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D E C I S I O N
of 20 January 2006

Case Number: T 0898/03 - 3.4.02

Application Number: 93906997.7

Publication Number: 0628164

IPC: G01N 21/64

Language of the proceedings: EN

Title of invention:
Capillary array confocal fluorescence scanner and method

Applicant:
The Regents of the University of California

Opponent:
-

Headword:
-

Relevant legal provisions:
EPC Art. 56, 123(2)

Keyword:
"Inventive step: yes"

Decisions cited:
-

Catchword:
-

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Case Number: T 0898/03 - 3.4.02

D E C I S I O N
of the Technical Board of Appeal 3.4.02
of 20 January 2006

Appellant: The Regents of the University
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 18 March 2003 refusing European application No. 93906997.7 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. Klein
Members: M. Stock
M. Vogel

Summary of Facts and Submissions

I. The applicant and appellant has appealed against the decision of the examining division refusing European patent application 93 906 997.7 (publication WO93/17325) on the ground that it did not meet the requirements of Article 56 EPC. The examining division cited the following documents and reasoned that the subject-matter of claim 1 then on file did not involve an inventive step:

D1: EP-A-0 440 342 (UNIVERSITY OF CALIFORNIA) & US-A-5 091 652

D2: BioTechniques, Vol. 9, No. 1, 1990, ZAGURSKY et al:'DNA Sequencing Separation in Capillary Gels on a Modified Commercial DNA Sequencing Instrument', pp. 74-79

D3: Nucleic Acids Research, Vol. 18, No. 15, 1990, LUCKEY et al.: 'High-Speed DNA Sequencing by Capillary Electrophoresis', pp. 4417-4421

The examining division was in particular of the opinion that the person skilled in the art would replace the slab gel of D1 by an array of capillaries of D2 and at the same time the off-line raster scanning of D1 by the on-line real time scanning used in D2.

II. With a statement of grounds of appeal the appellant filed a set of amended claims 1 to 7 according to a main request. He also filed two statements (Annexes 1 and 2) together with curricula vitae of Professor Richard Mathies and Professor Tony Wilson, respectively.

Arguments of the appellant can be summarised as follows:

Even if the skilled person would have begun to consider replacing the gel slab of D1 with the capillaries of D2 a number of technical prejudices and difficulties would have dissuaded her or him from actually trying to do so.

Professor Mathies working for some time on various innovative apparatus to enable confocal scanning of electrophoresis capillary passages was surprised when a chance experiment demonstrated that the invention of claim 1, in which cylindrical walled capillaries are scanned with a continuous relative movement, might work.

The prejudices of Professor Mathies prior to making the invention are also reflected by the statement of Professor Wilson, indicating that he would have sought a solution which avoided probing through cylindrical capillary walls.

III. In preparation of the oral proceedings requested by the appellant the Board had forwarded preliminary comments in view of Articles 123(2), 84 and 56 EPC.

IV. With letter of 20 December 2005 the applicant filed an amended main request, first, second and third auxiliary requests accompanied with written submissions in advance of the oral proceedings.

V. In the oral proceedings which took place on 20 January 2006 the applicant filed amended claims 1 to 7 and an amended description and requested a patent be granted

on the basis of these documents. The independent claims read as follows:

"1. A scanner for exciting and detecting radiation from a plurality of adjacent capillary passages comprising:

a plurality of transparent capillaries (21) in side-by-side coplanar relationship, the capillaries having cylindrical walls providing capillary passages extending in a first direction;

a source of radiant energy of a first wavelength;

an objective lens (11) for receiving and focussing said radiant energy (29) at an excitation volume (21a) in said passages;

means (30) arranged to provide continuous relative movement between each of said passages and said radiant energy in a direction perpendicular to the capillaries so that said excitation volume (21a) is sequentially and repetitively at a specific position within each one of said capillary passages so as to excite material in said excitation volume (21a) and cause the material to radiate energy at a different wavelength;

said objective lens (11) serving to collect said radiant energy and direct it to an optical system which includes confocal spatial filter means (16) and spectral filter means (17) to transmit emitted radiant energy at said different wavelength and reject radiation at other wavelengths;

a detection system (18) for receiving said emitted radiation and generating a signal; and

computer means arranged to receive and process said signal to provide an output representative of the material at the excitation volume (21a) in each of said capillary passages (21)."

"7. A method of detecting fluorescence from DNA sequencing fragments electrophoretically separated in capillary passages of a plurality of cylindrical capillaries (21), comprising the steps of:

positioning a region of said plurality of capillaries (21) in side-by-side coplanar relationship;

exciting an excitation volume (21a) in said capillary passages with light energy of a first wavelength focussed therein by an objective lens (11) to cause fragments to fluoresce at a different wavelength;

providing relative continuous movement between said cylindrical capillaries (21) and said focussed light in a direction perpendicular to the capillaries whereby the excitation volume is sequentially and repetitively as a specific position within each one of the capillary passages;

collecting the fluorescently emitted light from said predetermined volumes in each of said capillary passages with said objective lens (11);

spectrally and confocal spatially filtering said fluorescently emitted light energy to reject light at said first wavelength and passing said emitted light at said different wavelength;

applying the filtered emitted light to a detector (18) to generate an output signal representative of the fluorescence from said fragments in each of said capillary passages; and

receiving and processing said signal to provide an output representative of the material at the excitation volume (21a) in each of said capillary passages (21)."

Reasons for the Decision

1. *Amendments*

1.1 The subject-matter of claim 1 is based upon claims 1 and 3 as published. Independent claim 7 is directed to a corresponding method based upon claim 16 as published. The generalisation of "means for moving said passages", found e.g. in original claim 1, to "relative movement between each of said passages and said radiant energy" indicated in claim 1 as amended, is justified in view of the description, page 8, lines 15 to 22, mentioning "scanning the beam across the capillary".

