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Datasheet for the decision of 23 January 2014

Case Number: T 1579/09 - 3.3.02

Application Number: 99967670.3

Publication Number: 1141712

IPC: G01N33/543

Language of the proceedings: EN

Title of invention:
COMPOSITE ARRAYS UTILIZING MICROSPHERES

Patent Proprietor:
Illumina, Inc.

Opponent:
BioArray Solutions Ltd

Headword:
COMPOSITE ARRAYS UTILIZING MICROSPHERES/ILLUMINA

Relevant legal provisions:
EPC Art. 100(a), 54, 56

Keyword:
Novelty and inventive step (yes)

Decisions cited:

Catchword:

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Case Number: T 1579/09 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 23 January 2014

Appellant: (Patent Proprietor)	Illumina, Inc. 9885 Towne Centre Drive San Diego, California 92121-1975 (US)
Representative:	Findeisen, Marco Witte, Weller & Partner Patentanwälte mbB Postfach 10 54 62 70047 Stuttgart (DE)
Appellant: (Opponent)	BioArray Solutions Ltd 35 Technology Drive Suite 100 Warren NJ 07059 (US)
Representative:	HOFFMANN EITLE Patent- und Rechtsanwälte Arabellastrasse 4 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 25 May 2009 concerning maintenance of the European Patent No. 1141712 in amended form.**

Composition of the Board:

Chairman: U. Oswald
Members: K. Giebeler
R. Cramer

Summary of Facts and Submissions

I. European patent no. 1 141 712, based on international application PCT/US99/31022 published as WO 00/39587, entitled "Composite arrays utilizing microspheres", was granted with 32 claims.

II. Opposition was filed against the granted patent under Article 100(a) EPC, lack of novelty and inventive step, Article 100(b) EPC, insufficiency of disclosure, and Article 100(c) EPC, added subject-matter.

III. The opposition division decided that the subject-matter of the claims of the main request (claims as granted) and of auxiliary request 1 before it lacked novelty over document A1 (Article 54 EPC), and that the subject-matter of the claims of auxiliary request 2 before it did not involve an inventive step (Article 56 EPC).

The opposition division further decided that the patent could be maintained in amended form under Article 101(3)(a) EPC, on the basis of auxiliary request 3 before it.

IV. Appeals against the interlocutory decision of the opposition division were lodged by the patent proprietor and the opponent.

V. The board expressed its preliminary opinion in a communication dated 2 September 2013

VI. Oral proceedings before the board took place on 23 January 2014.

VII. The appellant-opponent, who was not represented at the oral proceedings, requested in writing that the decision of the opposition division be set aside and that the patent be revoked.

During the oral proceedings, the appellant-proprietor withdrew its previous main request (claims as granted), auxiliary requests 1 and 2 as submitted with the statement of grounds of appeal, and auxiliary request 3 as submitted with letter of 9 April 2010 (claims as considered allowable by the opposition division). It requested that the decision under appeal be set aside and the patent maintained in amended form on the basis of the claims submitted as auxiliary request 4 on 9 April 2010 (now the **main request**) or, alternatively, on the basis of auxiliary requests 5 to 7 submitted on 9 April 2010 (now auxiliary requests 1 to 3)

VIII. Claims 1, 6, 11, 12, 17 and 18 of the **main request** read as follows:

"1. A composite array composition comprising:
a) a substrate with a surface comprising a plurality of assay locations configured to allow parallel processing of multiple samples, each assay location comprising an array location comprising a plurality of discrete sites; and
b) a population of microspheres comprising at least a first and a second subpopulation, wherein said first subpopulation comprises a first bioactive agent and wherein said second subpopulation comprises a second bioactive agent;
wherein each of said discrete sites in said array locations contains only a single microsphere, and wherein said first and second subpopulation comprise a plurality of different identifier binding ligands,

wherein each of said assay locations comprises a library of bioactive agents."

"6. A composite array composition comprising:
a) a first substrate with a surface comprising a plurality of assay locations configured to allow parallel processing of multiple samples;
b) a second substrate comprising a plurality of array locations, each array location comprising a plurality of discrete sites; and
c) a population of microspheres comprising at least a first and a second subpopulation, wherein said first subpopulation comprises a first bioactive agent and wherein said second subpopulation comprises a second bioactive agent;
wherein each of said discrete sites in said array locations contains only a single microsphere and wherein said array locations are fitted into corresponding assay locations, and
wherein said first and second subpopulation comprise a plurality of different identifier binding ligands."

