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D E C I S I O N
of 12 October 2005

Case Number: T 0378/02 - 3.3.04

Application Number: 89905449.8

Publication Number: 0373203

IPC: C12Q 1/68

Language of the proceedings: EN

Title of invention:

Method and apparatus for analysing polynucleotide sequences

Patentee:

OXFORD GENE TECHNOLOGY LIMITED

Opponents:

- 01: Hyseq Inc.
02: Nanogen Inc.
03: F.HOFFMANN-LA ROCHE & CO.
04: Abbott Laboratories
05: Multilyte Ltd.
06: Vysis Corp.

Headword:

Analysis of polynucleotide sequences/OXFORD GENE TECHNOLOGY

Relevant legal provisions:

EPC Art. 54, 56, 83, 84, 123(2)(3)

Keyword:

"Novelty, inventive step, sufficiency of disclosure,
clarity (yes), added subject-matter, extension of scope of
protection (no) "

Decisions cited:

T 0019/90, T 0409/91, T 0694/92, T 0412/93, T 0860/93,
T 0639/95, T 0860/95, T 0994/95, T 0188/97, T 0636/97,
T 0649/97, T 0728/98, T 1041/98, T 0193/01

Catchword:

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Case Number: T 0378/02 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 12 October 2005

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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
26 February 2002 concerning maintenance of the
European patent No. 0373203 in amended form.

Composition of the Board:

Chairman: M. Wieser
Members: G. Alt
G. Weiss

Summary of Facts and Submissions

- I. European patent No. 0 373 203 with the title "Method and apparatus for analysing polynucleotide sequences" was granted with twenty-three claims on the basis of European patent application 89 905 449.8 which was derived from International application WO 89/10977.
- II. The patent had been opposed by seven parties (opponents 01 to 07) under Article 100(a) EPC for not being an invention in the sense of Article 52(2) EPC, for lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), under Article 100(b) EPC on the ground of lack of sufficient disclosure (Article 83 EPC) and under Article 100(c) EPC on the ground of added subject-matter.

Opponent 07 withdrew his opposition during the opposition procedure and thus ceased to be a party to the procedure.

- III. The opposition division had decided that the claims of the main request before them violated the requirements of Article 123(2) EPC, but that the claims of the first auxiliary request met all requirements of the EPC.
- IV. Appeals were lodged by opponent 02 (appellant I), opponent 03 (appellant II), opponent 05 (appellant III) and opponent 06 (appellant IV).

Opponents 01 and 04 are parties to the proceedings as of right according to Article 107 EPC.

- V. The patent proprietor, who initially also lodged an appeal against the decision of the opposition division, withdrew this appeal with letter of 10 October 2005 and is therefore respondent in the present appeal procedure.
- VI. The board expressed its preliminary opinion in a communication dated 14 July 2005. Oral proceedings were held on 11 and 12 October 2005 in the absence of appellants II and IV and of the other parties, opponents 01 and 04. At these proceedings the respondent filed a new main request consisting of claims 1 to 22.

Independent claims 1, 10, 14, 15 and 18 thereof read as follows:

"1. A method of analysing a polynucleotide sequence by the use of a glass support, to a smooth impermeable surface of which is attached an array of the whole or a chosen part of a complete set of oligonucleotides of chosen lengths, the different oligonucleotides being attached through a covalent link and occupying separate cells of the array, which method comprises labelling the polynucleotide sequence or fragments thereof, applying the polynucleotide sequence or fragments thereof under hybridisation conditions to the array, and observing the location of the label on the surface associated with particular members of the set of oligonucleotides.

10. Apparatus suitable for analysing a polynucleotide sequence by the method of any one of claims 1 to 9 comprising a glass support and attached to a smooth impermeable surface thereof an array of the whole or a

chosen part of a complete set of oligonucleotides of chosen lengths, the different oligonucleotides being attached through a covalent link, occupying separate cells of the array, and being capable of taking part in hybridisation reactions.

14. Apparatus for determining the sequence of a polynucleotide comprising a glass support having attached to a smooth impermeable surface thereof an array of different oligonucleotides with defined sequences, the oligonucleotides occupying cells of the array and being attached through a covalent link to the surface and being capable of taking part in hybridisation reactions, wherein the defined sequence of an oligonucleotide of one cell of the array is different than the defined sequence of an oligonucleotide of another cell of the array.

15. Apparatus for analysing a polynucleotide, the apparatus comprising a glass support segregated into at least two defined cells, each cell having attached to a smooth impermeable surface thereof, through a covalent link, oligonucleotides with known sequence, capable of taking part in hybridisation reactions, where the sequence of the oligonucleotides of a first cell is different than the sequence of the oligonucleotides of a different cell.

