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Datasheet for the decision of 12 June 2007

Case Number: T 0470/04 - 3.3.06

Application Number: 96300860.2

Publication Number: 0728520

IPC: B01J 19/00

Language of the proceedings: EN

Title of invention:
Printing molecular library arrays

Patentee:
Affymetrix, Inc. (a Delaware Corporation)

Opponent:
PamGene B.V.

Headword:
Deprotection agent/AFFYMETRIX

Relevant legal provisions:
EPC Art. 56, 113(1)
RPBA Art. 10b(1)(3), 11(3)

Keyword:
"Admissibility of request submitted during oral proceedings: yes"
"Inventive step (yes): not obvious modification of prior art method"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0470/04 - 3.3.06

D E C I S I O N
of the Technical Board of Appeal 3.3.06
of 12 June 2007

Appellant: (Patent Proprietor)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 29 January 2004 revoking European patent No. 0728520 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: P.-P. Bracke
Members: L. Li Voti
A. Pignatelli

Summary of Facts and Submissions

I. The present appeal is from the decision of the Opposition Division to revoke the European patent No. 0 728 520, relating to a method of forming polymers having diverse monomer sequences on a substrate.

II. In its notice of opposition the Opponent sought revocation of the patent on the grounds of Articles 100(a), because of lack of novelty and inventive step of the claimed subject-matter, and of Articles 100(b) and (c) EPC.

The following documents were referred to *inter alia* by the Opponent in support of the opposition:

(1): WO-A-93/09668;

(7): J.D. Hulmes and Y.C. Pan: "Selective Cleavage of Polypeptides with Trifluoroacetic Acid: Applications for Microsequencing", Anal. Biochem., 197, 368-376 (1991).

III. In its decision the Opposition Division found that

– the invention was sufficiently disclosed;

– claims 11, 28 and 31 according to the then pending main request did not comply with the requirements of Article 123(2) EPC;

– the claims according to then pending first and second auxiliary requests complied with the

requirements of Article 123(2) EPC and were novel over the cited prior art;

– however, the claims according to these requests lacked an inventive step in the light of the teaching of documents (1) and (7).

IV. An appeal was filed against this decision by the Patent Proprietor (Appellant).

The Respondent (Opponent) informed the Board with letter of 18 April 2007 that it will not be represented at the oral proceedings.

Oral proceedings were held before the Board on 12 June 2005 in the absence of the Respondent.

During oral proceedings the Appellant submitted an amended set of 15 claims to be considered as the sole request.

This set of claims contains independent claims 1 and 11 reading as follows:

"1. A method of forming polymers having diverse monomer sequences on a substrate, said method comprising: providing a substrate comprising a layer of linker molecules thereon, each of said linker molecules having a protective group; applying a barrier layer overlying said layer of linker molecules, said applying step forming selected exposed regions of said layer of linker molecules exposing said selected exposed regions of said linker molecule layer to a deprotection agent solely in a vapor phase to remove the protective group;

and coupling selected monomers to form selected polymers on the substrate; wherein said deprotection agent is an acidic vapor selected from a group consisting of trichloroacetic acid, dichloroacetic acid and hydrochloric acid, and is at a temperature from 20 °C to 50°C; and wherein said polymer is selected from the group consisting of polynucleotides and oligonucleotides."

"11. A method of synthesizing a nucleic acid or a polynucleotide comprising the steps of: a) providing an oligonucleotide having a proximal end and a distal end, said proximal end coupled to a substrate having a surface, and said distal end comprising a removable protecting group; b) removing said protecting group with a deprotection agent solely in a vapor phase to expose a functional group; and c) covalently bonding an oligonucleotide to said exposed functional group; wherein said surface of said substrate is selectively protected by a mask during said removing step; and wherein said vapor phase deprotection agent is selected from a group consisting of trichloroacetic acid, dichloroacetic acid and hydrochloric acid, and is at a temperature of from 20 °C to 50°C."

Claims 2 to 10 and 12 to 15 relate to specific embodiments of the subject-matters of claims 1 and 11, respectively.

V. The Appellant submitted in writing and orally *inter alia* that

- document (1) disclosed methods for forming large arrays of polymers on a substrate involving a liquid phase deprotection step;

- it was not obvious for the skilled person in the light of the teaching of document (1) to try alternatively a deprotection agent solely in the vapor phase and to expect therewith a similar selective behaviour;

- the examples of the patent in suit showed that the use of an acidic reagent in the vapor phase under appropriate conditions permitted to achieve a complete deblocking of the exposed regions of the linker molecules layer without affecting the linkers layer below the protective barrier layer;

- document (7) related to the selective cleavage of polypeptides at specified sites by means of trifluoroacetic acid (TFA) for microsequencing polypeptides and did not concern any deblocking step in the preparation of polymer arrays on a substrate;

- moreover, this document showed that TFA had a different selectivity in liquid or in vapor phase;

- therefore, it was not obvious for the skilled person to apply the teaching of document (7) to the process disclosed in document (1).