"11. A method of decoding an array composition comprising:
a) providing an array composition comprising:
i) a substrate with a surface comprising a plurality of assay locations configured to allow parallel processing of multiple samples, each assay location comprising an array location comprising a plurality of discrete sites; and
ii) a population of microspheres comprising at least a first and a second subpopulation, wherein said first subpopulation comprises a first bioactive agent and wherein said second subpopulation comprises a second bioactive agent;

wherein each of said discrete sites in said array locations contains only a single microsphere, and wherein said first and second subpopulation comprise a plurality of identifier binding ligands;
b) adding a plurality of decoding biding [*sic*] ligands to said array composition to identify the location of at least a plurality of the bioactive agents,
wherein each of said assay locations comprises a library of bioactive agents."

"12. A method of decoding an array composition comprising
a) providing an array composition comprising:
i) a first substrate with a surface comprising a plurality of array locations, each array location comprising a plurality of discrete sites;
ii) a second substrate with a surface comprising a plurality of assay locations configured to allow parallel processing of multiple samples, and wherein said array locations are capable of being fitted into said assay locations;
iii) a population of microspheres comprising at least a first and a second subpopulation, wherein said first subpopulation comprises a first bioactive agent and wherein said second subpopulation comprises a second bioactive agent;
wherein each of said discrete sites in said array locations contains only a single microsphere, and wherein said first and second subpopulation comprise a plurality of identifier binding ligands;
b) adding a plurality of decoding biding [*sic*] ligands to said array composition to identify the location of at least a plurality of the bioactive agents."

"17. A method of determining the presence of one or more target analytes in one or more samples comprising:

a) contacting said one or more samples with a composition comprising:
i) a substrate with a surface comprising a plurality of assay locations configured to allow parallel processing of multiple samples, each assay location comprising an array location comprising a plurality of discrete sites; and
ii) a population of microspheres comprising at least a first and a second subpopulation, wherein said first subpopulation comprises a first bioactive agent and wherein said second subpopulation comprises a second bioactive agent;
wherein each of said discrete sites in said array locations contains only a single microsphere, and wherein said first and second subpopulation comprise a plurality of identifier binding ligands; and
b) determining the presence or absence of said target analyte,
wherein each of said array locations comprises a library of bioactive agents."

"18. A method of determining the presence of one or more target analytes in one or more samples comprising:
a) adding said one or more samples to a first substrate comprising a plurality of assay locations configured to allow parallel processing of multiple samples, such that said one or more samples is contained at a plurality of said assay locations;
b) contacting said one or more samples with a second substrate comprising:
i) a plurality of array locations, each array location comprising a plurality of discrete sites, wherein at least one assay location is in fluid contact with at least one array location; and
ii) a population of microspheres comprising at least a first and a second subpopulation wherein said first

subpopulation comprises a first bioactive agent and wherein said second subpopulation comprises a second bioactive agent;
wherein each of said discrete sites in said array locations contains only a single microsphere, and wherein said first and second subpopulation comprise a plurality of identifier binding ligands; and
c) determining the presence or absence of said target analyte."

Claims 2-5 are dependent on claim 1, claims 7-10 are dependent on claim 6, claims 13-16 are dependent on claims 11 and 12, and claims 19-30 are dependent on claims 17 and/or 18.

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

A1: WO 97/40385
A2: US 5,545,531
A3: WO 98/40726
A5: WO 93/06121.

X. The appellant-opponent did not provide any comments with respect to the claims of the main request, either in writing or orally.

XI. The submissions by the appellant-proprietor, insofar as they are relevant for the present decision, can be summarised as follows:

- The claimed subject-matter was novel (Article 54 EPC), because the arrays disclosed in document A1 neither comprised a plurality of assay locations configured to allow parallel processing of

multiple samples, nor did each assay location of the disclosed arrays comprise an array location.

- Moreover, the claimed subject-matter involved an inventive step (Article 56 EPC), because the skilled person would not have combined the teaching of the closest prior art document A2 relating to chip arrays with either of documents A3 or A1 relating to bead arrays.

Reasons for the Decision

1. The appeals are admissible.

Main Request

2. Amendments (Article 123(2) EPC)

Compliance with Article 123(2) EPC of the amendments to the claims according to the main request is undisputed. The board sees no reason to doubt that the requirements of Article 123(2) EPC are fulfilled.

3. Sufficiency of disclosure (Article 83 EPC)

Although the opposition was originally based on the ground of lack of sufficiency of disclosure, the opponent withdrew this objection during the first-instance proceedings. The board has no reason to doubt that the claimed invention is sufficiently disclosed (Article 83 EPC).

4. Novelty (Article 54 EPC)

4.1 Claim 1 relates to a composite array composition comprising (a) a substrate with a surface comprising a plurality of assay locations configured to allow parallel processing of multiple samples, each assay location comprising an array location comprising a plurality of discrete sites; and (b) a population of microspheres comprising at least a first and a second subpopulation, wherein said first subpopulation comprises a first bioactive agent and said second subpopulation comprises a second bioactive agent; wherein each of said discrete sites in said array locations contains only a single microsphere, and wherein said first and second subpopulations comprise a plurality of different identifier binding ligands, wherein each of said array locations comprises a library of bioactive agents.

