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**Datasheet for the decision
of 10 September 2008**

Case Number: T 0607/05 - 3.3.04

Application Number: 97116541.0

Publication Number: 0834575

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:

Identification of nucleic acids in samples

Patentee:

Affymetrix, Inc. (a Delaware Corporation)

Opponents:

Combimatrix Corporation (03)
Clondiag Chip Technologies GmbH (04)

Headword:

Nucleic Acids/AFFYMETRIX

Relevant legal provisions:

EPC Art. 54(2)(3), 76(1), 84, 114(2), 123(2)(3)
RPBA Art. 13

Keyword:

"Main Request: Added subject-matter (no) - Clarity (yes) -
Novelty (no)"

"Auxiliary Request I: Novelty (no)"

"Auxiliary Request II: Novelty (no)"

"Auxiliary Request III: Admission into the procedure (no)"

Decisions cited:

G 0008/93, T 0794/94, T 0077/97, T 0633/97, T 0378/02

Catchword:

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Case Number: T 0607/05 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 10 September 2008

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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
24 January 2005 concerning maintenance of
European patent No. 0834575 in amended form.

Composition of the Board:

Chairman: U. Kinkeldey
Members: M. Wieser
R. Moufang

Summary of Facts and Submissions

- I. Appeals were lodged by the Patent Proprietor (Appellant I), Opponent 02, Opponent 03 (Appellant II), Opponent 04 (Appellant III) and Opponent 05 against the interlocutory decision of the Opposition Division dated 24 January 2005 according to which European patent no. 0 834 575 could be maintained in amended form on the basis of claims 1 to 6 of auxiliary request 2 before it, pursuant to Article 102(3) EPC (1973). The patent in suit has the title "Identification of nucleic acids in samples" and was granted on the basis of divisional application EP 97116541.0, divided from earlier application EP 92904971.6, published as WO 92/10588, filed on 6 December 1991 and claiming priority from US 624,114 filed on 6 December 1990.
- II. Five oppositions had been filed against the patent in suit.
- Opponent 01, with letter dated 10 March 2003, Opponent 02, with letter dated 27 April 2006 and Opponent 05, with letter dated 15 February 2006, withdrew their oppositions.
- III. The Opposition Division decided that the subject-matter of the main request before it, i.e. of the claims as granted, did not meet the requirements of Article 76(1) EPC, and that the subject-matter of auxiliary request 1 before it lacked novelty over document WO 89/10977 and thus contravened Article 54(2) EPC.

- IV. The Board expressed its preliminary opinion in a communication dated 13 February 2008 and summoned the parties to oral proceedings.
- V. With letter dated 9 July 2008, Appellant I filed new documents and new auxiliary requests.
- VI. With letter dated 19 August 2008, the Board was informed that Appellant II would not attend the oral proceedings.
- VII. Oral proceedings before the Board took place from 9 to 10 September 2008.

Appellant I requested that the decision under appeal be set aside and the patent be maintained in amended form on the basis of the main or, in the alternative, the first, second or third auxiliary request, all filed during these oral proceedings.

Appellant III requested that the decision under appeal be set aside and that the patent in suit be revoked. The same request had been made in writing by Appellant II.

- VIII. The main request consists of 9 claims. Claims 1 and 2 read as follows:

"1. A method for identifying or distinguishing a target nucleic acid in a sample comprising:

(a) providing an array of at least 100 different probes bound to a substrate in known locations and at a

density of at least 1000 different probes per square centimetre;

(b) applying the sample to the substrate to obtain a hybridization pattern of the sample; and

(c) comparing the hybridization pattern with a reference pattern to identify or distinguish the target nucleic acid."

"2. A method as claimed in claim 1, wherein the reference pattern is obtained by applying a second nucleic acid to the or another said substrate."

IX. Claim 1 of auxiliary request I read as follows:

"1. A method for identifying or distinguishing a target nucleic acid in a sample comprising:

(a) providing an array of at least 100 different probes bound to a substrate in known locations and at a density of 3000 to 1000000 different probes per square centimetre;

(b) applying the sample to the substrate to obtain a hybridization pattern of the sample; and

(c) comparing the hybridization pattern with a reference pattern to identify or distinguish the target nucleic acid."

X. Claim 1 of auxiliary request II read as follows:

"1. A method for identifying or distinguishing a target nucleic acid in a sample comprising:

(a) providing an array of at least 100 different probes bound to a substrate in known locations and at a density of at least 1000 different probes per square centimetre;

(b) applying the sample to the substrate to obtain a hybridization pattern of the sample;

(c) obtaining a reference pattern by applying a second nucleic acid to the or another said substrate; and

(d) comparing the hybridization pattern with said reference pattern to identify or distinguish the target nucleic acid."

XI. Claim 1 of auxiliary request III read as follows:

"1. A method for identifying or distinguishing a target nucleic acid in a sample comprising:

(a) providing an array of at least 100 different probes bound to a substrate in known locations and at a density of at least 1000 different probes per square centimetre, and wherein said locations are less than 50 μm x 50 μm ;

(b) applying the sample to the substrate to obtain a hybridization pattern of the sample;

(c) obtaining a reference pattern by applying a second nucleic acid to the or another said substrate; and

(d) comparing the hybridization pattern with said reference pattern to identify or distinguish the target nucleic acid."

XII. The following documents are mentioned in the present decision:

- (1) The international application PCT/NL90/00081 published as WO 90/15070
- (2) WO 89/10977
- (7) WO 92/10588
- (20) J. Biotechnology, vol.35, 1994, pages 217 to 227
- (21) Declaration of Prof. Cass, 2003, in the matter of EP 99202455.4
- (22) Genomics, vol.13, 1992, pages 1008 to 1017
- (75) Witness Statement of Dr Blanchard, 19 January 2001, in the High Court of Justice
- (76) Expert Report of Dr Wallace, 18 January 2001
- (99) Expert Report of Dr Gamble, 8 March 2001
- (100) Biosensors & Bioelectronics, vol.11, no.6/7, 1996, pages 687 to 690

(101) Nucleic Acids Research, vol.22, no.8, 1994,
pages 1368 to 1373

(102) Letter from Prof. Southern to Mr Steffenhagen,
April 1994

(103) Nucleic Acids Research, vol.21, no 9, 1993,pages
2267 to 2268

XIII. The submissions by Appellants II and III, insofar as they are relevant to the present decision, can be summarized as follows:

Late-filed documents

All of documents (27) to (82), not considered by the Opposition Division, should be allowed into the procedure. Documents (99) to (103), filed by Appellant I two months before the oral proceeding, should be disregarded.

