution on the surface.

44. In view of the above, the subject-matter of claim 8 is regarded as being novel (Article 54 EPC 1973).

Claims 10 and 11

45. Independent claims 10 and 11, which are directed to a substrate with a surface comprising a microarray of distinct polynucleotides, are identical to, respectively, claims 13 and 14 according to the first auxiliary request in the opposition proceedings. Claim 14 is drafted as a "product-by-process claim" (see section XV above).

46. In the decision under appeal, the opposition division found that, having regard to documents (1), (5), (7), (18), (19) and (24), the claimed substrates were novel.

47. On appeal, appellant II contested the findings of the opposition division in respect of documents (5), (18), (19) and (24), and raised a fresh objection of lack of novelty relying on document (21).

48. Document (5) describes methods for the manufacture of matrices of defined oligonucleotides attached to or synthesized on a solid substrate. In the view of the opposition division, document (5) did not describe any microarray with an **achieved** density of at least about 1000 discrete regions of polynucleotides per cm^2, nor a microarray of polynucleotides with a length of 50 subunit bases. What the opposition division regarded to be achieved in document (5) was merely the synthesis of eight trimers of cytosine and thymine on a glass support (see page 93 of document (5)).

49. In its statement of grounds of appeal, appellant II questioned this finding by referring to its notice of opposition, in which the passages on page 29, lines 13 to 15; page 13, line 37 to page 14, line 6; page 48, line 13; and page 14, line 4 of document (5) were cited in connection with the feature "***nucleotides having each a length of at least 50 subunits***". In these passages the polymers synthesized on a substrate are characterised vaguely as "of all lengths", "large" or "much longer ... than a preselected length". Like the opposition division, the board is unable to see in the passages indicated above a clear and unambiguous disclosure of a substrate having a microarray of polynucleotides of at least 50 subunits in length.

50. As concerns the feature "***the microarray has at least about 1000 discrete regions of polynucleotides per cm^2***", appellant II pointed to the paragraph bridging pages 28 and 29 of document (5), in which the possibility of manufacturing matrices with high densities up to in excess of one million regions/cm^2 using the VLSIPS technology was mentioned. However, the board regards this statement in document (5) as a theoretical possibility, "wishful thinking" rather than actual fact. The board is convinced that, as the opposition division observed in its decision, at the relevant date of the present patent such high density matrices could not be achieved using the methods described in document (5). No persuasive evidence to the contrary was submitted by appellant II on appeal.

51. Similar considerations arise when the disclosure content of document (18) is assessed. The passage of Example 1 indicated by appellant II in connection with the feature "***at least about 1000 discrete regions of polynucleotides per cm^2***" points to the possibility of using a two-dimensional array of microdots in which a ten cm square **could** contain up to 10^5 individual tests on a ten cm square (see paragraph bridging pages 31 and 32, in particular lines 1 and 2 on page 32). However, the array prepared in Example 1 of document (18) is, actually, a one-dimensional array on a 100 mm length strip, the spots having a diameter of at least 0.3 mm. Assuming that a distance of 0.1 mm is left between the spots, one cm length would contain 25 spots. If this density is extrapolated to a two-dimensional array, one square cm would contain only 625 spots per square cm. ie. less than 1000 spots per cm^2. Moreover, it should be noted that Example 1 concerns an array of

microdots of **human serum**, rather than polynucleotides of at least 50 subunits in length.

52. In Example 4 of document (18), to which appellant II also pointed, salmon sperm DNA or ***Escherichia coli*** ribosomal RNA are spotted on Millipore sheets with a grid printed on it, leaving 3 mm x 3 mm marked squares in which the samples are applied. Like the opposition division (see page 11, first full paragraph of the decision under appeal), the board is unable to accept that a person skilled in the art could derive from this example a density of at least 1000 discrete regions per cm^2. There is no indication whatsoever in this passage how many samples were applied in the marked squares.