By forming "arrays of arrays", with each of the plurality of assay locations comprising an array location, and each of said array locations comprising a library of bioactive agents present on microspheres, simultaneous analysis, i.e. parallel rather than serial processing, on a number of samples is possible (page 3, paragraph [0012] of the patent in suit).

4.2 Document A1, which is the only document that was cited in the context of novelty, relates to the electric field-induced assembly of planar bead arrays at the interface between an electrode and an electrolyte solution (page 8, lines 12 to 17). These planar bead arrays allow the implementation of biochemical analytical techniques (page 8, line 32 to page 9, line 1).

The contents of Examples V and VIII of document A1 are of particular relevance with respect to the claimed

subject-matter. Example V describes a planar array of a multi-component mixture of beads which differ in the nature of the chemical or biochemical binding sites they offer to analytes in solution (page 26, lines 13-17). Beads can be transferred from a microtiter plate to a planar cell in a layout-preserving way (Figure 6 (a) to (c)). In one embodiment, each position in the panel contains a cluster of beads of the same type (page 29, lines 31-33), i.e. each type of bead is present in multiple copies (page 28, line 27). Example VIII relates to the screening of compound and combinatorial libraries in a planar format. In one embodiment, the binding between target and a labelled probe may occur in solution, within microtiter plate wells, and the probe-target complexes are captured by complexation to encoded beads in each well. The resulting bead-captured probe-target complexes are then transferred to the planar cell to form a planar array (see page 41, lines 19-30 and Figure 10).

4.3 The terms "bead" and "microsphere" are used interchangeably in the patent in suit (see paragraph [0015]), the cited prior art and the present decision.

4.4 The question arises whether any of the composite array compositions disclosed in document A1 comprises a plurality of assay locations configured to allow parallel processing of multiple samples, each assay location comprising an array location, wherein each of said array locations comprises a library of bioactive agents.

4.5 In the composite array compositions of document A1, the multi-component mixture or library of beads is distributed on one single planar array. In the arrays disclosed in Example V, each cluster of identical beads

may be considered as a separate assay location, but these assay locations contain only one type of bioactive agent, not a whole library of bioactive agents, as required by claim 1. In the arrays obtained in the procedure shown in Figure 10 and described in Example VIII, each cluster of beads originating from one bead-captured probe-target complex formed in one well of a microtiter plate may be considered to represent an assay location, but, again, only one type of bioactive agent, and not a whole library of bioactive agents, is present in an assay location.

4.6 Hence the composite array composition according to claim 1 is not disclosed in document A1.

4.7 As concerns the composite array composition according to independent claim 6, which comprises a first substrate with a surface comprising a plurality of assay locations and a second substrate comprising a plurality of array locations, there is no disclosure in document A1 of any array composition comprising such first and second substrates. Therefore, the subject-matter of claim 6 is novel over document A1. In fact, the novelty of such two-component arrays was never challenged by the appellant-opponent.

4.8 The same applies to the methods of independent claims 11, 12, 17 and 18, and to the subject-matter of dependent claims 2-5, 7-10, 13-16, and 19-30.

4.9 Since neither document A1, nor any of the other cited documents discloses the claimed subject-matter, the board concludes that the requirement of novelty (Article 54 EPC) is fulfilled.

5. Inventive step (Article 56 EPC)

5.1 Document A2 represents the closest prior art for the subject-matter of claim 1. This document discloses "arrays of arrays", whereby a composite array comprising a plurality of test wells (e.g. microtiter plates) is provided, each test well containing a biological chip array, thereby allowing the parallel processing of multiple samples (abstract; Figure 4). Hence document A2 has the same purpose and aims at the same objective as the claimed invention, namely the parallel processing of multiple samples.

5.1.1 Document A1 does not disclose "arrays of arrays" in the sense that it does not disclose composite array compositions comprising a plurality of assay locations on a substrate with a surface, whereby each assay location comprises more than one type of microspheres comprising a bioactive agent (see point 4.5 above). Therefore, the board considers that document A1 does not represent the closest prior art for the subject-matter of claim 1.

5.2 The technical problem to be solved by the claimed subject-matter in the light of document A2 is the provision of an alternative composite array composition.

5.3 The solution to this problem proposed by claim 1 is a composite array composition characterised in that it comprises at least a first and a second subpopulation of microspheres, wherein the first subpopulation comprises a first bioactive agent and wherein the second subpopulation comprises a second bioactive agent, wherein each of said discrete sites in said array locations contains only a single microsphere, wherein said first and second subpopulations comprise a

plurality of different identifier binding ligands, and wherein each of said array locations comprises a library of bioactive agents.