Main Request and Auxiliary Request I

The claims contained amendments which were not allowable in the light of the requirements of Articles 76(1), 123(2) and (3) EPC. Their subject-matter was not clear (Article 84 EPC).

Document (1) was prejudicial to the novelty of claim 1 since a reference pattern in the context of step (c) of claim 1 did not equate to a reference experiment, but could be any pattern providing information about the probes on the array. The comparison to such reference pattern was disclosed in document (1) and inevitably

resulted in identifying or distinguishing a nucleic acid.

Auxiliary Request II

Document (2) disclosed a method comprising all the features of claim 1 and was thus prejudicial to the novelty of the subject-matter of that claim. The document provided an enabling disclosure of arrays as defined in step (a) of claim 1.

Auxiliary Request III

Claim 1 raised numerous questions and problems. Therefore, this auxiliary request should not be allowed into the procedure at such late stage.

- XIV. The submissions by Appellant I, insofar as they are relevant to the present decision, can be summarized as follows:

Late-filed documents

The Opposition division was correct to disregard documents (27) to (82). Moreover, also document (90) should not be allowed into the procedure. Documents (99) to (103) had particular relevance to clarify the disclosure in document (2) and should therefore be allowed into the procedure.

Main Request and Auxiliary Request I

The subject-matter of claim 1 was novel over document (1) since this document did not disclose step (c) of

the claim, which required physically comparing the hybridization pattern with a reference pattern. Merely using the knowledge of what sequences are located in which position did not represent a comparison with a reference pattern. The matrix pattern referred to on page 5, paragraph [0033] of the patent in suit was also not a reference pattern in the sense of step (c) of claim 1.

Auxiliary Request II

The subject-matter of claim 1 was novel over document (2) because this document did not disclose a method for identifying or distinguishing a target nucleic acid in a sample comprising features (a), (c) and (d) of claim 1. Furthermore, the teaching of document (2) did not enable the provision of arrays as defined in step (a) of claim 1.

Auxiliary Request III

Claim 1 was based on page 29, lines 25 to 27 of the application as originally filed. The request should be allowed into the procedure.

Reasons for the Decision

Parties to the procedure

1. Opponents 01, 02 and 05, who have all withdrawn their oppositions (see section II above) are no longer parties to the procedure. The withdrawal of the oppositions by Opponents 02 and 05 has to be regarded as withdrawal of

their appeals (decision G 8/93, OJ EPO 1994, 887, point (2) of the reasons).

Late-filed documents

2. Within the time limit of nine month, set by Article 99(1) EPC 1973, the parties have filed documents (1) to (26). Documents (27) to (92) have been filed by the parties during the opposition procedure after expiry of this time limit.

3. The Opposition Division has decided that documents (27) to (82) were not allowed into the procedure as their content did not appear to be *prima facie* relevant, but that documents (84) to (90), which were considered to be of relevance for the issues of inventive step (Article 56 EPC) and sufficiency of disclosure (Article 83 EPC), were admitted into the procedure. No definitive decision was given with regard to the admissibility of documents (91) and (92) (point (17.2) of the appealed decision).

At the oral proceedings before the Opposition Division Opponent 04 (Appellant III) withdrew the request to introduce document (83) into the procedure (point (17.1) of the appealed decision).

4. During the appeal procedure the parties in addition filed eleven documents ((93) to (103)), five thereof (documents (99) to (103)) were filed by Appellant I only two months before the date set for oral proceedings by the Board.

In the communication dated 13 February 2008 (point (11)) the parties were informed that the Board preliminarily considered it appropriate only to allow the introduction of those documents filed by the parties after the expiry of the time limit set by Article 99(1) EPC 1973 on which they have based their arguments.

5. According to established case law of the boards of appeal the examination as to relevance is an important criterion for the boards when exercising their discretion under Article 114(2) EPC to disregard facts and evidence not submitted in due time. Late filed documents which contain no more information than documents filed on time and which do not disclose matter which could change the outcome of the decision can thus be disregarded (see Case Law of the Boards of Appeal, 5th Edition 2006, section VI.F.3.1).

Late filed documents to which none of the parties had referred to in order to substantiate any of their arguments cannot be considered as being of relevance for the outcome of the present decision and are therefore disregarded according to Article 114(2) EPC.

These are documents (29), (31) to (73), (75), (77) and (83).

At the oral proceedings, the parties present (Appellants I and III) did not comment on this position of the Board.

6. Nevertheless, Appellant I, late on the second day of the oral proceedings wanted to refer to document (75). This document, a witness statement, made at the High Court of

Justice, Chancery Division, Patents Court and dated 19 January 2001 has been filed by Appellant II during the opposition procedure with a letter dated 29 September 2004. Neither Appellant II nor any other party has referred to this document during the entire opposition procedure or the written appeal procedure to substantiate any of their arguments.

The right to be heard of all parties involved has to be safeguarded if the Board intends to take into account late-filed facts or evidence. In the present case, none of the other parties could have expected that Appellant I late at the oral proceedings would refer to late-filed document (75), which has not been referred to by any of the parties in the four years after it has been filed without any comment as to its relevance. Thus, the very limited time for considering the impact of this document would amount to a serious limitation of their right to be heard (Article 113 EPC). Therefore the Board does not admit document (75) into the procedure (Article 114(2) EPC).

7. In decision T 633/97 of 19 July 2000 the Board found that the complexity of the examination necessitated by the late filed material was a criterion for considering it. Once oral proceedings have been arranged in appeal cases, the decision to admit new evidence into the procedure should be governed primarily by a general interest in the appeal proceedings being conducted in an effective manner, i.e. dealing with all issues raised by the parties, while still being brought to a close within a reasonable time. Complex fresh subject-matter filed at short notice before or during oral proceedings ran the risk of being not admitted to the proceedings without

any consideration of its relevance or allowability (see point (2) of the reasons).

