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**Datasheet for the decision
of 12 October 2010**

Case Number: T 0113/10 - 3.3.08

Application Number: 02708496.1

Publication Number: 1370863

IPC: G01N 33/487

Language of the proceedings: EN

Title of invention:

Patch-clamping and its use in analysing subcellular features

Applicant:

Ionscope Ltd.

Headword:

Patch-clamping/IONSCOPE

Relevant legal provisions:

EPC Art. 54, 56, 83, 84, 113(1)(2), 123(2)
EPC R. 111(2)

Relevant legal provisions (EPC 1973):

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Keyword:

"Main request - Articles 123(2), 84, 83 (yes)"
"Novelty (yes)"
"Inventive step (yes)"
"Reimbursement of appeal fee (no)"

Decisions cited:

J 0006/79

Catchword:

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Case Number: T 0113/10 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 12 October 2010

Appellant: Ionscope Ltd.
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 2 November 2009
refusing European patent application
No. 02708496.1 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
D. S. Rogers

Summary of Facts and Submissions

I. European patent application No. 02 708 496.1 with the title "Patch-clamping and its use in analysing subcellular structures" was filed as International application under the Patent Cooperation Treaty and published as WO 02/077627.

II. Claims 1, 7 and 11 of the application as filed read as follows:

"1. A method for investigating a cell, which comprises bringing a probe close to the surface of the cell or a part thereof, at a controlled distance therefrom; and into contact with the surface, essentially normal to the surface, to achieve patch-clamping.

7. A method according to any preceding claim, wherein the distance of the probe from the surface is modulated and controlled in response to the modulated ion current.

11. Apparatus suitable for conducting a method according to any of claims 1 to 8, which comprises the probe, means for measuring and/or controlling the distance of the probe from a surface, means for bringing the probe into contact with the surface, and a patch-clamp amplifier."

III. The European Patent Office acting as International Preliminary Examining Authority issued a Written Opinion expressing the view that the subject-matter of claims 1 and 11 as filed lacked novelty in view of document (1) (see paragraph XV below). Moreover, the Authority stated that the subject-matter of the

- dependent claims 2 to 10, 12 and 13 did not appear to fulfil the requirement of novelty.
- IV. In reply to the Written Opinion, the applicant submitted that the subject-matter of claim 7 was novel and involved an inventive step.
- V. The Authority issued an International Preliminary Examination Report (IPER) holding that the subject-matter of claims 1 and 11 lacked novelty and that the dependent claims did not appear to meet the requirements of the PCT with respect to novelty or inventive step.
- VI. After the application entered into the European phase, the examining division of the European Patent Office issued a communication pursuant to Article 96(2) EPC 1973, in which the objections raised in the IPER were maintained. Additionally, an objection under Article 84 EPC 1973 was raised in respect of claims 9 and 10. The examining division invited the applicant to file amended claims taking into account the comments made in the communication.
- VII. The applicant replied to the communication of the examining division, but did not file amended claims. In its reply, the appellant maintained the claims of the application as filed as the sole request and argued that there was patentable subject-matter in the application. Furthermore, it submitted that it was *"... perhaps unfortunate that the argument submitted during the international phase was never taken into account. Given the specific request [...], I had hoped that the subject matter of claim 7 would be given*

particular consideration, and I now ask that this is done, and for the same reasons. [...] In the circumstances, I believe it is reasonable to delay formal revision of the claims". The appellant did not request oral proceedings.

- VIII. By a decision posted on 2 November 2009, the examining division refused the application under Article 97(2) EPC, on the grounds that, in the light of document (1), both the method of claim 1 and the apparatus of claim 11 of the application as filed lacked novelty in the sense of Article 54(1) and (2) EPC.
- IX. The applicant (appellant) lodged an appeal against the decision of the examining division. Together with the statement of grounds of appeal, two sets of amended claims were filed as main request and auxiliary request, respectively. The appellant requested, *inter alia*, a reimbursement of the appeal fee and remittal of the case to the examining division. As a subsidiary request, oral proceedings were requested.
- X. The examining division did not rectify its decision and referred the case to the board of appeal pursuant to Article 109(2) EPC.
- XI. The appellant was summoned to oral proceedings. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) attached to the summons, the board made observations on some of the issues to be discussed at the oral proceedings, in particular issues relating to Articles 84, 54 and 56 EPC, and expressed a provisional opinion with respect

to the appellant's request for reimbursement of the appeal fee.

- XII. In reply to the communication by the board, the appellant filed a further set of claims as second auxiliary request.
- XIII. At the oral proceedings held on 12 October 2010, the appellant replaced all sets of claims then on file with a fresh set of claims (claims 1 to 4) as its main request, and withdrew its request for remittal of the case to the examining division.
- XIV. Claim 1 of the set of claims according to the main request reads:

"1. A method for investigating a cell, which comprises bringing a probe close to the surface of the cell, at a controlled distance therefrom; scanning the surface with the probe, and generating an image; identifying a part of the surface that is of interest; and bringing the probe into contact with said part, essentially normal to the surface, to achieve patch-clamping, wherein the distance of the said probe from the surface is modulated and controlled in response to the modulated ion current."