53. Documents (19) and (24), which, as a consequence of the adverse finding on the priority of claims 10 and 11 (see paragraphs 21 to 23 above) are comprised in the state of the art under Article 54(3)(4) EPC 1973 and Article 54(2) EPC 1973, respectively, were said by appellant II to be novelty-destroying. The board disagrees with this view.

54. Document (19) describes densities of up to 30-40/cm^2 for nucleic acid arrays (see page 13, lines 31 to 35). It is also mentioned in this document that in arrays on substrates such as glass, quartz or small beads with densities greater than $10^4/cm^2$, small array members are typically used. However, arrays with such a density which also show the further features specified in claim 10 and 11, in particular the feature "***nucleotides having each a length of at least 50 subunits***" are not described.

55. In document (24), 22 cm x 22 cm membranes containing 20,735 clones (see Abstract) or 57,600 clones (see page 198, right column) are described. The highest density achieved (119 clones/cm^2) is, thus, much lower than the 1000 discrete regions per cm^2 specified in claims 10 and 11.

56. Thus, neither document (19) nor document (24) anticipates the subject-matter of claims 10 and 11.

57. The fresh objection to claims 10 and 11 relying on document (21), which was raised for the first time on appeal, is disregarded for essentially the same reasons given in connection with claim 1 (see paragraphs 38 to 41 above).

58. Summarising the above: the arguments put forward by appellant II in support of its objection of lack of novelty fail to convince the board. Thus, the subject-matter of claims 1, 8, 10 and 11 is found to be novel.

Article 56 EPC 1973 - Inventive step

Claims 1 and 8

59. On appeal, appellant II relied on documents (18), (21), (24) and (34) in support of its objection of lack of inventive step in respect of claims 1 and 8.

Document (18) as the closest state of the art

60. Document (18) describes devices and kits for immunoassays, especially solid phase immunoassays on a solid porous support (eg. a nitrocellulose membrane) to

which antigens and/or immunoglobulins are bound by direct application. The use of such supports is said to make it possible to effect an unlimited number of antibody-antigen reactions simultaneously and in one operation (see Abstract). The antigens or immunoglobulins can be applied in any suitable pre-selected geometry, eg. as a line or an array of microdots.

61. The antigens or immunoglobulins are applied to the solid support by direct contact (see the paragraph bridging pages 10 and 11 of document (18) quoted in paragraph 31 above). In Example 1, the solution containing the antigens or immunoglobulins is spotted manually using a microsyringe ("***preferably a Hamilton microsyringe***") graduated in 0.1 µl steps, on to a strip of Millipore® membrane (see page 30, lines 16 to 19 of document (18)).

62. The method of claim 1 differs from the method described in document (18) in that it comprises the step of dispensing the reagent solution by tapping the capillary tube on the substrate with a certain impulse, which causes the meniscus in the capillary channel to break so as to release a selected volume of the solution being dispensed. A further difference concerns the dispensing device, which in the method of claim 1 is characterised by having a capillary channel formed by spaced-apart, coextensive elongate members.

63. In the decision under appeal, the opposition division formulated the objective technical problem to be solved by the present invention as "***how to provide by mass fabrication a microarray by depositing, at a high***

density, a solution of polynucleotides having a length of at least 50 subunit bases onto the solid support(s)" (see paragraph 7.1 of the decision under appeal).

64. Appellant II criticised, *inter alia*, that "mass fabrication" and "high density" were not required in the claims at issue. In this respect the board observes that, while it is true that these advantageous effects of the invention are not specified in the claims, this does not mean that they do not represent particular aspects of the problem to be solved by the invention as claimed. The board, however, accepts appellant II's criticism as concerns the inclusion of polynucleotides and their length in the formulation of the problem to be solved.

65. Accordingly, the technical problem to be solved in view of document (18) is re-formulated as the provision of an improved method suitable for automation which allows dispensing, rapidly and reliably, of a desired volume of a reagent at discrete regions onto a solid support at a high density.