Document (99), a twenty-one pages expert opinion filed by Appellant I two month before the oral proceedings, which has been originally signed by the author more than seven years ago, refers to a plurality of documents in support of its statements. However, many of the cited documents are not clearly designated and cannot therefore be consulted by the reader.

Document (102) is a letter of the inventor of document (2) dated 1994 and filed by Appellant I also two months before the oral proceedings. The passages cited by Appellant I do not allow to draw any conclusion as to the nature and configuration of the assays referred to in document (102).

Accordingly, documents (99) and (102) are disregarded according to Article 114(2) EPC.

Main Request

Amendments - Article 76(1) EPC

8. According to item (a) of claim 1, the first step of the claimed method consists in the provision of "an array of at least 100 different probes bound to a substrate in known locations and at a density of at least 1000 different probes per square centimetre".

Appellants II and III argued that the provision of such array was not disclosed in the earlier application EP 92904971.6, published as WO 92/10588 (document (7)),

from which the European application underlying the patent in suit was divided.

In detail they put forward that document (7) did not disclose an array of 100 probes bound to a substrate at the claimed density, which was covered by the scope of claim 1. Moreover, they argued that document (7) only disclosed arrays according to claim 1 (a) which were generated by the VLSIPS technology and wherein the probes were oligonucleotide probes of the same length. The omission of these features in claim 1 had the effect that the subject-matter of the claim extended beyond the content of the earlier application as filed.

9. Document (7), at page 11, lines 17 to 22, discloses that the VLSIPS technology allows to synthesize a very large number of different oligonucleotide probes on a substrate at high densities. The "very large number of different oligonucleotide probes" is defined as being "in excess of about 10^2 , 10^3 , 10^4 , 10^5 , 10^6 or even more".

The Board is convinced that a skilled person reading this passage would consider that the term "about 10^2 " at least comprises the numbers 99, 100 and 101, with the consequence that the term "in excess of about 10^2 " has to be understood as to comprise 100.

On page 38, lines 12 to 13, document (7) discloses that the VLSIPS technology **may** be used to synthesize the probes at specific positions on a substrate, so that, in the context of Article 76(1) EPC, the Board sees no need to restrict the scope of the claim to arrays exclusively restricted to this technology.

It can be derived from page 10, lines 15 to 30 of document (7) that the probes of the arrays are not limited specifically to oligonucleotides.

Finally, it can be taken from page 41, line 17 onwards of document (7) that it is not an obligatory requirement of the arrays disclosed that all probes have the same length.

10. Appellant II argued in the written procedure, that document (7) on page 11, lines 17 to 22 disclosed two lists of probe numbers and probe densities, which provided twenty-five possible combinations. By referring to decision T 77/97 of 3 July 1997, it was argued that this did not amount to a disclosure of all possible individual combinations. As one of these individual combinations (100 probes at a density of 1000 probes per square centimetre) was contained in claim 1, the claim contravened the requirements of Article 76(1) EPC.

Claim 1 (a) refers to an array of **at least** 100 different probes at a density of **at least** 1000 different probes per square centimetre. As such the values 100 and 1000 are not isolated single embodiments selected from a list of alternatives, but they define limits of the array size disclosed on page 11 of document (7). This situation is different from the one underlying decision T 77/97 (*supra*; see point (6) of the reasons), where it was necessary to arrive at specific compounds falling within a generic chemical formula by selecting from two lists of discrete separate, chemically distinct entities.

11. Basis for claim 4, requiring that "at least some of the probes are oligonucleotides" can be found in the passage

bridging pages 37 and 38 of document (7) from which it can be deduced that both, oligonucleotides and non-oligonucleotides can be probes on the arrays.

12. A further objection was directed to claims 7 and 8, which did not contain the feature that the probes bound to the substrate had to be different probes.

Claims 7 and 8 are dependent from claim 1, which contains this feature. The omission of a feature in dependent claims cannot have the effect that the requirements of Article 76(1) EPC are violated, if said feature is explicitly referred to in the independent claim.

13. Therefore claims 1 to 9 of the main request are found to meet the requirements of Article 76(1) EPC.

Amendments - Article 123(2) and (3) EPC

14. As the relevant passages of document (7), discussed in points (8) to (12) above, are literally contained in the present divisional application as originally filed, claims 1 to 9 do meet the requirements of Article 123(2) EPC.

By defining in claim 1(a) that the arrays have a density of at least 1000 **different** probes, the scope of protection has been restricted with regard to claim 1 as granted. Thus, also the requirements of Article 123(3) EPC are met.

Clarity - Article 84 EPC

15. Appellant II argued that claim 1 lacked both, support and clarity, due to the use of the term "at a density of at least 1000 different probes per square centimetre".

The Board is convinced that the subject-matter of claim 1 finds technical support in the description of the patent in suit as required by Article 84 EPC. Paragraphs [0090], [0120], [0122] and [0168] are just a few examples of parts of the description that save this purpose.

Moreover, the Board does not see that a claim referring to an array of 100 different probes at a density of 1000 different probes per square centimetre lacks clarity. 100 different probes within an area of 0.1 square centimetre would provide such an array.

The requirements of Article 84 EPC are therefore met.

Novelty - Article 54(3) EPC

16. Claim 1 is directed to a method for identifying or distinguishing a target nucleic acid in a sample comprising the steps (a) providing an array of at least 100 different probes bound to a substrate in known locations and at a density of at least 1000 different probes per square centimetre; (b) applying the sample to the substrate to obtain a hybridization pattern of the sample; and (c) comparing the hybridization pattern with a reference pattern to identify or distinguish the target nucleic acid.

