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Datasheet for the decision of 7 March 2012

Case Number: T 0853/11 - 3.3.06

Application Number: 99202441.4

Publication Number: 972564

IPC: B01J 19/00, C07H 21/00

Language of the proceedings: EN

Title of invention:
Method of forming arrays of polymers

Patent Proprietor:
Affymetrix, Inc. (a Delaware Corporation)

Headword:
Polymer array/AFFYMETRIX

Relevant legal provisions (EPC 1973):
EPC Art. 56

Keyword:
"Inventive step (all requests): no"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0853/11 **-** 3.3.06

D E C I S I O N
of the Technical Board of Appeal 3.3.06
of 7 March 2012

Appellant: (Patent Proprietor)
Affymetrix, Inc. (a Delaware Corporation)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 26 November 2010 revoking European patent No. 972564 pursuant to Article 101(3)(b) EPC.

Composition of the Board:

Chairman: P.-P. Bracke
Members: P. Ammendola
J. Geschwind

Summary of Facts and Submissions

I. This appeal is from the decision of the Opposition Division posted on 26 November 2010 to revoke the European patent No. 0 972 564 relating to a method for forming arrays of polymers.

II. The patent-in-suit was granted with only one claim (hereinafter the granted claim) reading as follows:

> "*1. A method of forming a polymer array comprising a substrate and 100 or more groups of polymers with diverse, known sequences coupled to the surface thereof in discrete, known locations, the density of said groups being at least 1000 per* cm^2*, wherein said discrete known locations are separated from one another by inert regions, and wherein said polymers are delivered to said locations by spotting.*"

III. A sole Opponent had initially sought revocation of the patent for, *inter alia*, lack of novelty and inventive step (Article 100(a) EPC 1973), but had then withdrawn its opposition.

IV. During the opposition proceedings reference was made by the Opposition Division, *inter alia*, to the documents:

(2) = EP-A-0 063 810;

(3) = WO-A-92/10588

and

(6) = WO-A-84/031 51.

V. In the decision subject of the present appeal the patented method was found not novel and not based on an inventive step.

The Opposition Division indicated (in the discussion on novelty) that document (2) disclosed a method of forming a two dimensional array of antigens or antibodies coupled to the surface of the substrate in discrete, known locations that are separated from one another by inert regions. In particular, reference was made to the disclosure in this citation given in claims 1, 7, 12, 29 and 32 and at page 4, last paragraph; page 8, last paragraph - page 10, first paragraph; the paragraph bridging pages 31-32; and to the indication at page 16 that a "blocking solution" is applied after the spotting of the polymer.

In the discussion of inventive step, the subject-matter of the granted claim was found to only differ from the photolithographic methods of document (3) in that the former required to deliver the polymers to the substrate surface by spotting. Indeed, in the opinion of the Opposition Division, this citation also disclosed the presence of inert regions at page 11, lines 6-34 in combination with claims 1-5, 7, 11 and 13.

Since documents (2) and (6), among others, already disclosed that dense arrays could be produced by means of spotting, the combination of document (3) with, *inter alia*, document (2) or document (6) rendered obvious the subject-matter of the granted claim.

VI. The Patent Proprietor (hereinafter Appellant) appealed this decision requesting as main request that the patent be maintained on the basis of the granted claim.

In the statement setting out the grounds of appeal (which was enclosed with amended versions of the patent claim labelled as auxiliary requests) the Appellant:

i) requested oral proceedings,

ii) considered, *inter alia*, that the antigens or antibodies in the arrays of document (2) were no polymer with known sequence,

and

iii) refuted the inventive step reasoning in the decision under appeal by arguing as follows:

The photolithographic methods disclosed in document (3) did not involve positional spotting of the materials acting as probes.
On the contrary, the spotting of antibodies was applied in the method of document (6) and, thus, was to be regarded as the objectively closest prior art. The Appellant also argued, however, that the spotting method of this latter citation resulted in less dense arrays containing closely spaced spots and that also the antibodies used therein were no polymers with known sequences.