18. A method for generating, for the apparatus of claim 14, an array of oligonucleotides of chosen lengths within discrete cells of a glass support material having a smooth impermeable surface comprising the steps of

- a) segregating the smooth impermeable surface of the support material into discrete cell locations;
- b) coupling a nucleotide to a first set of cell locations;
- c) coupling a nucleotide to a second set of cell locations;
- d) coupling a nucleotide to a third set of cell locations;
- e) and continuing the sequence of coupling steps until the desired array has been generated,

the coupling being effected at each location either to the surface of the support or to a nucleotide coupled in a previous step at that location."

VII. Appellants I to IV requested that the decision under appeal be set aside and that the patent be revoked.

The respondent requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 22 of the main request filed at the oral proceedings on 11 October 2005.

VIII. The following documents are referred to in this decision:

- OD1: EP-A-0 235 726
- OD2: EP-A-0 171 150
- OD6: Cell, col. 12, 1977, pages 23-36, Dunn, A. and Hassell, J.
- OD13: WO 85/01051
- OD15: Nucleic Acids Research, vol. 11, no. 13, 1983, pages 4365-4377, Frank, R. et al.
- OD18: WO 88/01302

OD19: WO 86/03782
OD20: US 4,395,486
OD32: WO 93/22480
OD33: Genomics, vol. 13, 1992, pages 1008-1017,
Southern, E.M. et al.
OD38: Nucleic Acids Research, vol. 15, no. 13,
1987, pages 5373-5390, Gingeras, T.R. et al.
OD41: US 4,704,353
OD45: WO 84/03151
OD50: EP-A-0 130 523
OD61: Nucleic Acids Research, vol. 15, no. 13,
July 1987, pages 5353-5371, Ghosh, S. S. and
Musso, G.F.
OD87: US 4,591,570
AD95: Gelb, L.V. and Gubbins, K.E.
"Characterization of porous glasses by
adsorption: Models, simulations and data
inversion" referring to Nature, vol. 206,
1965, pages 693-696, Haller, W. (reference
number [4])
AD96: Nucleic Acids Research, vol. 15, no. 7,
1987, pages 2891-2909, Kremsky, J.N. et al.
AD97: Nucleic Acids Research, vol. 15, no. 7,
1987, pages 2911-2916, Wolf, S.F. et al.
AD100: Nature Biotechnology, vol. 15, December
1997, pages 1359-1367
AD101: US 4,000,252
AD102: US 4,145,406
AD103: US 4,205,952
AD104: US 4,254,082
AD106: US 4,323,647
AD107: US 4,442,204

Lecture by Prof Ekins given on 11 April 1988 and post-
published paper corresponding to said lecture

IX. The arguments of appellants I to IV as far as they are relevant for the present decision may be summarized as follows:

Clarity

The term "...a glass support, to a smooth impermeable surface of which is attached..." not only encompassed the covalent attachment of the oligonucleotides directly to the glass surface, but also the indirect attachment through a second layer situated on top of the glass surface. This second layer was defined only by the two relative terms "smooth" and "impermeable", which made it impossible to exactly define the nature of this layer.

Even if the terms "smooth" and "impermeable" were considered to define the direct surface of the glass support, this definition was ambiguous because of the existence of different kinds of glass with different degrees of smoothness.

Novelty

Document OD2 described a method for screening by hybridisation of a plurality of unknown nucleic acids covalently attached to a solid support. Several materials were disclosed as support materials including, inter alia, "glass (e.g. solid, fibre etc)" (page 6). This definition implicitly included glass with a smooth and impermeable surface. Since the document also disclosed all the other features of the subject-matter of claims 1, 14 and 15, it destroyed the novelty.

Sufficiency of disclosure

The claimed method embraced high density arrays. However, the specification failed to enable the production of such arrays because, as stated in the patent in suit, the automatic equipment for achieving them had not yet been produced at the priority date and the level of time and effort needed for the adaptation of existing equipment according to the suggestions in the patent in suit amounted to an undue burden. According to decisions T 994/95, T 188/97, T 412/93 and T 639/95 sufficiency of disclosure should be denied under such circumstances.

Statements in post-published documents OD32 and OD33, saying that large-scale nucleic acid sequence analysis was not achievable due to the lack of automated equipment and that even with automated methods synthesis of a large number of oligonucleotides was not easy, corroborated the view that the claimed invention had not been sufficiently disclosed at the priority date of the patent.

Document AD100, published in 1997, dealt with a high-density array for monitoring the expression of the yeast genome and was therefore exemplary for modern array techniques. However, some aspects of the method disclosed therein were not implemented in the method of the patent in suit. This discrepancy demonstrated that the invention was not sufficiently disclosed.

Inventive step

Either the lecture of Prof. Ekins or one of documents OD1 or OD2 was the closest prior art document.