17. Document (1) concerns an international patent application filed on 7 June 1990 and published on 13 December 1990. The application was supplied to the European Patent Office in one of its official languages and the national fee provided for in Article 39(1) PCT has been paid; the requirements of Article 158(2) EPC 1973 are thus fulfilled. Since the filing date of document (1) is earlier than the priority date of the patent in suit, the content of document (1) is comprised in the state of the art pursuant to Article 54(3) and (4) EPC 1973 for the commonly designated contracting states, irrespective of whether or not the priority of the patent in suit is validly claimed.

18. Document (1) concerns methods of synthesising polymers of a known chemical sequence at known locations on a substrate, using lithographic techniques which make it possible to direct light to relatively small and precisely known locations on the substrate (page 5, lines 8 to 13). As polymer sequences bound to the substrate ("ligands"), peptides and nucleic acids are suggested amongst others (page 9, line 36; page 10, line 1; page 14, lines 32 to 37). Sequences of nucleic acids may be synthesized to establish DNA or RNA binding sequences (page 12, lines 22 to 24). More than about 10 and up to more than about 10^8 different sequences are provided on a single substrate (page 28, lines 28 to 33), and the surface area covered by an individual polymer is between about 1 cm^2 and 10^{-10} cm^2 , for instance $10 \times 10 \text{ }\mu\text{m}$ (page 28, lines 21 to 25).

Once the desired sequences have been synthesized on the substrate, the entire substrate is exposed to a receptor of interest; the receptor will preferentially bind to

certain regions of the substrate which contain complementary sequences (page 34, lines 15 to 21; page 6, lines 19 to 21). For identification of locations where binding takes place, the substrate is placed in a microscope detection apparatus (page 6, lines 21 to 24). Through knowledge of the sequence of the material at the locations where binding is detected, it is possible to quickly determine which sequence binds to the receptor (page 5, lines 25 to 28). The disclosed techniques can be used to screen large numbers of polymers (page 5, lines 14 to 16). According to page 41, lines 8 to 11, not only can the presence or absence of a receptor on a ligand be detected, but also the relative binding affinity of receptors to a variety of sequences can be determined.

Document (1) thus discloses a method in which those locations on the substrate where binding takes place are detected and in which, through the knowledge of the sequences at these locations, sequences present in the receptors are determined and thereby identified (page 19, lines 9 to 12, page 6, lines 16 to 24 and page 5, lines 25 to 28). The disclosed method for identifying or distinguishing a target nucleic acid in a sample comprises the step of providing an array of at least 100 different nucleic acid probes bound to a substrate in known locations (page 28, lines 28 to 33) and at a density in the order of between 1 and 10^{10} different probes per square centimetre, as the surface area covered by an individual polymer is between 1 and 10^{-10} cm² (page 28, lines 21 to 25). The method further comprises the step of applying a sample to the substrate to obtain a hybridization pattern of the sample (see for instance on page 34, lines 15 to 21). Hence, the Board

is convinced that document (1) discloses a method comprising steps (a) and (b) of claim 1.

19. It has in fact not been contested by Appellant I that document (1) provides an array as defined in step (a) of claim 1, and that the analysis of hybridization of a sample to the array is also disclosed in the document (see in particular Appellant I's letter dated 3 November 2003, page 22, lines 23 to 30, which was filed as response to the notices of opposition).

However, Appellant I denied that feature (c) of claim 1, i.e. the comparison of the hybridization pattern with a reference pattern to identify or distinguish the target nucleic acid, was disclosed in document (1). Appellant I submitted that document (1) relied on the knowledge of the sequence of each individual probe at the location where binding is detected. "Thus, D1 discloses the characterization of a sample, not by comparing the hybridisation pattern with a reference pattern but by determining which individual probes bind to the sample" (Appellant I's letter dated 27 October 2005, page 10, lines 6 to 11). In the absence of a clear and unambiguous disclosure in document (1) of a step of obtaining a reference pattern and physically comparing it with the obtained hybridization pattern in order to identify or distinguish the target nucleic acid, Appellant I argued, that the document was not novelty-destroying for claim 1.

20. In order to answer the controversially discussed question whether or not feature (c) of claim 1 is disclosed in document (1), the Board considers it necessary to determine what, in the context of the

patent in suit, is to be understood by a comparison of a hybridization pattern with a reference pattern.

Having regard to the patent in suit, the Board takes the position that such reference pattern may be a hybridization pattern obtained from a reference experiment, but that step (c) of claim 1 is not restricted to this embodiment.

21. Firstly, dependent claim 2 states that "the reference pattern is obtained by applying a second nucleic acid to the or another said substrate", and page 2, line 43 of the patent in suit also states that the reference pattern "may" be obtained in the way specified in claim 2. Obtaining the reference pattern by a reference hybridization experiment is thus a preferred embodiment, but not a mandatory feature of claim 1.

22. Secondly, page 3, lines 38 to 39 of the patent in suit states that "[b]ecause the oligonucleotide probes are positionally defined, the location of the hybridized duplex can directly translate to the sequences which hybridize". Page 5, lines 27 to 33, of the patent in suit, under the heading "A. General", further states that "the present invention provides the ability to prepare a substrate having a very high density **matrix pattern** of positionally defined specific recognition reagents. (...) Because the reagents are positionally defined, the sites of the interactions will define the specificity of each interaction. As a result, a map of the patterns of interactions with specific reagents on the substrate is convertible into information on the specific interactions taking place, e.g., the recognized features" (emphasis added by the Board).

23. The Board considers that from these passages, a skilled reader would understand that it is the knowledge of the sequences present in the individual positions of the support, i.e. the matrix pattern, which allows to conclude which sequences present in the sample must have given rise to the sites of interaction in the hybridization pattern. In this sense, the reference pattern can be the information on the pattern in which the nucleic acid sequences are arranged on the substrate and thus corresponds to the pattern of the nucleic acid probes on the substrate before conducting the hybridization experiment. According to the patent in suit, a target nucleic acid in a sample can in fact be identified or distinguished by a comparison of the hybridization pattern with this reference pattern.
24. The Board concludes that step (c) of the method of claim 1 encompasses the comparison of the hybridization pattern obtained in step (b) with the pattern represented by the known positional arrangement of the nucleic acid probes on the substrate as the reference pattern, in order to identify or distinguish the target nucleic acid.