If nevertheless the photolithographic methods of document (3) were taken as starting point for the assessment of inventive step, the problem credibly

solved by the patented subject-matter vis-à-vis this prior art was the provision of a further method to make relatively large, high-density arrays of polymer sequences, without the need for a complex multi-stage photolithographic method.

However, the skilled person starting from document (3) would have in mind the pioneering nature of the technology described in this citation.

Furthermore, even though producing arrays by means of spotting was known, still the available prior art did not disclose the use of spotting to produce arrays as defined in the granted claim.

Finally, in the extraordinarily unlikely event that the skilled person would effectively destroy the teaching in document (3) in order to solve the posed problem, it would be counter-intuitive to deliberately separate with inert regions the probe locations in high-density arrays.

Thus, in its analysis, the Opposition Division had simply and illogically assumed that particular prior art teachings could be changed beyond recognition to suit the convenience of an inventive step argument.

VII. The Board summoned the Appellant to oral proceedings to be held on 7 March 2012.

A communication with the Board's preliminary opinion was enclosed to the summons. It comprised the following passages:

"*The following issues might need to be discussed at the oral proceedings:*

… inventive step (Article 56 EPC) of the subject-matter of the claim of the patent as granted in view of the prior art cited in the reasons of the decision under appeal";

"*The vague wording used in the patent-in-suit leaves … open the meaning of the term "inert regions".*"

and

"*The Board finds … not convincing the argument of the Appellant that the patented subject-matter would not represent an obvious alternative to the photolithographic method of document (3). …*
The Board notes, in particular, that the coupling of minuscule amounts of polymeric materials (of known structure and, thus, capable of acting as specific recognition agents) onto predefined and distinct microscopic areas of a substrate is already achieved in the arrays of document (3).
The Board also finds that a person searching for an alternative to this prior art would take into consideration the disclosure e.g. in document (2) that spotting allows similar minuscule amounts of preformed polymeric materials to be specifically localized in a precise fashion onto distinct microscopic areas of a substrate, thereby allowing a maximum density of 1000 test areas per cm^2 of the substrate. Accordingly, the Board is of the preliminary opinion that it would be obvious for the skilled person starting from the method for producing arrays for detection of antigens or

antibodies described in document (3) to consider that substantially similar arrays can also by produced by the spotting method described in document (2) (see in document (2) claims 12 and 29 and the paragraph bridging pages 31 to 32).".

VIII. The Appellant replied with a letter dated 8 February 2012, announcing its absence at the forthcoming hearing and withdrawing its previous request for oral proceedings.

It also enclosed to this letter one amended version of the claim labelled as **Auxiliary Request,** replacing all its previous auxiliary requests. This amended claim differs from the granted one (see above Section II) only in that the words "*polymer*" and "*polymers*" of this latter have respectively been replaced by "*oligonucleotide*" and "*oligonucleotides*".

The final requests filed in writing by the Appellant in the present appeal proceedings are, therefore, that the decision under appeal be set aside and that the patent be maintained on the basis of the originally granted claim (**Main Request**) or, alternatively, of the claim according to the **Auxiliary Request** enclosed to the letter dated 8 February 2012. The Board understands the Main Request as being that the opposition be rejected.

IX. In the letter dated 8 February 2012 the Appellant considered that the only disclosure in document (2) which would specifically get to the question of relatively high density arrays was the passage bridging pages 31 and 32. However, this passage started by referring to microdots of 0.3mm, and first observed

that a standard 100mm length strip could contain 300 individual antigens spotted in a one-dimensional array (this latter being, in the Appellant's opinion, an entirely theoretical discussion in this citation). It was the immediately following sentence which started at the top of page 32 which would get to the question of density as such, and this referred to up to 100000 individual tests in a ten cm square. Having stated that 100mm length strip could contain 300 microdots in a one-dimensional array, if 100,000 such dots were to be provided in a two-dimensional array in a 10cm square, this would not allow for any appreciable separation at all. In all directions the microdots would effectively occupy the space available without allowing room for deliberate provision of inert regions.

As to the issue of inventive step the Appellant argued the claimed subject-matter of either the Main Request or the Auxiliary Request would be inventive even for the skilled person starting from document (3), because at the relevant time, there was no motivation for altering the photolithographic method.