66. The board is satisfied that this problem is solved by the method according to claim 1. The claimed method uses a reagent-dispensing device having an elongate capillary channel formed by spaced-apart, coextensive elongate members. The capillary channel is adapted to hold a selected quantity of the reagent solution, and has a tip region at which the reagent solution in the channel forms a meniscus. Deposition of the reagent at a defined position on a solid support is effected by tapping the tip of the dispensing device against the support, with an impulse effective to break the

meniscus in the capillary channel. When the meniscus breaks, the liquid in the tip flows into the capillary space between the tip and the surface of the support, and forms a liquid bead (see Figure 2C of the patent) which remains on the support when the dispensing device is withdrawn.

67. The dispensed volume - ie. the volume of the bead - depends on several parameters, the most important being the size of the area spanned by the tip of the dispensing device, the hydrophobicity of the surface of the support, the time of contact of the tip with the surface, the rate of withdrawal of the tip from the support, and the viscosity of the dispensed liquid reagent (see paragraph [0064] of the patent). According to the invention these parameters can be adjusted in order to achieve the deposition of a desired volume in a reliable and repeatable fashion.

68. The advantages of the reagent-dispensing device having an elongate open-sided capillary channel as specified in claim 1, in comparison with the capillary tubes of the state of the art, are outlined in paragraph [70] of the patent: (i) the open channel facilitates rapid and efficient washing and drying of the tip before reloading; (ii) the reagent can be loaded directly by passive capillary action; (iii) the open capillary reservoir can retain sufficient reagent for the printing of numerous arrays; (iv) open capillaries are less prone to clogging than closed capillaries; and (v) open capillaries do not require a perfectly faced bottom surface for fluid delivery.

69. None of the documents on file suggests forming an array using a dispensing device which has an elongate capillary channel formed by spaced-apart, coextensive elongate members. Nor do they suggest tapping the tip of such a dispensing device loaded with a reagent solution against the support, with an impulse effective to break the meniscus in the capillary channel and deposit a selected volume of the reagent solution onto the support.

70. In the decision under appeal, the opposition division cited document (6) as the sole document on file which discloses tapping the tip of a capillary tube to initiate the discharge of a sample onto a slide (see column 1, third paragraph under the heading "Technical field" of document (6)). However, the opposition division found that it would not have been obvious to a person skilled in the art to combine of the teachings of documents (24) and (6), because document (6) did not relate to the field of microarrays, but concerned a device and a method for preparing blood smears on glass slides (see point 7.5 of the decision under appeal).

71. The board shares the view of the opposition division that the technical fields of documents (18) and (6) are rather distant. It is also noted that document (6) describes the traditional method of preparing blood smears by tapping the capillary tube against the surface of a glass slide as "*a relatively imprecise technique*" due to the difficulties in controlling the quantity of blood deposited by the capillary tube on the glass slide (see column 1, lines 49 to 55 of document (6)). Thus, when seeking to prepare a microarray with a high density, a person skilled in the

art would not regard tapping the capillary tube against the support to be a reliable method for applying defined small quantities of the reagent onto the solid support.

72. For these reasons, the board concludes that, in view of document (18), either alone or in combination with document (6), the subject-matter of claim 1 was not obvious to a person skilled in the art.

73. The same applies to the apparatus according to claim 8. The devices described in document (18) for applying the antigens or immunoglobulins onto the solid support are simple capillary tubes or pipettes or syringes, or more sophisticated devices using propellants (see passage of document (18) quoted in paragraph 31 above). If a person skilled in the art, starting from document (18), did not envisage a method of preparing a microarray by tapping a capillary tube containing an analyte against the solid support as defined in claim 1, he/she had no reason to try to modify any of the devices described in document (18).

Further documents on which appellant II relied

74. The board, exercising its discretion, decides to disregard also the objection of lack of inventive step based on document (21), which - like the novelty objection based on the same document - was raised for the first time on appeal. Since document (21) was on file from the very outset of the opposition proceedings, the objection could, in the board's view, have been raised before the opposition division. The board pointed to these circumstances in its communication

under Article 15(1) RPBA, and also expressed its intention to discuss the issue during the oral proceedings. However, appellant II neither replied to the board's communication nor attended the oral proceedings.