In his lecture Prof. Ekins reported about a multi-analyte microspot immunoassay system allowing the determination of a large number of different proteins in a sample and using glass as a support. Starting from this prior art it would have been obvious to the skilled person that the same multispot format could be used for nucleic acid hybridisation assays since it was well-known that antibodies and nucleic acids were alternative types of binding agents that could be used interchangeably in assays as suggested in documents AD101 to AD108.

Documents OD1 or OD2 both related to nucleic acid assays in array format. The problem to be solved in the light of their disclosure was the provision of a further, alternative assay. The solution to this problem was the use of a support made of glass with a smooth and impermeable surface.

This solution was obvious in view of either of documents OD13 or OD61 disclosing methods to covalently immobilise DNA on controlled pore glass. A skilled person would have realized that these techniques were also suitable for coupling of nucleic acid to glass with a smooth impermeable surface and would therefore have replaced the support material of documents OD1 and OD2 by that type of material.

Moreover, the aspect of attaching a receptor and an analyte in a regular pattern on a surface was not confined to the situation where both receptor and analyte were nucleic acids. Therefore, it was legitimate to look at disclosures relating to the attachment of a different substance to a surface, for example at documents OD45 or the related US patent OD87 dealing with immunoassays and mentioning specifically the use of a "flat, planar surface such as glass or a plastic coverslip". Documents such as AD101 to AD108 relating generally to binding assays confirmed that nucleic acid and antibody antigen binding were equivalent and that the same support material could be used.

Finally, document OD41, relating to photoresponsive redox detection, disclosed that oligonucleotides could be bound to glass surfaces.

- X. The respondent's arguments as far as they are relevant for the present decision may be summarized as follows:

Clarity

Relative terms in claims are allowable if they are clear in view of the complete specification, see for example decisions T 860/93, T 860/95, T 649/97, T 1041/98 and T 193/01. This was the case here, because it was clear from the disclosure in the patent as a whole that the definition "a glass support, to a smooth and impermeable surface of which" meant ordinary glass like window glass or glass of which microscope slides were made.

Moreover, a second layer on the top of the glass surface was nowhere disclosed in the patent in suit.

Novelty

Document OD2 did not disclose smooth impermeable glass as a support because the type of glass referred to in document OD2 had to be flexible. This was not a property of the type of glass defined in claim 1 of the patent in suit.

Sufficiency of disclosure

The appellants did not provide evidence substantiating difficulties when repeating examples of the patent or proving errors in its technical details. Without such evidence an objection under Article 83 EPC could not be successful in view of decision T 19/90.

It may be true that document AD100 disclosed process parameters which were different from those in the patent in suit. However, showing that something worked in a different way was not a proof that it did not also work the other way.

Inventive step

The lecture by Prof. Ekins could not be considered to be the closest prior art document because it did not relate to nucleic acid hybridisation. Rather, the closest prior art was represented by document OD1. The patent in suit was distinguished therefrom by the use of a support made of glass with a smooth impermeable surface for covalent attachment of nucleic acids.

The problem to be solved was the provision of an improved apparatus and method for parallel analysis of nucleic acid by hybridisation.

Up to the time when the invention was made, porous supports were considered to be necessary since they could bind more nucleic acid. Neither was there a hint in the closest prior art, document OD1, to use a different support material, nor could the skilled person, trying to solve the posed problem, arrive at the claimed solution in an obvious way by combining the teaching in OD1 with any other prior art document on file because none of them pointed to the covalent attachment of nucleic acid to glass with a smooth and impermeable surface.

Reasons for the Decision

Amendments and extension of scope

1. The claims have the following basis in the application documents as originally filed:

Claim 1 differs from claim 8 as originally filed by the term "glass" in front of the term "support". This amendment and the corresponding amendments in claims 10, 14, 15 and 18 are based on page 11, lines 24 to 25 and claim 6 as originally filed.

Claims 2 to 7 are based on claims 9 to 14 and claim 8 is based on claim 7 as originally filed.

Support for claim 9 comes from the application documents as originally filed as a whole because the gist of the method disclosed therein is that the bound known sequence is tested with an unknown sequence. The presence of oligonucleotides in cells is disclosed on page 11: "The method described here envisages that the matrix will be produced by synthesising oligonucleotides in the **cells** of an array...".

Claim 10 is a combination of claims 1 and 8 as originally filed.

Claims 11 to 13 correspond to claims 2 to 4 as originally filed.

Claim 14 is based on claim 1 and point 4 of the description as originally filed. The expression "capable of taking part in hybridization reactions" which is likewise introduced in claim 15, is found in claim 1 as originally filed.

Claim 15 relies on Example 2 disclosing the attachment of two oligonucleotides with different sequences to the surface of the support and claim 3 referring to an array comprising one or more pairs of oligonucleotides.

Claims 16 and 17 correspond to claims 5 and 7 as originally filed.

Claims 18 and 19, 21 and 22 refer in a generic form to specific examples 3 and 5. This generalisation is supported by the application documents as a whole and therefore does not add subject-matter.