In particular, this prior art already delivered dense arrays containing many thousands of sequences per square cm. It was not known, however, whether other methods could do the same thing and, thus, create a large number of individually addressable sequences at known locations in a very dense array.

Moreover, the skilled person had no motivation to completely drop this methodology in the midst of its exciting development (the photolithographic approach having been first described in WO 90/15070 in 1990),

i.e. no motivation to depart from a methodology that went way beyond the capabilities of the preceding conventional probing techniques and that was capable of delivering far more than what the granted claim required as a minimum.

The Appellant also stressed that the technology described in WO 90/15070 was reflected in an issued European patent, and that the European Patent Office had awarded to the inventors of the photolithographic technology one of the "European Inventor of the Year" awards in the very first year, 2006, that such awards were made. As also apparent from an entry from the EPO website - a copy of which was enclosed to the Appellant's letter of 8 February 2012 - even at the time in which the Appellant wrote this letter the photolithographic methodology was still regarded as "The Rosetta Stone of Functional Genetics".

Hence, it was not logical to assume merely because one method provided a desirable end result that it would be obvious to try and do it by another, completely different way. This would be counterintuitive and the present invention was to be seen as having inventive step vis-à-vis document (3).

X. Oral proceedings took place as scheduled in the announced absence of the Appellant, i.e. of the sole Party to these appeal proceedings.

Reasons for the Decision

Rejection of the opposition (Appellant's Main Request)

1. Interpretation of the granted claim.

It is apparent to the skilled reader of the patent-in-suit as a whole that the subject-matter of the granted claim (see Section II of the Facts and Submissions) is essentially a method for fabricating miniaturized screening arrays that are suitable, for instance, for determination of binding affinity, because they carry on the solid substrate surface at least 100 diverse positionally distinguishable miniscule groups of known polymer sequences, such as oligonucleotides or peptides, having a specific binding ability towards one of the possible components of a material to be screened (see e.g. paragraphs [0001] and [0011] of the patent-in-suit). In other words, each polymer group (i.e. a group of polymers with the same sequence) attached on a discrete known location on the array's surface constitutes a screening **probe**.

The essential requirement of the patented method is that the polymer sequences (i.e. the probe constituents) are "*delivered*" onto the desired discrete known locations "*by spotting*". In particular, according to the patent-in-suit, each distinct probe may either be formed in a single delivery step, i.e. by spotting on each selected location a miniscule amount of a selected **preformed polymer sequence**, or may require multiple deliveries, i.e. the repeated positional spotting of miniscule amounts of **monomers** in the required order, for the synthesis *in situ* of the desired probe

constituent (see e.g. paragraphs [0011], [0016] and [0080] of the patent-in-suit).

The miniscule dimensions of these probes formed by spotting are indirectly defined by the requirement in the granted claim that there must be at least 1000 probes per cm^2, as well as by the further requirement therein that the probes must be separated by "*inert regions*".

As indicated in the communication of the Board enclosed to the summons to oral proceedings, and undisputed by the Appellant in its subsequent letter of 8 February 2012, the patent-in-suit leaves open the meaning of the term "*inert regions*". Indeed, no definition of the minimum dimensions and/or the kind of "*inertness*" that these regions must possess is given in the patent description.

Under such circumstances it is certainly reasonable and justified to interpret this expression in view of the fact that the essence of the invention is manifestly that of providing a method for fabricating arrays for screening studies. Hence, an "*inert region*" in the context of the granted claim can be, for instance, any portion of the substrate surface (of any appreciable size) that separates the probes and is substantially less binding/reactive than the probes (towards the target materials to be screened).

2. Since it has become evident to the Board that the subject-matter of the granted claim is contrary to the requirements of Article 56 EPC 1973 for the reasons discussed here below, it has turned out unnecessary for

the Board to decide on the novelty of the granted claim vis-à-vis the prior art.

3. Inventive step.

3.1 The Opposition Division has considered the patented method obvious for the skilled person starting from the teachings of document (3). The Appellant has considered document (6) to be more relevant in this respect than document (3) because only the former document relates to a spotting technique.