VI. The Respondent submitted in writing *inter alia* that

- document (1) envisaged chemical vapor deposition techniques also;
- therefore, it provided an incentive to the skilled person to try alternatively the application of the deprotection agent in the vapor phase;
- the skilled person, knowing from document (7) that TFA was a deprotection agent which could be applied both in the liquid and in the vapor phase, would have thus tried to apply a deprotection agent in the vapor phase in the process disclosed in document (1) also;
- therefore, the claimed subject-matter lacked an inventive step.

VII. The Appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of claims 1 to 15 as filed during oral proceedings.

The Respondent requested in writing that the appeal be dismissed.

Reasons for the Decision

1. *Admissibility of the request submitted during oral proceedings*

1.1 During oral proceedings before the Board, which were not attended by the Respondent, the Appellant submitted an amended set of 15 claims.

Since the amended set of claims was based on a combination of claims already on file (see point 2 below), was submitted as a response to objections raised by the Board during oral proceedings, did not modify the main point of discussion defined by the decision under appeal and by the statement of the grounds of appeal, i.e. lack of inventive step, and could be easily dealt with by the Board at the oral proceedings, the Board concludes that these requests are admissible under the circumstances of the case (see RPBA Art. 10b(1) and (3)).

1.2 Moreover, the Board is not obliged to delay its decision in the proceedings by reason only of the absence at the oral proceedings of the duly summoned Respondent who may then be treated as relying only on its written case (see RPBA Art. 11(3)).

Therefore, the Board's decision on the new set of amended claims submitted during oral proceedings does not contravene the requirements of Article 113(1) EPC.

2. *Articles 123(2) and (3) EPC*

The Board is satisfied that the requirements of Articles 123(2) and (3) EPC are fulfilled.

In fact, claim 1 is a combination of claims 8, 9, 10 and 18 and claim 11 a combination of claims 33, 34, 37 and of the additional features of claim 10 of the set of claims according to the first auxiliary request discussed in the decision under appeal and found to comply with the requirements of Article 123(2) EPC by the department of first instance (see point 12.1 of the reasons for the decision under appeal).

Furthermore, the dependent claims 2 to 7 are based on claims 11 to 16, claim 8 on claim 19, claims 9 and 10 on claims 21 and 22, claims 12, 13, 14 and 15 on claims 35, 36, 38 and 39, respectively, of said first auxiliary request.

Since the Respondent did not contest in writing that the first auxiliary request discussed in the decision under appeal meets the requirements of Article 123(2) EPC, it is not necessary to give further details.

Moreover, the independent claims 1 and 11 are more restricted in scope than the granted independent claims.

3. *Article 83 EPC*

The Board is satisfied that the invention is sufficiently disclosed as found in point 12.2 of the reasons for the decision under appeal.

4. *Novelty*

The Board is satisfied that the claimed subject-matter is novel since the claimed subject-matter is more limited than the subject-matter found to be novel by the department of first instance (see point 12.3 of the reasons for the decision under appeal).

Since the Respondent did not submit further arguments with respect to the novelty of the claimed subject-matter, further details are unnecessary.

5. *Inventive step*

5.1 The claimed invention relates to the synthesis and placement of oligonucleotides and polynucleotides on selected parts of a substrate for creating sources of chemical diversity for use in screening for biological activity (see page 2, lines 5 to 10).

As explained in the description, various techniques for the synthesis of arrays of oligonucleotides on a substrate, e.g. the use of small rubber tubes as reaction chambers and of standard dimethoxytrityl (DMT) based chemistry were known from the prior art. However, these techniques had the drawback that they did not enable the synthesis of a sufficiently large number of polymer sequences for effective economical screening and did not enable to form arrays of oligonucleotides at selected regions of the substrate (see page 2, lines 11 to 17).

Therefore, the patent in suit defined the technical problem underlying the invention as the provision of an alternative method based on DMT chemistry or other suitable oligonucleotide synthesis chemistry which allowed preparing high density arrays of oligonucleotides (page 2, lines 31 to 32).

5.2 Document (1) discloses methods for forming high density arrays of polymers such as oligonucleotides and polypeptides on a substrate (see page 2, lines 25 to 33 and claim 1).

As agreed by both parties, the Board takes document (1) as the most suitable starting point for the evaluation of inventive step.

5.3 Document (1) discloses in particular two methods of forming polymers having diverse monomer sequences on a substrate by delivering a reagent to the substrate either by flowing the reagent within a channel defined on predefined regions or by "spotting", i.e. by applying droplets of the reagent on predefined regions (page 12, lines 27 to 34).