Claim 20 is based on page 11 disclosing that the size of cells may vary depending on the complexity of the array and that 100 microns is a comfortable upper limit, whereas 10 microns may also be possible to achieve.

2. The insertion of the term "glass" limits the support materials that can be used in the claimed method and therefore results in a restriction of the claimed subject-matter vis-à-vis the subject-matter of the claims as granted.
3. Hence, the claims fulfil the requirements of Articles 123(2) and (3) EPC.

Clarity

4. The appellants argue that the term "... a glass support, to a smooth impermeable surface of which is attached..." not only encompasses the direct, covalent attachment of the oligonucleotides to the glass surface, but also their indirect attachment through a second layer situated on top of the glass surface. Since this layer is only defined by the two relative terms "smooth" and "impermeable", it is impossible to exactly define its nature and consequently the claim lacks clarity.
 - 4.1 In the board's view, the comma after the term "support" in connection with the reference "of which" in the expression after the comma "to a smooth impermeable surface of which" makes it clear that the definition provided by the expression after the comma refers to the surface of the glass support itself.

4.2 Moreover, support for this interpretation comes from the disclosure of the patent as a whole, which pursuant to Article 69 EPC must be taken into account in order to arrive at a technically sensible interpretation of a claim. At no place the patent in suit discloses a second layer and although in all examples the oligonucleotides are immobilized on a microscope slide which is chemically modified with an aliphatic linker, this modification does not create a second surface in addition to the surface of the glass support.

4.3 Thus, the board considers that in view of points 4.1 and 4.2 above, the second interpretation, i.e. the presence of a second, different material layer, is ruled out.

5. The appellants further argue that even if the terms "smooth" and "impermeable" are considered to define the direct surface of the glass support, such a definition of the surface is ambiguous, because "smooth" is a relative term.

5.1 Relative terms constitute a potentially unclear element due to their characteristic to change their meaning according to the context. In the case law such terms were nevertheless considered as clear and their use in a patent therefore allowed, if their meaning was clear in the context of the whole disclosure. This was the case, for example, in the following decisions and for the following terms: T 860/93 (OJ EPO 1995, page 47) - "water-soluble"; T 860/95 of 27 October 1999 - "a long period of time"; T 649/97 of 8 December 2000 - "transparent"; T 1041/98 of 22 October 2001 - "thin plate"; T 193/01 of 4 June 2004 - "thin film composite".

In contrast, in decision T 728/98 of 12 May 2000 the term "substantially pure" was considered unclear per se and in the light of the description.

- 5.2 The board agrees that "smooth" is a relative term. Thus, the question is whether its meaning is clear in the context of the patent in suit.

As stated above, in all the examples the glass support is represented by a microscope slide whereas the attachment of oligonucleotides to controlled pore glass (part 5.3 of the patent) is marked "for reference purposes". Hence, the frame for the degree of smoothness is delimited: The glass surface is smoother than controlled pore glass and as smooth as glass of ordinary microscope slides or smoother.

Thus, in the board's view, in the context of the disclosure of the patent in suit as a whole, the term "smooth" represents a clear definition of which form the glass support may take and does therefore not render the claim unclear.

6. Hence, the claims fulfil the requirement of Article 84 EPC.

Sufficiency of disclosure

7. According to the case law of the Boards of Appeal the disclosure of a patent must allow the skilled person to perform the invention over the whole range claimed without undue burden (for example decisions T 409/91, OJ EPO 1994, page 653 or T 694/92, OJ EPO 1998, page 97).

8. Doubts as to whether an invention can be carried out in the whole claimed area must according to decision T 19/90 (OJ EPO 1990, page 476) be substantiated by verifiable facts.

9. The method according to claim 1 comprises the covalent attachment of oligonucleotides to different cells on a surface. The cells are arranged in the form of a rectangular matrix, i.e. an array. This arrangement permits any spot to be readily identified by reference to coordinates giving the row and column number of the particular spot. Claim 1 does not contain a restriction as to the number of spots per surface area. Hence, it covers methods for analysing polynucleotides at a high density of nucleic acid spots.
 - 9.1 The appellants argue that the patent in suit does not enable the generation of such arrays because automatic equipment for their preparation was either not available at all at the priority date of the patent in suit or, at least, its preparation amounted to an undue burden. In order to substantiate their argument they rely on a statement in part 5.2 of the patent in suit saying that "automatic equipment for applying the precursors has yet to be developed", on a statement on page 8 of the post-published document OD32 that "at the present time there is a need for methods of nucleic acid sequence analysis which can be automated so that they can be applied on a large scale" and on a statement on page 1008 of post-published document OD33 that "it is not easy to synthesize large numbers of oligonucleotides even with automated methods".