Dependent claims 2 to 4 concern particular embodiments of the method of claim 1.

- XV. The following documents are referred to in the present decision:

(1): Y.E. Korchev et al., October 1997, Journal of Microscopy, Vol. 188, pages 17 to 23;

(2): Y.E. Korchev et al., August 1997, Biophysical Journal. Vol. 73, pages 653 to 658;

(3): WO 00/63736, published on 26 October 2000.

XVI. The submissions made by the appellant, as far as they are relevant to this decision, may be summarized as follows:

Article 123(2) EPC - Amendments

The amended claim 1 had a basis in claims 1 and 7 in combination with the passage on page 2, lines 18 to 22 of the application as filed.

Article 54(1) and (2) EPC - Novelty

None of documents (1), (2) or (3) described a method in which the same probe was used for first imaging the surface of a cell and then patch-clamping at an identified structure.

Article 56 EPC - Inventive step

The invention exploited the mechanism of scanning ion-conductance microscopy using a patch-clamp pipette. This allowed simple and reliable distance control without the need for the expensive optical detection equipment required by scanning nearfield optical microscopy.

Document (3) was the closest state of the art. This document described a method for investigating a cell in which two different probes were used, one probe for imaging and a second probe for patch-clamping. It was not obvious to use the same probe for both localising a subcellular structure and patch-clamping at that structure. The advantages accrued by the combination of the two techniques, scanning and patch-clamping, were unexpected.

Having regard to documents (1) and (2), the subject-matter of claim 1 involved an inventive step, because the experiments suggested in these documents could not be conducted in practice, without distance modulation. Distance modulation provided a quantum leap in reliability, and could deal with partial blocking of the probe caused by molecules being absorbed thereon. This problem could not be avoided if working with cells which could secrete proteins and needed complex culture media.

Refund of the appeal fee

The decision under appeal was not sufficiently reasoned in the sense of Rule 68(2) EPC 1973 [now Rule 111(2) EPC; observation by the board] because it made no effort to explain why the subject-matter of claim 7 as filed did not comply with the EPC. The appellant considered that the examining division had failed to address the claim 7 issue specifically, due to there being no request on file in which the features of claim 7 had been incorporated into claim 1, although the presence of such a request was not a pre-condition

for the consideration of this issue. There was no reason whatsoever for the examining division to have failed to have considered this point.

Although of course it was incumbent on the applicant to provide a set of claims that was suitable for acceptance, there could have been no doubt of the intention behind the applicant's submission in examination proceedings, and of the scope of the claims to be considered. The request, i.e. the combination of original claims 1 and 7, was clearly made even if not presented formally. If the examining division had disagreed with the applicant's statement that "I believe it is reasonable to delay formal revision of the claims", it could not be doubted that the applicant would have filed formal amendments, on request.

XVII. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of claims 1-4 of the main request filed during the oral proceedings, and that the appeal fee be refunded.

Reasons for the Decision

Articles 123(2), 84 and 83 EPC

1. The amended claims 1 to 4 according to the main request conform to Article 123(2) EPC. As concerns claim 1, the basis in the application as filed indicated by the appellant - claims 1 and 7 as filed in combination with the further steps disclosed on page 2, lines 18 to 11 of the description - is accepted. Claims 2 to 4 are

considered to have a basis in, respectively, claims 4, 5 and 8 of the application as filed.

2. The requirements of Article 84 EPC are considered to be fulfilled. The clarity objections raised by the examining division during examination (see paragraph VI above) do no longer apply, because the objected claims 9 and 10 have been deleted in the set of claims presently on file.
3. No objections were raised by the examining division in respect of Article 83 EPC and the board sees no reason to raise any on its own motion.

Article 54(1) and (2) EPC - Novelty

4. Document (1), which the examining division regarded as prejudicial to the novelty of the method according to claim 1 of the application as filed, describes a specialized scanning ion conductance microscope (SICM) for imaging living cells in which a glass micropipette is used as the sensitive probe. The micropipette filled with electrolyte is connected to a high-impedance current amplifier and mounted on a computer-controlled three-axis translation stage. When a cell sample immersed in a water solution is investigated, the position of the pipette tip in relation to the surface of the sample strongly influences the ion current through the pipette - as the separation between the tip and the sample diminishes, the ion current declines. Thus, no direct physical contact with the sample is needed (see page 22, right column, second sentence under the heading "4. Conclusions"), the distance between the micropipette and the surface of the cell

sample in the vertical axis being controlled using the signal provided by the ion current (see the passage describing the scanning ion conductance microscope on page 18, paragraph bridging the left and right columns).