75. Moreover, since document (34) is not admitted into the proceedings (see paragraphs 5 and 8 above), the objection of lack of inventive step relying on this document is also disregarded.

76. As concerns document (24), which the opposition division regarded as the closest state of the art for the assessment of inventive step in respect of the claims of the previous auxiliary request identical to the present claims 1 and 8, the board notes that, since claims 1 and 8 enjoy the first priority claimed in the patent (ie. 17 June 1994; see paragraphs 26 and 27 above), document (24), which was published on 30 June 1994, is not part of the state of the art to be considered under Article 56 EPC 1973.

Claims 10 and 11

Document (24) as the closest state of the art

77. Claims 10 and 11 do not enjoy the first priority claimed in the patent (17 June 1994; see paragraphs 23 to 25 above). Consequently, document (24) forms part of the state of the art to be considered under Article 56 EPC 1973.

78. Document (24) describes the application of robotic technology to the large-scale analysis of cDNA

libraries. Individual bacterial colonies containing a cDNA clone made from human brain tissues are picked and arrayed automatically in quadruple density (384-well) microtiter plates. After DNA amplification by PCR directly in the microtiter plates using a fully automated water bath system, the PCR products are automatically transferred to nylon membranes in a high density pattern using a robotic device (see Abstract).

79. The picking head of the robotic device used for transferring the PCR products from the wells of the microtiter plate onto the nylon membranes consists of a 96-pin array of which individually spring loaded pins are pushed down using a single pneumatic cylinder (see page 193, left column, section 2.2, second sentence from the end). It is also indicated the head may accommodate 96, 384 or even 2304-pin devices (see sentence bridging pages 193 and 194).

80. Figure 6 of document (24) shows a picture of the spotting pattern obtained using the described robotic device. The nylon filter (22 cm x 22 cm) contains 20,736 PCR products as discrete spots, ie. the support contains, on average, **42.84 clones/cm²**. The clones have been spotted in 2304 boxes (48 x 48) with 9 clones arrayed in a 3 x 3 format.

81. Thus, starting from the method of manufacturing a microarray described in document (24), a person skilled in the art seeking to achieve a higher spot density up to at least 1000 discrete regions per cm^2 on the solid support would have to use a microtiter plate having wells at the desired density, because the spot density achievable by the method described in document (24)

seems to be limited not by the pin arrangement in the picking head, but by the well density on the microtiter plate where the PCR reaction takes place.

82. Even if one assumes that in view of document (24) it was obvious to a person skilled in the art to try to increase the well density on the microtiter plate, the board is not satisfied that he/she had a reasonable expectation of success in achieving the required density of at least 1000 discrete regions per cm^2, especially in view of the fact that neither document (24) nor any of the further documents cited by appellant II describe how to obtain such a microtiter plate.

83. Summarising the findings above: the reasons put forward by appellant II in support of its objection of lack of inventive step fail to persuade the board that the claimed subject-matter was obvious to a person skilled in the art. Thus, the requirement of Article 56 EPC 1973 is considered to be met.

Article 83 EPC 1973 - Sufficiency of disclosure

84. In the decision under appeal, the opposition division found that the patent disclosed the invention as claimed in claims 13 and 14 then on file, which were identical to present claims 10 and 11, in a manner sufficient clear and complete for it to be carried out by a person skilled in the art (see Article 83 EPC 1973).

85. This finding has not been contested on appeal, and the board sees no reason to disagree with the view of the opposition division. Thus, the requirement of Article 83 EPC 1973 is considered to be fulfilled.

Conclusion

86. The grounds on which appellant II based its appeal do not prejudice maintenance of the patent in amended form according to appellant I's main request.

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 maintain the patent on the basis of claims 1 to 14 of the main request filed during the oral proceedings and a description and figures to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski L. Galligani