- 9.2 The board is not convinced by this line of argumentation. Stating, as in document OD32, that there is a need for a certain method does not necessarily mean that no other methods existed before. Likewise, saying as in document OD33 that something is not easy to carry out does not mean that it is impossible. And indeed, the patent in suit itself demonstrates in Example 5 that a pen plotter can be adapted to deliver nucleotides to a glass surface for synthesis of oligonucleotides and how that can be done: "The pen of the plotter had been 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 the chemicals could be delivered to the surface of the glass slide which lay on the bed of the plotter: A microcomputer was used to control the plotter and the syringe pump which delivered the chemicals. The pen, carrying the delivery tube from the syringe, was moved into position above the slide, the pen was lowered and the pump activated to lay down the coupling solution. Filling the pen successively with G, T and A phosphoramidite solutions an array of twelve spots was laid down in three groups of four, with the different oligonucleotide sequences." Hence, the board concludes that automatic equipment could be made.
10. Furthermore, the appellants, by referring to decisions T 994/95 of 18 February 1999, T 188/97 of 08 February 2001, T 412/93 of 21 November 1994 and T 639/95 of 21 January 1998 argue that, according to the case law of the Boards of Appeal, sufficiency of disclosure has to be denied when the total amount of required experimentation is so high as to amount to an

- undue burden. They conclude that, even if the automatic equipment could be made, the amount of time and effort needed for its preparation would be so high as to amount to an undue burden.
- 10.1 An objection of this kind, to the effect that carrying out an invention involves undue burden, must, like an objection that the invention cannot be carried out or cannot be carried out over the whole claimed scope, be substantiated by verifiable facts (see point 8 above). In contrast to the situation in the decisions of the Boards of Appeal cited in point 10 above, the board does not in the present case have at its disposal any convincing evidence of how high the amount of effort needed would be, and can therefore not come to the conclusion that an undue burden is involved.
- 10.2 Hence, the available evidence does not allow the board to arrive at the judgement that the manufacture of automatic equipment for preparing large arrays amounts to an undue burden. Consequently, the objection of lack of sufficiency of disclosure based on this argument must fail.
11. In a further line of argumentation the appellants submit that the claimed method as such cannot be carried out as it neglects the teaching in post-published document AD100 which discloses a modern method for preparing a high-density array which differs in some aspects from the one disclosed in the patent in suit. However, this argument must also fail. A piece of evidence describing a specific solution to a posed problem cannot be considered to be a proof that a different solution to the same problem is not operable.

Thus, there is no evidence on file that a skilled person, when trying to prepare a high-density array, would fail as a result of deviating from the teaching in document AD100.

12. According to the relevant case law of the Boards of Appeal the question of the allowable width of a claim in relation to sufficiency depends on the evidence on file in each case. Therefore, in some cases the boards found on the basis of the available evidence that the subject-matter of broad claims was not disclosed by the specification in a manner sufficiently clear and complete for it to be carried by a skilled person, for example T 694/92 (supra), whereas in others they found that it was, for example T 412/93 (supra). This view is also expressed by the board in decision T 636/97 of 26 March 1998.
13. The board finds that the appellants in the present case did not provide evidence showing that the invention claimed is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. Therefore, the requirements of Article 83 EPC are met.

Novelty

14. The appellants consider document OD2 as novelty-destroying to the subject-matter of claims 1, 14 and 15. It is argued that this document implicitly discloses the use of a glass support, to the smooth impermeable surface of which are covalently bound nucleic acids.

15. The implicit disclosure content of a document is the information which the skilled person derives from it directly and unambiguously on the basis of his/her common general knowledge in combination with the explicit disclosure of that document.
16. Thus, at first, the explicit disclosure content of document OD2 has to be determined. Document OD2 relates to a method of analyzing an analyte in a sample including optional control procedures. The compound to be analysed may be a protein or a nucleic acid. The general description of the support is as follows:

"The solid support itself may assume a variety of configurations such as, eg, a flat rectangular sheet; a round sheet; a rod; a stick; a cylinder; etc. Preferably, the support is a flat, rectangular sheet. For obvious reasons the solid support is preferably water-insoluble and flexible. The solid support may be made of a material selected from the group consisting of: polyvinyl, polystyrene, cellulose, nylon or glass (eg, solid, fiber, etc)" (page 6).

"The solid support is insoluble in the solution being analyzed and is preferably sufficiently flexible to provide for ease of manipulation. The support of the invention may assume a variety of configurations and may be round and flat, card-like, e.g., square or rectangular and flat, tubular, a rod, a stick, cylinder, etc. The support used may obviously be any material capable of maintaining its general configuration during use" (page 21-22).

The specific examples describe attachment of immunoglobulins to a polystyrene support. On page 44 it is mentioned that "nucleic acids and polysaccharides binding to plastic surfaces may be facilitated by a polycationic linking polymer such as polylysine".