Having regard to the description of the patent in suit (page 3, line 47 to page 4, line 8; page 4, line 19 to page 5, line 10; page 12, lines 31-35), the board is satisfied that the problem is solved.

5.4 It has to be decided whether or not the composite array composition according to claim 1 is made obvious by the cited prior art.

5.5 Document A3 discloses a microsphere-based analytic chemistry system in which microspheres carry different chemical functionalities (e.g. antibodies or oligo-nucleotides) which change an optical signature of the microspheres in the presence of targeted analytes. The microspheres may be mixed together while the ability is retained to identify the functionality on each bead using an optically interrogatable encoding scheme (abstract; page 24, lines 3-7; page 27, lines 9-16). Preferably, the beads are encoded using dyes entrapped within the beads (page 6, lines 19-21). Many subpopulations of beads can be encoded by using different dyes and different ratios of dye pairs (page 13, lines 1-5). In one embodiment, an analytic chemistry sensor is provided by locating the separate subpopulations of beads within separate wells formed at the ends of optical fibres of a bundle (page 7, lines 5 to 7). The subpopulations of beads may be randomly distributed in an array across the bundle end. Only those beads that exhibit a positive optical response need to be decoded to identify the corresponding functionality. The burden is thus placed on the

analysis rather than on sensor manufacture (page 7, lines 10-21).

5.6 The board considers that a skilled person faced with the problem posed would be motivated to combine the teaching of the closest prior art document A2 with that of document A3, because document A3 discloses the advantage of having to decode only those microspheres exhibiting a positive response and the possibility of placing the burden on the analysis rather than on sensor manufacture. However, document A3 does not disclose the use of a first and a second subpopulation of microspheres which comprise a plurality of identifier binding ligands. Instead, document A3 suggests using dyes for encoding the microspheres, and teaches that the dyes should preferably be entrapped within the microspheres, because bonding dyes covalently to the microspheres' surface "consumes surface binding sites desirably reserved for the chemical functionalities" (page 11, lines 1-2). Therefore, when combining the teachings of documents A2 and A3, the skilled person would not arrive at a composite array composition according to claim 1.

The use of binding ligands as identifier tags for microspheres was known from other prior art documents (see for instance document A5), but the skilled person faced with the problem posed and starting from the disclosure of document A2 would not be motivated to replace the dyes suggested in document A3 with identifier binding ligands, because identifier binding ligands would likewise consume surface binding sites, and document A3 recommends reserving the surface binding sites for the chemical functionalities.

5.7 The board furthermore considers that a skilled person faced with the problem posed would not combine the teaching of the closest prior art document A2 with that of document A1, because document A1 focuses on the electrochemical manipulation of the beads during the use of the planar arrays. A skilled person faced with the problem posed would not envisage applying the principle of an electric field-induced assembly of planar bead arrays, as suggested in document A1, to microtiter plates as used in document A2. Moreover, document A1 teaches the transfer of bead suspensions from a microtiter plate to a planar electrode surface, which then forms part of the electrochemical cell to be used in bioanalytical assays (Example IV; Figure 6(a)); hence the skilled person would not derive from the document that bead arrays could be placed in microtiter plates for performing bioanalytical assays.

5.8 The board concludes that the composite array composition of claim 1 does not derive in an obvious manner from the prior art.

5.9 As concerns the two-component composite array composition according to claim 6, the board considers that document A2 likewise represents the closest prior art and that the technical problem to be solved is the provision of an alternative composite array composition.

The solution to this problem proposed by claim 6 is a two-component composite array composition characterised *inter alia* by the presence of a first and a second subpopulation of microspheres, said first and second subpopulation comprising a plurality of identifier binding ligands.

Having regard to the description of the patent in suit (page 3, lines 47-54; page 4, line 9 to page 5, line 10; page 12, lines 31-35), the board is satisfied that the problem is solved.

For reasons analogous to those set out for claim 1 in points 5.6 and 5.7 above, this solution does not derive in an obvious manner from the prior art.

The board thus concludes that the subject-matter of claim 6 is not derivable in an obvious way from the prior art.

5.10 The same considerations apply to the methods of independent claims 11, 12, 17 and 18, and to the subject-matter of dependent claims 2-5, 7-10, 13-16, and 19-30.

5.11 In view of the above, the subject-matter of claims 1-30 of the main request involves an inventive step.

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 in amended form on the basis of the main request (claims 1 to 30 submitted as auxiliary request 4 on 9 April 2010), and a description to be adapted thereto.

The Registrar: The Chairman:

N. Maslin U. Oswald

Decision electronically authenticated