The comparison of the hybridization pattern obtained by applying a sample to the substrate with the pattern of the probes arranged on the substrate, which comparison results in identifying or distinguishing a target nucleic acid in the sample, is however disclosed in document (1). Notably, page 5, lines 25 to 28 of document (1) states that "[t]hrough knowledge of the sequence of the material at the locations where binding is detected, it is possible to quickly determine which

sequence binds to the receptor" and page 19, lines 9 to 12 states that "[t]he sequence of the polymer at the locations where the receptor binding is detected may be used to determine all or part of a sequence which is complementary to the receptor". Consequently, document (1) discloses a method which does not only comprise steps (a) and (b), but also step (c) of claim 1.

25. In view of the above considerations, the Board concludes that document (1) clearly and unambiguously discloses a method according to claim 1. Therefore, the subject-matter of claim 1 does not fulfil the requirements of Article 54(3) EPC.

Auxiliary Request I

Novelty - Article 54(3) EPC

26. Claim 1 of auxiliary request I differs from claim 1 of the main request in that the specified density is "3000 to 1000000" instead of "at least 1000" different probes per square centimetre.

The Board considers that in view of the fact that document (1) discloses arrays having regions with surface areas as small as 10^{-10} cm² (see page 28, lines 21 to 25), which correspond to probe densities in the order of 10^{10} probes per square centimetre, claim 1 of auxiliary request 1 lacks novelty under Article 54(3) EPC for the same reasons as outlined above for claim 1 of the main request. Consequently, the subject-matter of claim 1 of auxiliary request I does not fulfil the requirements of Article 54(3) EPC.

Auxiliary Request II

Novelty - Article 54(2) EPC

27. In claim 1 of auxiliary request II, the features of claims 1 and 2 of the main request are combined. Claim 1 of auxiliary request II is thus directed to a method for identifying or distinguishing a target nucleic acid in a sample comprising steps (a) and (b) referred to in claim 1 of the main request; step (c) obtaining a reference pattern by applying a second nucleic acid to the or another said substrate; and step (d) comparing the hybridization pattern with said reference pattern to identify or distinguish the target nucleic acid. The latter step (d) corresponds to step (c) of claim 1 of the main request.

By introducing the feature of claim 2 of the main request into claim 1 of auxiliary request II, novelty of the subject-matter of the claims of said latter request with respect to document (1) was no longer at stake.

28. However, document (2) is highly relevant for the novelty of the subject-matter of auxiliary request II. Document (2) is an international patent application which was published before the priority date of the patent in suit and thus constitutes prior art under Article 54(2) EPC.

28.1 Said document relates to apparatuses and methods for analysing polynucleotide sequences. An array of oligonucleotides is attached to a support such as a glass plate and forms the target for a hybridization reaction. By applying labelled polynucleotide sequences

or fragments thereof to the array under hybridization conditions and observing the location of the label on the surface, a set of filled cells corresponding to the oligonucleotides present in the analysed sequence and a set of "empty" sites corresponding to the sequences which are absent in the analysed sequence, are obtained (page 2, line 3 to page 3, line 1).

- 28.2 According to document (2), this methodology can for instance be used in a method of molecular analysis which identifies sequence differences. Such differences can be revealed by hybridising two nucleic acids, for example genomic DNA of two genotypes or the mRNA populations of two cell types, to an array of oligonucleotides which represent all possible sequences. Positions in the array which are occupied by one sequence but not by the other show differences in the two sequences (page 6, lines 4 to 13).
- 28.3 The format, construction and size of arrays needed to analyse sequences are discussed in chapter 4.3, starting on page 7, line 34 of document (2). Page 8, lines 9 to 11 describes an array having all 256 tetranucleotide sequences as probes. The table on page 8 describes various arrays, one being a cosmid array having 1.0×10^6 probes in a matrix having a side of 100 mm (page 8, line 25). As indicated in the table, the pixel size is 100 μm (page 8, line 22).
- 28.4 The issue of laying down the matrix is dealt with in chapter 5.2, starting on page 11, line 9 of document (2). It is stated that "[a]utomatic equipment for applying the precursors has yet to be developed, but there are obvious possibilities; it should not be difficult to

adapt a pen plotter or other computer-controlled printing device to the purpose" (page 11, lines 14 to 18). It is further stated that the smaller the pixel size of the array the better, and that 100 microns would be a fairly comfortable upper limit. "On a smooth impermeable surface, such as glass, it may be possible to achieve a resolution of around 10 microns, for example by using a laser typesetter to preform a solvent repellent grid, and building the oligonucleotides in the exposed regions" (page 11, lines 24 to 29). When discussing the problem that laying down a very large number of lines or dots could take a long time if the printing mechanism were slow, reference is made to a low cost ink jet printer which could print at speeds of about 10,000 spots per second (page 11, line 33 to page 12, line 2).

- 28.5 Example 5 of document (2) describes that to test an automated system for laying down the precursors, the pen of a pen plotter was replaced by a component fabricated from Nylon, which had the same shape and dimensions as the pen, but which carried a polytetrafluoroethylene (PTFE) tube, through which chemicals could be delivered to the surface of the glass slide which lay on the bed of the plotter. This modified pen plotter was used for the addition of the seventh base of a cosL oligonucleotide (page 20, lines 19 to 30).
29. Appellants II and III submitted that document (2) was novelty-destroying for the claimed method, whereas Appellant I denied that document (2) described a method comprising all the features of claim 1 and additionally submitted that document (2) did not provide an enabling disclosure of arrays as defined in step (a) of claim 1.