5. Furthermore, document (1) discloses a method for investigating a cell using the described scanning ion-conductance microscope, which method comprises bringing the probe (i.e. the micropipette) close to the cell surface at a controlled distance therefrom, scanning the surface with the probe, generating an image and identifying a part of the surface that is of interest (see Summary on page 17, left column).
6. Document (1) does not, however, describe two of the features characterising the method according to claim 1 as presently on file, namely that (i) the distance between the probe and the surface is modulated and controlled in response to the modulated ion current, and that (ii) after scanning, the probe is brought into contact with the identified part of the surface, essentially normal to the surface, to achieve patch-clamping.
7. With respect to feature (ii), which was present also in claim 1 of the application as filed, the examining division held in the decision under appeal that, even though document (1) was concerned mainly with an apparatus for non-contact scanning ion-conductance microscopy, it was explicitly described in the last sentence of the Summary on page 17, and in the passage on page 23, left hand column of document (1) that such a system could be used for patch-clamping and micromanipulation, both of these techniques requiring

- contact as specified in claim 1. On this account, the examining division found that the subject-matter of claim 1 lacked novelty in the light of the disclosure of document (1).
8. The board disagrees with this finding. In the board's judgement, a person skilled in the art cannot derive, clearly and directly, from document (1) a method of investigating a cell in which, after the surface has been scanned, an image generated and a part of interest identified, the **same** probe is brought into contact with the cell surface to perform patch-clamping.
 9. In the passage of the Summary of document (1) to which the examining division referred, it is stated that the SICM apparatus described therein "*... has considerable ability to operate, potentially simultaneously, in applications as diverse as real-time microscopy, electrophysiology, micromanipulation and drug delivery*" (see Summary, last sentence). Even if it may be true that - as the examining division held - micromanipulation involves contacting the probe with the surface of the sample, the novelty of the claimed method cannot be prejudiced by the passage quoted above because claim 1 requires not only contact with the surface, but "*... contact with the surface, essentially normal to the surface, to achieve patch-clamping*". A method which combines the two techniques, i.e. scanning the surface to generate an image and then performing patch-clamping with the same probe is, however, not derivable from this passage.
 10. Nor can the method of claim 1 be derived from page 23, left column of document (1). From this passage, in

particular from the statement "[the scanning ion conductance microscope] *can also double as a fully fledged patch-clamp apparatus, and can be used for micromanipulation of living cells, microsurgery, microinjection or drug delivery*" a person skilled in the art could learn that the described SICM apparatus as such may be used for different applications, *inter alia*, patch-clamping. However, there is no clear and direct disclosure of a method of investigating a cell in which scanning the cell surface and identifying a part of interest is followed by patch-clamping using the **same** probe.

11. As regards feature (i) characterising the method according to claim 1 as presently on file (see paragraph 6 above), there is no disclosure whatsoever in document (1) concerning either the modulation of the distance between the probe and the surface, or the control of the distance in response to the modulated ion current.
12. In view of the above, the board concludes that the subject-matter of independent claim 1 is new. The same applies, *mutatis mutandis*, to the subject-matter of dependent claims 2 to 4.

Article 56 EPC - Inventive step

13. Document (3), which was cited in the International Search Report for the present application, is regarded as the closest prior art.
14. Document (3) describes a method for functional mapping of cells (eg. ion channel mapping) which combines

scanning ion-conductance microscopy (SICM) and scanning near-field optical microscopy (SNOM). The method comprises bringing the tip of a scanning micropipette to a position adjacent to (i.e. at a certain distance from) an ion channel on the surface of a cell in order to deliver locally either ions, agonists or other agents, or light. In a particular embodiment, the electrical response of the cell is monitored using a separate patch-clamp pipette (see Example 2 and Figure 3). A frequency-modulated operation mode for controlling the distance of the micropipette to the surface of the cell is described in the passage on page 7, lines 3 to 11, and in Figure 2B.

15. The method described in document (3) is conceived for the same purpose as the method of claim 1, namely investigating a cell, and shares with the claimed method the most relevant technical features. However, it differs from the method of present claim 1 in that the two techniques are applied concurrently using different probes: a micropipette for scanning and/or delivering locally ions, agonists or other agents, and a patch-clamp pipette.
16. Having regard to document (3), the technical problem to be solved can be formulated as providing a simplified method for investigating a cell, in particular for mapping and investigating ion channels on the surface of the cell, which requires less technical equipment in order to be performed.
17. The solution provided in claim 1 is a method of investigating a cell in which the same probe (micropipette) is used for first scanning the surface

of the cell and identifying a part of interest, and then performing patch-clamping. The board is satisfied that the problem as formulated above has been solved.