3.1.1 According to the established jurisprudence of the Boards of Appeal the state of the art suitable as starting point for the assessment of inventive step is normally a prior art document disclosing subject-matter conceived for the same purpose as the claimed invention and additionally having the most relevant technical features in common.

3.1.2 The Board notes that the patent-in-suit initially acknowledges in paragraphs [0008] and [0009] that the photolithographic methods (first described in the WO 90/15070 and also known as VLSIPS™) results in high-density screening arrays wherein the probe constituents are e.g. peptides or oligonucleotides with known sequences. The addressed technical problem is then defined in the patent-in-suit by stating in paragraph [0010] that "*The VLSIPS™ techniques have met with substantial success. However, in some cases it is desirable to have alternate/additional methods of forming polymer sequences which would not utilize, for example, light as an activator, or which would not utilize light exclusively*".

3.1.3 The Board notes that document (6) does not address the problem of fabricating high-density screening arrays. Indeed, this citation does not disclose arrays with probe densities of 1000 or more per cm^2 (see in document (6) page 3, lines 1 to 11; page 5, lines 17 to 19). Moreover, this citation is silent on the stepwise synthesis *in situ* of probes as well as on the use of libraries of preformed oligonucleotides or peptides.

On the contrary, document (3) (although not mentioning spotting) is manifestly one of the patents dealing with the same photolithographic method for the fabrication of high-density screening arrays that is acknowledged as the prior art of departure in paragraphs [0008] to [0010] of the patent-in-suit. Moreover, this citation discloses (e.g. in claim 13 in combination with page 27, lines 27 to 36, and with the paragraph bridging pages 28 and 29) the positionally distinct attachment of, *inter alia*, libraries of preformed oligonucleotides.

3.1.4 In view of the above considerations, the Board finds document (3) to disclose prior art more relevant than that disclosed in document (6) and, in particular, that the methods of document (3) for making high-density arrays starting from libraries of preformed oligonucleotides represent the most reasonable starting point for the assessment of inventive step in respect of the embodiments of the patented method also based on the spotting of preformed oligonucleotides.

3.2 As already indicated in the communication enclosed to the summons to oral proceedings (see above Section VII of the Facts and Submissions) the Board finds that the

subject-matter of the granted claim actually solves vis-à-vis document (3) the technical problem of **providing an alternative** to the photolithographic methods, i.e. solves the technical problem indicated in patent-in-suit (see the passage of paragraph [0010] of the patent-in-suit cited above at point 3.1.2). This has not been disputed by the Appellant.

3.2.1 The Appellant has however argued that the person skilled in the art would have no motivation to search for an alternative to the method of document (3), i.e. would have no reason for departing from the pioneering and very successful photolithographic techniques which had allowed for the first time to obtain very high probe densities and, in particular, probe densities much higher than the lower limit of 1000 probes per cm^2 set in the granted claim (see the Appellant's arguments summarized in Sections VI and IX of the Facts and Submissions).

3.2.2 The Board considers instead that it is inherently advantageous for the skilled person to also have at his disposal further ways for solving the same technical problems that have already been solved in the prior art. Thus, the fictional skilled person would normally search for and arrive at any obvious alternative to the prior art, independently as to whether the prior art presents or not particular disadvantages or difficulties, as well as independently on the public recognition of the pioneering nature and of the advantages of the prior art. The Board incidentally notes that even the passage of paragraph [0010] of the description of the patent-in-suit cited above at point 3.1.2, appears to imply similar considerations.

The Board notes further that document (3) explicitly mentions the possibility of fabricating arrays with a density of probes of 1000 per cm^2 or even much less (see in document (3) from page 28, line 25 to page 29, line 4), thereby proving to the skilled reader thereof that also the variants of this prior art methods resulting in somewhat less dense arrays with a probe density of about 1000 per cm^2 represent a realistic reduction into practice of the teaching in this citation.

3.2.3 Hence, the Board concludes that the skilled person **would** actually attempt to solve the posed technical problem, i.e. would search for further methods for fabricating the arrays that were already delivered by the photolithographic methods, **including** those for fabricating arrays with a density of probes of about 1000 per cm^2.