30. The Board will first address the controversial question whether or not document (2) describes a method comprising all the features of claim 1.
- 30.1 Appellant I submitted that document (2) did not describe a method for identifying or distinguishing a target nucleic acid in a sample, as required by the introductory part of claim 1. The references to fingerprinting in document (2) only meant that a fingerprint was taken, but not that a comparison with a reference was made to actually identify or distinguish a nucleic acid. Consequently, step (d) of claim 1 was also not described in document (2). Furthermore, the passage on page 6, lines 4 to 13 of document (2) addressed a method in which one looked at differences in specific sequences, but this did not involve identifying or distinguishing a nucleic acid.
- 30.2 The Board cannot agree with Appellant I with respect to the passage on page 6, lines 4 to 13 of document (2), since the identification of a sequence difference still amounts to the identification or distinction of a nucleic acid, even if the sequence would already be known. Claim 1 does not require that the sequence of the nucleic acid which is identified or distinguished be unknown. The method described in said passage furthermore involves that the two nucleic acids are hybridised to the array (page 6, lines 7 to 10). Thus, a hybridization pattern and a reference hybridization pattern are obtained, as required by steps (b) and (c) of claim 1. Step (d) of claim 1 is also disclosed, since according to the sentence in lines 11 to 13 on page 6, positions in the array which are occupied by one sequence but not by the other show differences in the

two sequences, and it is this comparison of a hybridization pattern with a reference pattern by which a target nucleic acid is identified.

Therefore, the Board considers that document (2) describes a method for identifying or distinguishing a target nucleic acid in a sample comprising steps (b), (c) and (d) of claim 1.

30.3 Appellant I furthermore argued that document (2) did not disclose arrays with probe densities as high as those specified in step (a) of claim 1. The first part of document (2), which extended up to section 5.2 on page 11, merely provided an overall background and theoretical explanations. The table on page 8 of the document only illustrated the magnitude of the task of constructing a matrix needed to analyse entire genomes, but did not constitute a teaching of actually providing the arrays. The pixel size of 100 μm referred to in said table and on page 11, line 22 was a mere desideratum which the skilled reader would not have considered as workable. The arrays specified in the table on page 8 would thus not have been combined with the features of the methods described elsewhere in the document.

30.4 The Board cannot follow this line of argument. Document (2), which is an international patent application, describes on page 1, lines 3 to 16 prior art methods used for the molecular analysis of nucleic acid sequences. However, already in line 20 of page 1, reference is made to "[t]his invention", and in the following text, various aspects of said invention are described. The table on page 8 is an integral part of this description of the invention. The Board thus sees

no reason why the skilled reader would not use arrays as taught in said table in the methods provided by the document, notably in the method described on page 6, lines 4 to 13.

In the table on page 8, line 22 refers to a pixel size of 100 μm , which corresponds to a density of 10000 probes per cm^2 . The array suggested in line 25 of the same page consists of 10^6 different 10mers, the side of the matrix being 100 mm due to the pixel size of 100 μm . Page 11 of document (2) refers to 100 microns (1 micron being the same as 1 μm) as a "fairly comfortable upper limit" (lines 22 to 23) and states that with a smooth impermeable surface such as glass, "it may be possible to achieve a resolution of around 10 microns" (lines 24 to 26). The suggested resolution of 10 microns corresponds to a density of 10^6 probes per cm^2 . Also for arrays of this density, the Board sees no reason why a skilled reader would not consider to apply them in the methods suggested in document (2).

The Board thus concludes that document (2) suggests providing arrays with more than 100 probes and with pixel sizes of 10 and 100 μm , i.e. arrays encompassed by the definition of step (a) of claim 1, and using these arrays in a method according to claim 1.

31. Consequently, document (2) teaches a method comprising all the features of claim 1.

Enablement of document (2)

32. According to the established case law of the boards of appeal, a disclosure is novelty-destroying only if the

teaching it contains is reproducible (see "Case Law of the Boards of Appeal of the European Patent Office", 5th edition 2006, section I.C.2.12.).

In the present case, Appellant I argued that document (2) did not provide an enabling disclosure of arrays having pixel sizes of 100 or 10 μm , i.e. arrays as defined in step (a) of claim 1.

It thus has to be examined whether or not document (2) provides an enabling disclosure of such arrays.

In decision T 378/02 of 12 October 2005, which concerns the European patent arising from document (2), the Board was convinced that the requirements of Article 83 EPC were met (see points (7) to (13) of the reasons for the decision). As this finding in decision T 378/02 is not to be considered as *res iudicata* for the present case, the Board looks afresh at this issue on the basis of the evidence on file.

33. Appellant I argued that the so-called "rubber tubing" technique described in Example 3 of document (2), and also referred to in the post-published documents (20), (22) and (103), was not suitable to arrive at the high density arrays referred to in claim 1. According to page 17, line 33 to page 18, line 11 of document (2), lengths of silicone rubber tubing of a diameter of 1 mm were glued with silicone rubber cement to the surface of plain microscope slides in the form of a "U". Clamping these masks against a derivatised microscope slide produced a cavity into which the coupling solution was introduced through a syringe. In this way only the part of the slide within the cavity came into contact with

the phosphoramidite solution. Off-setting this mask by 3 mm up or down the derivatised slide in subsequent coupling reactions produced the oligonucleotides truncated at the 3' or 5' ends.

The Board agrees with Appellant I that due to the thickness of the silicone rubber tubing of 1 mm, the arrays obtained with this techniques have pixel sizes in the order of 1 mm, corresponding to densities in the order of 100 probes per cm², and that, therefore, the "rubber tubing" technique is not suitable to provide arrays with densities as specified in claim 1.

34. However, document (2) does not only describe the "rubber tubing" technique, but also suggests providing the arrays in question by using a computer controlled printing device, such as a pen plotter or an ink-jet printer (see points (28.4) and (28.5) above).

In this respect, Appellant I submitted that it would have involved undue burden and/or inventive skill to perform the developmental work necessary to put these suggestions into practise.

35. Document (76), an expert report of Dr Wallace, was referred to by Appellants II and III in the context of enablement of document (2). According to points 1.7.1 and 1.7.2 of document (76), Dr Wallace is an engineer specialized in fluid mechanics, who has twenty years experience in the design, fabrication, and operation of ink-jet print heads and printing systems, including conventional printing and other uses of ink-jet technology such as biomedical applications.

Document (76) provides a detailed analysis of the state of the art in ink-jet technology as of May 1988, and also comments on the feasibility of oligonucleotide array synthesis using ink-jet technology in 1988. It also reports about three successful efforts of oligonucleotide array synthesis using ink-jet technology in the 1990's, and that two of the three resulted in commercial success, and the third in a successful proof of principle demonstration (see point 9.1).