1.2 Therefore, the Board is satisfied that the amendments are in accordance with the requirements of Article 123(2) EPC.

2. *Novelty*

The Board agrees with the examining division that the claimed subject-matter is novel.

3. *Inventive step*

3.1 Contrary to the opinion of the examining division, the Board considers that document D2 represents the closest prior art as it is also related to, what is called in the present application, capillary array electrophoresis (CAE).

3.2 Employing the terminology used in claim 1, D2 with the connected description, discloses a scanner for exciting and detecting radiation from a plurality of adjacent

capillary passages comprising a plurality of transparent capillaries in a spaced apart coplanar relationship, the capillaries having cylindrical walls providing capillary passages extending in a first direction; a source (laser) of radiant energy of a first wavelength (488nm); a lens for receiving and focussing said radiant energy at an excitation volume in said passages; means arranged to provide relative movement between each of said passages and said radiant energy in a direction perpendicular to the capillaries so that said excitation volume is sequentially and repetitively at a specific position within each one of said capillary passages so as to excite material in said excitation volume and cause the material to radiate energy at a different wavelength; said radiant energy at said different wavelength being directed to an optical system which includes spectral filter means (filter stack) to transmit emitted radiant energy at said different wavelength and reject radiation at other wavelengths; a detection system (PMT) for receiving said emitted radiation and generating a signal; and computer means arranged to receive and process said signal to provide an output representative of the material at the excitation volume in each of said capillary passages.

3.3 The subject-matter of claim 1 differs from this prior art in that

(a) the lens for focussing said radiant energy at said first wavelength is an objective lens serving to collect said radiant energy at said different wavelength and direct it to the optical system which includes confocal spatial filter means;

(b) the relative movement between the passages and the exciting radiant energy is continuous;

(c) the capillaries are in side-by-side relationship.

The objective problem solved by features (a) to (c) addresses enhancement of the signal-to-noise ratio, see application as published, page 3, lines 20 to 35.

3.4 D2, see Figure 2B, does not use a confocal excitation and detection scheme as expressed by feature (a). Moreover, contrary to feature (b) the laser beam is directed sequentially to each of the individual capillaries by a mirror mounted on a shaft of a digitally-controlled stepper-motor. It is mentioned at page 76, see the sentence bridging the second and third columns, that "positioning of the capillaries with respect to the laser step positions is critical for maximal excitation and fluorescent detection." From this follows that the steps are relatively coarse and cannot be considered as providing a continuous scanning like in the present invention. This was also not intended by the authors of D2 since only matching of the step positions with the maximal excitation was considered. The capillaries in D2 are also not in side-by-side relationship, but are spaced apart, i.e. positioned at a distance from each other, as is shown in Figure 1B and can be gathered from the text, see page 76, the paragraph bridging the second and third column, mentioning 12 or 36 capillaries distributed over the width of the elongated front-end of the photomultipliers detector tubes used, which is 8cm.

3.5 Confocal excitation and detection according to feature (a) is described in document D1, see Figures 1 and 2 with the connected description, disclosing a scanner for exciting and detecting radiation not from a plurality of adjacent capillary passages, but from a plurality of slab gels 16 on a plate 17. According to column 4, lines 24 to 28, the probe volume 15 can be scanned either by translating the objective or by translating the sample holder. Even if a person skilled in the art decided to apply the confocal excitation and detection described in D1 to an array of capillaries known from D2, she or he would not apply continuous scanning according to feature (b) in view of the fact, that, in D2, it is suggested to match the laser step positions with the capillaries in order to obtain optimal excitation and detection. In any case, however, the Board can accept the appellant's argument that the skilled person would have anticipated problems with scattering of excitation light and overlap of fluorescence from adjacent capillaries, if a side-by-side relationship of the capillaries were chosen according to feature (c), and hence have kept the capillaries at a distance from each other.

3.6 In D3, see Figure 1 with the connected description, there is disclosed a CE (capillary electrophoresis) scanner using a 90° detection geometry, i.e. fluorescence is detected under an angle of 90° with respect to the laser beam. The exciting laser beam "is focused onto the capillary in a 50µm spot to fill the inner diameter of the tube", see page 4417, right-hand column, first paragraph. Even though the skilled person could derive from D3 that it was important to detect fluorescence over the entire inner width of the

capillary, it is evident that the 90° detection geometry is not suitable for an array of capillaries.

3.7 The examining division has reasoned that it was obvious for the skilled person to replace the off-line raster scanning of the slab gel according to D1 by the on-line real time scanning mode used in capillary electrophoresis according to D2. However, the appellant has provided convincing arguments that the skilled person would also have replaced the continuous scanning used in D1 by stepped positioning of the laser with respect to the capillaries as suggested by D2 and thus would not have arrived at the invention.

4. Therefore the Board considers that the scanner according to claim 1 and a corresponding method of detecting as set out in claim 7 involve an inventive step within the meaning of Article 56 EPC. Dependent claims 2 to 6 are related to embodiments of the scanner defined in claim 1 and as such are also allowable. The description has been adapted to the amended claims and supplemented by citations of documents D1 and D2 in order to satisfy Rule 27 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent in the following version:

Description:

Pages: 1, 3, 4, 7 to 13, 15 to 17, as originally filed;
2, 2a, 5, 5b, 6 and 14, filed during the oral proceedings;

Claims:

Nos.: 1 to 7, filed during the oral proceedings;

Drawings:

Sheets: 1/11 to 11/11, as originally filed.

The Registrar: The Chairman:

P. Martorana A. G. Klein