3.3 The solution to the posed problem proposed in the patent-in-suit, i.e. the method defined in the granted claim, undisputedly differs from the prior art in the requirement that e.g. the preformed oligonucleotides with known sequences are mandatorily delivered to the selected locations by using spotting techniques.

The Appellant has not disputed **explicitly** the conclusion in the decision under appeal that this would be the **sole** difference between the patented method and the disclosure provided in document (3) at page 11, lines 6-34 in combination with claims 1-5, 7, 11 and 13.

Nevertheless, its submissions (see above section VI and IX of the Facts and Submissions) appear to possibly imply that no inert region is present in the arrays fabricated in document (3).

The Board notes that the portions of this citation referred to by the Opposition Division do not describe expressly inert regions separating the probes. Hence, the Board considers it justified in the present case to carry out the assessment of inventive step under the assumption, favourable to the Appellant, that the patented method **differs** from the prior art of departure not only because in the former the preformed probe constituents (such as e.g. oligonucleotides) are delivered **by spotting** to the discrete known locations, but also because of the mandatory presence of **inert regions** separating the probes in the arrays resulting from the patented method.

3.4 The Board considers evident to the skilled reader of document (3) that the embodiments of this prior art based on the use of libraries of preformed probe constituents necessarily imply a (single) **individual** delivery step for each **preformed** oligonucleotide onto the reactive substrate surface, whereby this latter remains only attached onto a selected miniscule substrate location, i.e. onto an area of the substrate surface sufficiently small to allow a density of probes of e.g. 1000 per cm^2 or even higher.

Accordingly, the assessment of inventive step boils down to the question whether the skilled person searching for an alternative, in particular, to the photolithographic methods of document (3) which involve

individual delivery of the preformed oligonucleotides onto selected miniscule areas on the substrate surface, would have considered obvious to solve the posed problem by directly spotting on the selected substrate locations just the needed amounts of each preformed oligonucleotide, and to do so in such a way that the resulting distinct probes are separated from each other by portions of the substrate surface that are inert (according to the meaning of inert regions indicated above at point 1).

3.4.1 In the opinion of the Board, the skilled person searching for a solution to the posed problem and starting from the embodiments of the prior art based on the use of libraries of preformed oligonucleotides, would certainly have taken into consideration any other prior art methods for fabricating vast screening arrays, and, in particular, those comprising the individual delivery of preformed probe constituents.

Thus, the skilled person would have certainly found and considered relevant the instruction in document (2), claims 12 and 29 in combination with page 16, lines 18 to 21, page 18, lines 17 to 27, and with the paragraph bridging pages 31 to 32, that conventional **spotting** techniques (such as the use of certain Hamilton microsyringes) allow to deliver on the substrate surface "microdots" of, *inter alia*, 0.3mm diameter of each individual antibody (i.e. preformed probe constituents), so as to fabricate screening arrays with a density of distinct probes of 1000 per cm^2.

Hence, it would also be evident to the skilled person searching for a solution to the posed problem, that the

positional spotting used in document (2) for delivering preformed antibody probes to miniscule areas of the array's substrate surface, is also suitable for delivering on this latter any other preformed probe materials and, thus, also suitable for performing the individual delivery of preformed oligonucleotides onto selected miniscule locations on the substrate, i.e. the same individual delivery obtained by using photolithographic techniques in the methods of document (3).

The Board notes further that the same citation explicitly teaches:

- at page 16, lines 18 to 21, that the regions of the solid substrate which do not react with the spotted antibodies should preferably be blocked (i.e. also rendered inert towards the target material)

and

- in the paragraph bridging pages 31 and 32, the possibility of using a substrate with printed grids made of an hydrophobic ink capable of preventing the diffusion of the spotted antibody solution beyond the printed squares.

In the opinion of the Board, these instructions indicate to the skilled reader of document (2) that any (realistic) reduction into practice of the spotting techniques described therein (inclusive those generating 0.3mm "microdots") requires to set the points of spotting so as **to prevent any overlap** among the "microdots" of antibodies and, thus, inevitably, to

generate (more or less large) probe-free inert regions separating the probes.