In the summary of conclusions of said document (pages 6 to 7), it is stated that "[d]rop and cell (pixel) sizes of 25 μm would not have been a significant technical challenge for commercial printer manufacturers in 1988" (point 1.9.3), and that a person skilled in the art in 1988 could have synthesized oligonucleotide arrays using ink-jet printing technology (point 1.9.7). Point 1.9.8 states that using small drop diameters and a solvent repellent grid, both achievable by one of ordinary skill in 1988, synthesis of oligonucleotide arrays with cell sizes in the 10-100 μm range was possible using ink-jet printing technology in 1988.

36. Appellant I submitted that the author of document (76) had no knowledge of DNA synthesis and did not give sufficient reasons for his assertion that it would have been possible to synthesize DNA arrays using ink-jet technology.

37. The Board considers that when attempting to put into practise the suggestions in document (2) of providing oligonucleotide arrays using a computer controlled printing device, the person to consult would be an expert in printing devices, with some additional

background in biological or biomedical applications. In this respect, the author of document (76), Dr Wallace, would be exactly the kind of skilled person to consult. In view of the comprehensiveness and preciseness of document (76), the Board does furthermore not consider the document deficient with respect to the reasons given for the author's findings and conclusions.

38. During the oral proceedings, Appellant I argued that the lack of enablement of document (2) was also apparent from the post-published document (100). The authors of this document, although highly skilled, reported in the abstract that they were "attempting" to produce high-density arrays using ink-jet printer heads. Whilst mentioning that arrays with spot sizes of 50 microns or even 5 microns could be achieved using the photolithographic techniques of the inventors of the patent in suit, and that arrays obtained according to the methods of documents (101) and (103), authored by Prof. Southern, had feature sizes in the order of millimetres, the authors of document (100) proposed to construct an automated machine to make custom high-density oligonucleotide arrays cheaply and efficiently. According to document (100), this involved two key features; the first was a mechanism for localizing and separating small reagent droplets by producing so-called surface tension wells, and the second challenge was to design ink-jet pumps to deliver small amounts of synthesis reagents to the appropriate wells (page 688, columns 1 and 2). Appellant I concluded that both of these key features required that an invention be made, and pointed out that even six years after the priority date of the patent in suit, the authors of document (100)

were still not in the position to put together all the elements suggested in document (2).

39. The Board is not convinced by this line of argumentation. The first of the two key features of the strategy of the authors of document (100) involved using conventional photolithography to produce 100 micron circles of photoresist on the wafer surface and creating a highly hydrophobic coating onto the surrounding of the resist-protected circles. The resist is then removed, "exposing the circular regions of the wafer for further modification and DNA synthesis following generally the procedures of Southern *et al.*" (page 688, column 1, last paragraph). The Board cannot recognize that arriving at this first key feature would have required that an invention be made, as document (2) already suggests using a laser typesetter to preform a solvent repellent grid in order to achieve a resolution of around 10 microns (page 11, lines 24 to 28). From the evidence on file, the Board sees no reason to believe that putting this suggestion of a solvent repellent grid into practise would have involved inventive skill or undue burden. This is also supported by the statement of Dr Wallace in document (76), page 39, point 7.4.1, that he would interpret the reference to a laser typesetter in said passage of document (2) as a proposal to use photolithographic techniques to generate the solvent repellent grid.
40. The second key feature identified by the authors of document (100) "is to deliver small amounts of synthesis reagents to the appropriate wells. Our strategy uses microfabricated ink-jet pumps, similar to those used in certain ink-jet printers..." (page 688, column 2,

lines 1 to 4). Since, however, document (2) already suggests using ink-jet printing technology to deliver small amounts of synthesis reagents to the wells on the support, and Dr Wallace confirms in document (76) that small drop diameters were technically feasible in 1988 (see point (35) above), the Board likewise sees no reasons to believe that inventive skill or undue burden was necessary to put the suggestion already made in document (2) into practise.

41. Appellant I further submitted that providing oligonucleotide arrays using ink-jet printing technology involved additional problems such as the precise positioning of the printing nozzle (registration) and the adaptation of the chemistry to aqueous solvents, which, in order to be solved, required inventive skill and/or undue burden.

42. The Board is not convinced by these arguments. With respect to the issue of registration, point 6.4 on page 36 of document (76) explains that positioning components appropriate for mounting and moving a rigid substrate such as a glass slide were readily available in 1988 (point 6.4.1) and that alignment of the printhead(s) to the substrate could be accomplished. Furthermore, document (100) states on page 689, column 1, lines 1 to 4, following the explanations of the two key features of the described strategy, that "with these essential technologies in place, it then becomes a matter of **straightforward electrical and mechanical engineering** to scan the array across a set of pumps using a computer-controlled x-y translation stage" (emphasis added by the Board). There are no indications in document (100) that registration would cause any

serious problems, and there is also no other evidence on file from which the Board could conclude that when putting the suggestions of document (2) into practise, problems with registration would indeed have occurred which, in order to be solved, would have required inventive skill or undue burden.

Similarly, the Board concludes from the evidence on file that in order to put the suggestions of document (2) into practise, the chemistry for synthesizing the oligonucleotides as described in said document and generally known before the priority date of the patent in suit would not have required major modifications which would have involved inventive skill or undue burden. In fact, the authors of document (100) state on page 688, column 1, that the arrays provided by documents (101) and (103) authored by Prof. Southern "demonstrate that the chemistry works and that the resulting oligos hybridize as expected" (lines 21 to 22), and that they intend to perform DNA synthesis "following generally the procedure of Southern *et al.*" (lines 49 to 50).

43. Appellant I further argued that synthesizing DNA arrays using ink-jet technology would require a re-design of the ink-jet printer in order to avoid incompatibility of parts of the printer with the solvents used, and that this would represent an engineering problem.