Claims characterizing the support read: "17. The system as defined by claim 1 wherein said solid support is insoluble and flexible, and is selected from the group consisting of: a flat, rectangular sheet; a round sheet; **and rod**; a stick; or a cylinder." and "18. The system as defined by claim 17 wherein said support is made of a material selected from the group consisting of: polyvinyl, polystyrene, cellulose, nylon or glass."

- 16.1 Hence, the skilled person derives from the whole explicit disclosure that the kind of glass contemplated as support in document OD2 should be water-insoluble and flexible.
17. The disclosure in document OD2 could be considered as novelty-destroying if the skilled person on the basis of his/her common general knowledge about immobilising nucleic acids were aware of any water-insoluble and flexible glass that, at the same time, had a smooth impermeable surface.
- 17.1 The common general knowledge is represented by basic handbooks and textbooks published before the relevant date of the document of which the implicit disclosure content is to be determined. However, such a type of document is not on file.

17.2 The only document in these proceedings published before the priority date of document OD2 and using a "glass" support is document OD15, published in July 1983. It discloses chemical synthesis of oligonucleotides on glass fibre filters. Even if, for the sake of argument, this document is considered to reflect common general knowledge because it was published long before the priority date of document OD2, the board considers that its contents would not have led the skilled person to imply that the reference in document OD2 to "glass" was to glass with a smooth and impermeable surface. The glass fibre filters disclosed in document OD15 fulfil the characteristics of the support described in document OD2, i.e. they are water-insoluble and flexible. They do not, however, comply with the definition in claim 1 because they are at least not impermeable.

17.3 Hence, the board judges that document OD2 does not implicitly disclose the use of a glass support to a smooth impermeable surface of which are attached oligonucleotides in an assay as defined in claim 1.

18. The reasons for finding the subject-matter of claim 1 novel apply as well to the subject-matter of claims 14 and 15 because the glass support as defined in claim 1 is a feature of these claims, too.

19. The subject-matter of the claims fulfils the requirements of Article 54 EPC.

Inventive step

20. The appellants take the view that a lecture held by Prof. Ekins or either of documents OD1 or OD2 are candidates for the closest prior art.

20.1 Prof. Ekins' lecture refers to a microarray format technique in the immunoassay field. Documents OD1 and OD2 both deal with the detection of nucleic acids.

In accordance with the problem and solution approach, the Boards of Appeal have developed in their case law certain criteria for identifying the closest prior art which provides the best starting point for assessing inventive step. It has been repeatedly pointed out that this should be prior art relating to subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention (cf. Case Law of the Boards of Appeal of the European Patent Office, 4th Edition 2001, chapter I.D.3).

20.2 The present invention relates to the field of nucleic acid analysis. Hence, in the board's judgement either of documents OD1 or OD2 and not the lecture of Prof. Ekins relating to protein analysis are appropriate documents.

20.3 If several documents relate to the same purpose, a secondary consideration for the selection of the closest prior art document is the highest degree of identity of technical features (cf. Case Law of the Boards of Appeal of the European Patent Office, 4th Edition 2001, chapter I.D.3).

- 20.4 In the assay of document OD2 a binding partner for the molecule to be analysed is affixed onto a surface, and the compound to be analysed, the analyte, binds to its fixed partner. The presence of the bound analyte is determined by a labelled molecule, a probe, which is either the analyte itself (competitive assay) or an antibody to the analyte (sandwich assay) (page 2).
- 20.5 In the method of document OD1 the nucleic acids to be analysed are labelled and the probes are immobilized on the support. The presence of the analyte is determined by binding of the labelled analyte to the bound probe. The method according to claim 1 relies on the same principle. Hence, document OD1 is the closest prior art document.
21. It was not disputed by the parties that document OD1 discloses all features of claim 1 with the exception of the support material to which the probes are attached. In this respect document OD1 states in general terms on page 9: "Useful solid supports are well known in the art and include those which bind nucleic acids either covalently or non-covalently. Non-covalent supports which are generally understood to involve hydrophobic bonding include naturally occurring and synthetic polymeric materials, such as nitrocellulose, derivatized nylon and fluorinated polyhydrocarbons, in a variety of forms such as filters, beads or solid sheets. Covalent binding supports (in the form of filters, beads or solid sheets, just to mention a few) are also useful and comprise materials having chemically reactive groups or groups, such as dichlorotriazine, diazobenzyloxymethyl, and the like, which can be activated for binding to polynucleotides."

The specific supports materials disclosed in the examples are nylon membranes or nitrocellulose.