These methods involve the steps of forming a substrate comprising a layer of linker molecules thereon; applying a protective group to the linker molecules; applying a mask to form selected exposed regions of said layer of linker molecules; applying a liquid deprotection agent such as TFA to the selected exposed regions to remove the protective group; coupling selected monomers to form selected polymers on the substrate and then repeating the steps of deprotecting and coupling to form an array of polymers on the

surface of the substrate (page 13, line 28 to page 14, line 1; page 14, lines 34 to 39; page 21, lines 2 to 18; page 22, lines 6 to 8; page 23, lines 9 to 10; page 25, lines 8 to 23; page 30, lines 20 to 26; page 31, lines 29 to 40).

Even though this document teaches with respect to the "spotting" method that chemical vapor deposition techniques can be applied to deposit highly uniform layers on selected regions of a surface (page 31, lines 19 to 21), this step cannot relate in the Board's view to the selective application of the deprotection agent which **has to be applied in droplets**. This step can instead relate, for example, to the deposition of a layer of protecting groups on the linker molecules attached to the substrate, as described in the passage on page 31, lines 32 to 34.

Therefore, the Board agrees with the decision of the department of first instance that the method disclosed in document (1) differs from that claimed in the patent in suit insofar as it involves a **liquid** phase deprotection step instead of a deprotection step by using a deprotection agent solely in the **vapor** phase (see point 12.3 of the reasons). The subject-matter of claims 1 and 11 submitted during oral proceedings differs further from the method disclosed in document (1) insofar as it requires the use of an acidic vapor selected from a group consisting of trichloroacetic acid (TCA), dichloroacetic acid (DCA) and hydrochloric (HCA) at a temperature from 20°C to 50°C.

5.4 Since document (1) had already solved the technical problem of providing a method based on DMT chemistry or other suitable oligonucleotide synthesis chemistry which allowed preparing high density arrays of oligonucleotides, the technical problem underlying the invention has to be formulated as the provision of an alternative method for preparing high density arrays of oligonucleotides or polynucleotides having a similar selectivity as the method of document (1).

The examples contained in the patent in suit show that the use of TCA as deprotection agent solely in the vapor phase and at a temperature between 20 and 50° C brings about a very good selective deprotection of the protected groups and complete protection below the barrier layer thereby permitting the synthesis of oligonucleotides (see examples 2B to 2G and 3).

Moreover, the Board has no reason to believe that a different result would be achieved by using DCA or HCA as deprotection agents instead of TCA and that this method would not be applicable to the synthesis of polynucleotides.

Therefore, the Board concludes that the technical problem underlying the invention has been successfully solved by means of the method claimed.

5.5 The questions to be answered in order to evaluate the inventiveness of the claimed subject-matter are thus whether the skilled person, in the light of the teaching of the prior art and of his common general knowledge, would have envisaged the use of one of the selected deprotection agents solely in the vapor phase

and at the selected temperature in a process as described in document (1) and would have expected to achieve a selectivity at least equal to that obtained in the process of the prior art.

As explained above document (1) relates to a process wherein the deprotection agent is added in the liquid phase only and does not suggest using a deprotection agent solely in the vapor phase.

Document (7), relating to the selective cleavage of polypeptides at specified sites by means of trifluoroacetic acid (TFA) for microsequencing polypeptides and not concerning the preparation of polymer arrays on a substrate, discloses that the selective cleavage of polypeptides immobilized on a substrate can be accomplished at specified sites by means of trifluoroacetic acid (TFA) in the liquid or in the vapor phase and that TFA has a different selectivity depending on the physical state in which it is applied (see page 368, summary in the left column and paragraph "Gas-phase TFA vs liquid-phase TFA" bridging pages 370 and 371; page 375, passage bridging left and right column).

Therefore, even though the skilled person knew from document (7) that TFA both in the liquid and in the vapor phase was able to deprotect protected groups of polypeptides, he could have not foreseen the selectivity of TFA in the vapor phase in a different process as described in document (1); moreover, the prior art did not contain any suggestion that the selectivity of the acids required in the claims of the patent in suit, i.e. TCA, DCA and HCA solely in the

vapor phase, could be sufficient for allowing the formation of a high density array of oligonucleotides.

5.6 The Board concludes that it was not obvious for the skilled person to apply the teaching of document (7) to the process disclosed in document (1) and to select acids different from TFA solely in the vapor phase and at a temperature from 20 to 50°C with the expectation of obtaining the selectivity necessary for forming high density arrays of polymers such as oligonucleotides and polypeptides on a substrate.

Therefore, the subject-matter of claims 1 and 11 involves an inventive step.

The subject-matter of dependent claims 2 to 10 and 12 to 15 is also inventive for the same reasons.

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 a patent with claims 1 to 15 as filed during oral proceedings before the Board and a description to be adapted.

The Registrar: The Chairman:

G. Rauh P.-P. Bracke