44. In view of point 5.4 on page 31 of document (76), the Board takes however the position that a skilled person would have known that compatibility of the printer material with the solvents used would be required, and that he/she would have been able to select the printer

material accordingly. Furthermore, document (2) describes in its Example 5 on page 20, lines 24 to 30, that the pen of the pen plotter had been replaced by a component, fabricated from Nylon, which carried a polytetrafluoroethylene (PTFE) tube, through which chemicals could be delivered to the surface of the glass slide, thus making it clear to the skilled reader that the materials of the equipment would need to be compatible with the chemicals used for DNA synthesis.

45. A further argument presented by Appellant I to support his position was that Prof. Southern, the inventor of document (2), did not pick up his own suggestions made in said document. This was demonstrated by the post-published document (101), authored by Prof. Southern, which described a different approach of making oligonucleotide arrays.
46. The Board considers that no conclusion on the question of enablement of document (2) can be drawn from the fact that Prof. Southern himself did not pursue the suggestions made in document (2), since this can have many possible reasons, such as personal or commercial reasons, which may be completely unrelated to the issue of enablement.
47. Appellant I furthermore referred to document (21), a declaration of Prof. Cass. In this declaration, Prof. Cass expresses concerns that putting the suggestions of document (2) into practise would be extremely difficult and would involve serious problems, such as removing excess reagents and by-products, spreading and evaporation of the solvent used, adaptation of a laser typesetter to lay down a solvent

repellent grid and registration. Without putting into question the expertise of Prof. Cass expressed in his declaration, the Board considers that in the light of the detailed explanations of Dr Wallace in document (76) (see points (35) and (37) above), said concerns do not seem to be serious obstacles for the skilled person to put the suggestions made in document (2) into practise. It is undisputed that after the priority date of the patent in suit, high density oligonucleotide arrays were successfully produced using ink-jet printing technology, and from the arguments and evidence presented, the Board is not convinced that the development work necessary to put the suggestions made in document (2) into practise required inventive skill or undue burden.

48. The Board recognizes that starting from the disclosure of document (2) relating to the production of oligonucleotide arrays of high density using a computer controlled printing device, a person skilled in the art would have had to invest a lot of time and effort to provide the equipment necessary to put the suggestions made in said document into practise. However, the Board concludes from the evidence on file that this putting into practise would not have required inventive skill or undue burden.

49. The Board is thus convinced that document (2) discloses a method according to claim 1 of auxiliary request II in an enabling way. Therefore, document (2) is prejudicial to the novelty of the subject-matter of claim 1 of that request. Consequently, the subject-matter of claim 1 of auxiliary request II does not fulfil the requirements of Article 54(2) EPC.

Auxiliary Request III

Admission into the procedure - Article 114(2) EPC

50. Auxiliary request III has been filed by Appellant I on the second day of the oral proceedings after he was informed that neither the main request nor auxiliary requests I or II met the requirements of the EPC.

The principles concerning amendments to a party's case are laid down in Article 13 of the Rules of Procedure of the Boards of Appeal (RPBA).

According to Article 13(1) RPBA, any amendment to a party's case after it has filed its grounds of appeal or reply may be admitted and considered at the Board's discretion. The discretion shall be exercised in view of inter alia the complexity of the new subject matter submitted, the current state of the proceedings and the need for procedural economy. Article 13(3) RPBA states that amendments sought to be made after oral proceedings have been arranged shall not be admitted if they raise issues which the Board or the other party or parties cannot reasonably be expected to deal with without adjournment of the oral proceedings.

51. The principles applicable to the admission into the procedure of new requests have been comprehensively discussed by this Board in a different composition in decision T 794/94 of 17 September 1998 (see point (2) of the reasons).

No guidelines which fetter the discretion of the Boards can be given, because the admission of late requests is to a high degree depending on the actual situation in each case (see decision T 794/94; supra, point (2.1.3)).

However, the following "advisable action" is provided in point (2.2.1) when putting forward late requests: "If it can quickly be checked that requests meet the requirements of Articles 123 and 84 EPC, and are necessary and appropriate to meet a ground for opposition, the chances of such a request being accepted even at a very late stage are much improved".

52. Claim 1 of auxiliary request III corresponds substantially to claim 1 of auxiliary request II, with the only exception that at the end of item (a) the following formulation has been added: "..., and wherein said locations are less than 50 μm x 50 μm ; ...".

Appellant I identified the disclosure on page 28, lines 25 to 27 of document (7), corresponding to page 29, lines 25 to 27 of the application as originally filed) as basis for this amendment, which reads:

"The regions for synthesis may be very small, usually less than about 100 μm x 100 μm , more usually less than about 50 μm x 50 μm ."

53. At a first glance, this amendment gives rise to the following considerations:

- Is the term "regions for synthesis" a basis for the term "locations" used in the claim (Articles 76(1) and 123(2) EPC)?

- If not, what is its exact meaning (Article 84 EPC)?
- Page 28 of document (7) belongs to section (III)(A), which refers to "Preparation of Substrate Matrix". Two alternative preparation pathways are disclosed in this section. Oligomer sequences are either synthesized in a separate step and then individually positionally attached to a substrate (page 27, line 27 to page 28, line 4, of document (7)) or, instead of separate synthesis of each oligonucleotide, they are synthesized in parallel on a defined matrix pattern as provided in document (1), disclosing the VLSIPS technology (starting on page 28, line 5, of document (7)). Claim 1(a) covers both alternatives. If the term "regions of synthesis ... less than about 50 μm x 50 μm " is considered to be disclosed in document (7) (and in the application as filed) only in connection with the second alternative, i.e. in situ synthesis of the oligonucleotides on the substrate, its introduction into claim 1 would amount to a non-allowable generalisation of a feature in a claim (Articles 76(1) and 123(2) EPC). If the term in question is considered to be disclosed also in connection with the first alternative, i.e. synthesis of the oligonucleotides in a separate step and afterwards attachment to a substrate, it is most unclear how this feature could define the array provided according to claim 1(a) (Article 84 EPC).

54. In view of new, unresolved issues caused by claim 1 of auxiliary request III, the Board cannot consider it to be a clearly allowable request, such as might be admitted into the proceedings at such a late stage, and the Board exercises its discretion under Article 114(2)

EPC not to admit this claim request into the proceedings.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

Registrar:

Chair:

P. Cremona

U. Kinkeldey