The Board considers appropriate to stress again that the absence of any minimum requirement in the granted claim as to the dimensions of the inert regions and as to the kind or level of "inertness", allows to consider as inert regions separating the probes in the sense of the granted claim (as interpreted at point 1 above) any appreciable region of the substrate that is free from probes and deprived of any residual reactivity possibly present therein by the blocking step.

Thus, the Board concludes that the combination of document (3) with document (2) renders evident to the skilled person searching for a solution to the posed problem, not only that the positional spotting (e.g. with certain Hamilton microsyringes) disclosed in document (2) is suitable for carrying out the individual delivery of libraries of preformed oligonucleotides so as to achieve the same probe densities as the photolithographic methods of document (3), but also that such positional spotting is to be carried out by avoiding any overlapping among the "microdots" of the probe constituents and, thus, by necessarily separating the probes by means of ologonucleotide-free regions whose possibly present residual reactivity is blocked.

Hence, the skilled person arrives at the subject-matter of the granted claim by combining the technical teachings in these two citations.

3.4.2 The Board finds that none of the Appellant's arguments referring to documents (2) and (3) (see above Sections VI and IX of the Facts and Submissions) represents a convincing objection to the above reasoning.

Indeed, the reasons for rejecting the Appellant's allegations as to the alleged lack of motivation for the skilled person to depart from the photolithographic methods, have already been discussed above at points 3.2.1 to 3.2.3.

The Appellant's further argument that in document (2) the theoretical instruction as to the possibility of creating 100000 antibody "microdots" of 0.3mm diameter on a 10 cm square substrate (i.e. 1000 "microdots" per cm^2) would result in covering the whole substrate surface with the antibodies, is found an unproved allegation. Indeed, even 100000 **squares** of 0.3mm **side** (which necessarily occupy more surface than the same number of "microdots" of 0.3mm diameter) appear to necessarily leave uncovered 10% of the surface of the 10 cm square substrate.

It appears also unconvincing the Appellant's observation that the antibodies used as probe constituents in the arrays fabricated in document (2) are (strictly speaking) no "*polymers with known sequences*". As already indicated above at point 3.4.1, at least in as far as the subject-matter of the granted claim encompasses the **single** delivery step of the **preformed** probe constituents on each selected location on the substrate surface, the skilled person searching for a solution to the posed problem has no reason to disregard the teachings contained in document (2) in

respect of similarly dense screening arrays in which the probes are also formed by a **single** delivery step of the **preformed** probe constituents on each selected location.

Finally, it is also found irrelevant the Appellant's argument that probe densities per cm^2 of 1000 just correspond to the lower limit of the subject-matter of the granted claim. Firstly, the lack of inventive step of just the embodiments of the patented method that result in arrays with a probe density of 1000 per cm^2 is sufficient at rendering the granted claim contrary to Article 56 EPC 1973. Moreover, document (2) contains no explicit or implicit statement that 0.3mm was the smallest diameter for the "microdots" possibly obtainable by using any microsyringe. Hence, the technical teaching of this citation is not necessarily limited to the possibility of making 0.3mm microdots, but depends, for instance, on the (smallest) volumes of the other microsyringes that were commercially available in the prior art.

3.5 Thus, the Board finds the subject-matter of the granted claim to be obvious in view of the combination of document (3) with document (2) and concurs with the finding of the Opposition Division that the patent as granted does not comply with the requirements of Article 56 EPC 1973. Accordingly, the Appellant's Main Request is found not allowable.

Auxiliary Request

4. Since the embodiments of the subject-matter of the granted claim based on the spotting of preformed

oligonucleotides are also embodiments of the amended claim according to the Auxiliary Request (see above Section VIII of the Facts and Submissions), the above reasons for finding that in particular these embodiments of the granted claim do not comply with the requirements of Article 56 EPC 1973, apply equally to the subject-matter of the Auxiliary Request. Thus, also this latter request is not allowable.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

D. Magliano P.-P. Bracke