18. Moreover, the board is persuaded that, having regard to the state of the art at the priority date as represented by the documents presently on file, the provided solution was not obvious to a person skilled in the art. The skilled person seeking to improve the method described in document (3) could not find in this document the slightest hint that the method described therein could be simplified by using the same micropipette for first scanning the cell surface and then patch-clamping.

19. Nor could the skilled person find in either document (1) or document (2) anything that suggested the solution provided by the claimed method. It is true that, as observed above (see paragraph 10), patch-clamping is described in the passage on page 23, left column of document (1) as a possible further application for the SCIM apparatus described therein. The same is true for the passage bridging the left and right columns on page 657 of document (2), which is identical in wording. However, the board understands these passages as suggesting fully independent applications of the SICM apparatus, rather than a method which combines two techniques applied in a certain sequence. In the board's view, the suggestion in document (1) - or document (2) - that the apparatus described therein is suitable for performing either technique cannot be regarded - without hindsight - as a suggestion to combine both techniques in a method for investigating a cell.

20. Since neither document (3) alone nor a combination of the teachings of this document with those of documents (1) and (2) suggests to the skilled person the method of claim 1, an inventive step within the meaning of Article 56 EPC must be acknowledged.

21. It follows from the above that the application as presently on file and the invention to which it relates fulfil the requirements of the EPC.

Refund of the appeal fee

22. Rule 103(1)(a) EPC, which has almost identical wording as Rule 67 EPC 1973, provides that the appeal fee shall be reimbursed in the event of interlocutory revision or where the board of appeal deems an appeal to be allowable, if such reimbursement is equitable by reason of a substantial procedural violation.

23. In the present case, the appeal is deemed to be allowable. Thus, the issue to be decided is whether or not the appellant's allegation of a substantial procedural violation is well-founded and, if so, whether or not reimbursement of the appeal fee is equitable.

24. According to the jurisprudence of the Legal Board of Appeal (see decision J 6/79, OJ EPO 1980, 225), the expression "substantial procedural violation" is to be understood, in principle, as meaning that the rules of procedure have not been applied in the manner prescribed by the EPC.

25. The appellant maintained that, in the decision under appeal no reasons were given as to why the subject-matter of claim 7 as filed did not comply with the EPC. Therefore, the decision was not sufficiently reasoned in the sense of Rule 68(2) EPC 1973 (now Rule 111(2) EPC).

26. The board disagrees with this view. It is undisputed that the decision under appeal was sufficiently reasoned within the meaning of Rule 111(2) EPC as regards the finding of lack of novelty in respect of the subject-matter of independent claims 1 and 11 as then on file, which was the ground on which the refusal of the application was based. Since the decision under appeal was not based on any grounds concerning dependent claim 7, the lack of reasons in respect of this claim cannot, in the board's view, be regarded as a deficiency of the reasoning in the decision, let alone as a substantial procedural violation of the applicant's right to be heard (Article 113(1) EPC). In the board's view, if the patent application is already to be refused because the subject-matter of the independent claims lacks novelty, it cannot be legitimately expected that further deficiencies concerning the dependent claims are dealt with in detail in the decision.

27. It should be noted that, in the present case, the grounds on which the decision under appeal was based were readily apparent from the communication of the examining division pursuant to Article 96(2) EPC 1973 (see paragraph VI above), and the appellant had an opportunity to present its comments. Whether or not the examining division took into account the arguments put

forward by the applicant in respect of claim 7 is, under the circumstances of the present case, immaterial, because the appellant's arguments were not pertinent to the objections raised by the examining division in its communication and the grounds given in the decision under appeal for the refusal of the application. The board considers that for the examining division not to address non-pertinent arguments in its decision does not amount to a substantial procedural violation.

28. Moreover, the board notes that, pursuant to Article 113(2) EPC, the examining division can decide upon a European patent application only in the text submitted to it by the applicant. Thus, as the applicant admitted, it was incumbent on it to file a set of claims that could, in its view, be suitable for acceptance, all the more in view of the fact that it had been invited to do so in the communication of the examining division pursuant to Article 96(2) EPC 1973 (see paragraph VI above). The board is not aware of any circumstances - nor did the appellant put forward any - that might have prevented it from filing amended claims which took into account the objections raised by the examining division in its communication. The mere allegation by the applicant that the subject-matter of claim 7 was novel and involved an inventive step cannot be regarded as a text of an application within the meaning of Article 113(2) EPC, on which the examining division could have decided.
29. In view of the above, reimbursement of the appeal fee is not justified.

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 grant a patent upon the following basis:
Claims: 1-4 of the main request
Description: page 1-11 of the specification
Drawings: figures 1-4;
all the above submitted during the oral proceedings before the board.

3. The request for the refund of the appeal is refused.

The Registrar:

The Chairman:

A. Wolinski

L. Galligani