22. The next step in assessing inventive step in accordance with the problem-solution-approach is the definition of the technical problem to be solved as the object of the invention in order to generate those effects to be achieved by the claimed subject-matter compared with that of the closest state of the art (cf. Case Law of the Boards of Appeal of the European Patent Office, 4th Edition 2001, chapter I.D.2).
- 22.1 The problem to be solved is defined differently by the parties. While the appellants consider it to be the provision of an alternative method of analysing a polynucleotide sequence, the respondent argues that it was the provision of an improved method.
- 22.2 According to the case law of the Boards of Appeal advantageous effects may only be taken into consideration, when formulating the problem underlying an invention, if they are supported by a comparison with the closest prior art (cf. Case Law of the Boards of Appeal of the European Patent Office, 4th Edition 2001, chapter I.D.4.4). Such comparative evidence with regard to document OD1 is lacking here. Hence, the board sees the problem as the provision of an alternative method for parallel analysis of nucleic acid by hybridisation and wherein the nucleic acid is covalently bound to the support.

23. The invention as claimed in claim 1 solves this problem by providing a process as disclosed in document OD1, but using an alternative support material, i.e. nucleic acid is attached to the smooth impermeable surface of a glass support.

Examples 1, 2, 3 and 5 of the patent in suit demonstrate synthesis of oligonucleotides on the surface of a microscope slide resulting in covalent attachment. Specific hybridisation of labelled polynucleotides with the bound oligonucleotides is detected.

Hence, the patent in suit demonstrates that the proposed alternative solution is suitable to solve the problem.

24. The next question to be considered here is whether the skilled person at the priority date of the patent in suit when seeking to solve the problem underlying the invention would have been led in an obvious manner by the closest prior art document OD1 or other documents on file to progress from the closest prior art to the proposed solution.
25. No suggestion is found in the closest prior art document OD1 to seek for an alternative support material, let alone glass with a smooth impermeable surface.
26. The appellants argue that the replacement of the materials disclosed in document OD1 by glass with a smooth impermeable surface is obvious in view of a

combination of document OD1 with either of documents OD13 or OD61.

27. Document OD13 is a patent application relating to the synthesis of oligonucleotides onto a polymeric support. "Glass" as support is mentioned once in the document on page 11: "A wide range of polymer supports can be used as the polymeric support of the present invention. The preferred polymer supports include polystyrenes, crosslinked polystyrenes, cross-linked polyamino acids, polyethyleneglycol, co-polymers of vinyl acetate and N-vinyl pyrrolidone, as well as other polyolefins, polyesters, polyamides, polyacrylates, polymethacrylates, metal oxides, clays, **various glasses** and grafts using combinations of any of these supports."

Document OD61, a scientific publication, discloses covalent attachment of oligonucleotides to long-chain alkylamine and carboxyl controlled pore glass having a pore size of 500 Angström and a diameter of 125 μ to 177 μ .

The appellants argue that a skilled person would have recognized that the coupling chemistry disclosed in either of documents OD13 or OD61 is suitable for attachment of oligonucleotides to the smooth impermeable surface of a glass support and that he/she would have consequently used it in the method of document OD1.

28. The board assumes for the purpose of the following reasoning that the coupling **method** disclosed in documents OD13 and OD61 might have been suited for

immobilizing nucleic acids on glass with a smooth and impermeable surface. But even if this is so, the question to be answered remains nonetheless whether or not the skilled person would have recognized in view of the prior art that glass with a smooth impermeable surface is suited as a support material in the context of the nucleic acid assay disclosed in document OD1.

29. The following documents illustrate support materials that had actually been used for nucleic acid immobilization up to the priority date of the patent in suit in May 1988.

29.1 As stated above, document OD61, published in July 1987, discloses attachment of oligonucleotides to alkylamine and carboxyl controlled pore glass. Document AD95 discloses in its introduction how controlled pore glasses (CPG) are prepared. The description ends with the sentence: "The borate phase is leached out by acid solutions at high temperatures. The remaining glass contains colloidal silica particles, which are removed by a treatment with NaOH followed by washing with water. The final glass has a porosity between 50% and 75%, and an average pore size between 4.5nm and 400nm. CPG has a surface area between 10 and 350 m²/g, depending on the pore size." Hence, controlled pore glass is a particulate material with a porous surface and therefore, different from glass having a smooth and impermeable surface.

29.2 The same is true for the glass fibre filters disclosed as support for structured arrangement of nucleic acids in document OD15, published in July 1983 (see point 17.2 above).

- 29.3 In document OD13, published in March 1984, specific examples of supports for immobilizing nucleic acid are a methacrylate polymer, Amberlite CG50, chloromethylstyrene beads, polyacrylmorpholide resin and a teflonwool/copolymer graft. This selection reflects the statement on page 12 that for the purpose of the method disclosed in document OD13 "polymeric supports with large surface areas consisting of a great number of bonding sites in proportion to weight are most preferred."
- 29.4 Document OD18, a patent application published in February 1988 and dealing with a nucleic acid hybridisation sandwich assay discloses supports based on beads of amino-, sulfhydryl- or carboxyl-derivatized controlled pore glass, dextran or polystyrene.
- 29.5 Beads as a support are, inter alia, also contemplated in document OD19, published in 1986: "A variety of solid supports are suggested for the immobilised sample single-stranded polynucleotide including activated glass beads, polyacrylamide, agarose or Sephadex beads and cellulose" (page 2), as well as in documents AD96 and AD97, both published in 1987 and disclosing covalent attachment to submicron latex beads.
- 29.6 Further support materials referred to are: Nylon membranes (OD1, published in 1987), modified or unmodified cellulose filters (OD20, published in 1983; OD50, published in 1985), or nitrocellulose (OD6, published in 1977).

- 29.7 Document OD38, entitled "Hybridization properties of immobilized nucleic acids" and published in 1987 summarizes as follows: "The nucleic acid hybridization protocol most familiar to molecular biologists involves the detection by radioactively labelled probes of target nucleic acids which have been immobilised on nitrocellulose or nylon filters. [...] During this same period, Gilham (6,7) described a chemistry of immobilization in which oligonucleotide-length DNA was covalently attached to cellulose supports..." The document itself describes a dextran support.
- 29.8 Hence, the prior art relating to nucleic acid immobilization on supports does not suggest glass with a smooth impermeable surface as support material.
30. On the other hand, glass plates had for a long time been a common support material in the field of immunology. Document OD45, published in 1984 (and the related US patent OD87, published in 1986) states: "The immunoassay device of this invention comprises a support which has on its surface an array of antibody-coated areas or spots. Preferably, the support is a solid substance having a flat, planar surface such as a glass or plastic coverslip."
31. Furthermore, there is a group of patent documents on file relating to binding assays (AD102 to AD104, published in 1979, 1980, 1981, respectively, AD106, published in 1982, AD107, published in 1984) mentioning DNA and antibodies in one breath when the types of binding partners suited for the respective assays are described. These documents seem to suggest to the skilled person that antibodies and nucleic acids are

alternative types of binding agents that can be interchangeably used in assays for their respective binding partners. The appellants conclude therefrom that these documents suggest that a support material which is good for antibodies is also good for nucleic acids.

32. Finally, document OD41, a US patent application published in 1987, relates to the determination of the site-specific redox state of a liquid system by employing a photoresponsive element. The document belongs to the field of electrochemistry. This is most apparent from the Figures showing electrical circuits, a diagrammatic view of the photoresponsive device and a graph of the observed voltage with varying redox compositions. However, the disclosed device is suggested also for analysing biological materials. In column 8 the following statement is found: "One could analyze for DNA or RNA sequences [...]. For example, one could bind probes to a glass surface, [...] ." The glass surface is later concretized as a "slide".

33. Hence the picture painted by the prior art documents on file may be summarized as follows:

i) In documents relating to the field of immunology glass had been disclosed as a support material since 1984 (OD45).

ii) In documents dealing generally with binding assays and which seem to suggest that antibodies and nucleic acids are alternative types of binding agents that can be treated in the same way, glass is referred to as a

support material as early as in 1979 (OD41, AD101 to 104, AD106, AD107).

iii) During the whole time period covered by the documents cited in points i) and ii) above and up to the priority date of the patent in suit in 1988, there is not a single disclosure or mentioning of a glass support with a smooth impermeable surface in the context of nucleic acid hybridization or synthesis.

34. The board agrees that the claimed subject-matter might look simple, since glass with a smooth impermeable surface is a common material available in every laboratory, for example in the form of microscope slides. However, if, as in the present case, none of the many documents relating specifically to the immobilization of nucleic acid on supports points to its use, although the field of nucleic acid hybridisation and synthesis had been - as can be seen from the many documents on file and the long period spanned by their publication dates - an area of active research for a long time before the priority date of the patent in suit and although glass had been used as a support in the neighbouring field of immunology, then the invention may be simple, but nevertheless it is not obvious.

35. It follows that even if the skilled person had recognized that the coupling method disclosed in documents OD13 or OD61 was in principle suited for immobilizing nucleic acid on glass with a smooth and impermeable surface, he/she would nevertheless not have been prompted to use that material as a support in the context of the nucleic acid assay disclosed in

document OD1. Consequently, the subject-matter of claim 1 is not rendered obvious by a combination of document OD1 with either of documents OD13 or OD61.

36. A glass support with a smooth impermeable surface is a feature of all the independent claims. Therefore, the reasoning above applies to claims 10, 14, 15 and 18, too.

37. The subject-matter of the claims meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance with the order to maintain the patent as amended in the following version:

description:

pages 3 to 5, 7, 8, 10 to 12 of the patent specification,

pages 2, 6 and 9 received during oral proceedings on 12 October 2005

claims:

No. 1 to 22 received during oral proceedings on
11 October 2005.

Registrar:

The Chairman:

P. Cremona

M. Wieser