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D E C I S I O N
of 6 April 2005

Case Number: T 0204/03 - 3.4.2

Application Number: 90909351.0

Publication Number: 0478626

IPC: G01N 21/76

Language of the proceedings: EN

Title of invention:

Detecting or quantifying multiple analytes using labelling techniques

Patentee:

GEN-PROBE INCORPORATED

Opponent:

Bayer Corporation
Akzo Nobel N.V.

Headword:

-

Relevant legal provisions:

EPC Art. 56

Keyword:

"Inventive step (yes) "

Decisions cited:

-

Catchword:

-



Case Number: T 0204/03 - 3.4.2

D E C I S I O N
of the Technical Board of Appeal 3.4.2
of 6 April 2005

Appellant: GEN-PROBE INCORPORATED
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Respondent: Bayer Corporation
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Representative: -

(Opponent) Akzo Nobel N.V.
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Decision under appeal: Decision of the Opposition Division of the
European Patent Office posted 12 December 2002
revoking European patent No. 0478626 pursuant
to Article 102(1) EPC.

Composition of the Board:

Chairman: A. G. Klein
Members: M. A. Rayner
M. J. Vogel

Summary of Facts and Submissions

I. The present appeal is against the decision of the opposition division revoking European patent 478 626 (application number 90 909 351.0) relating to analyte labelling.

II. In the proceedings, reference has been made, amongst others, to the following documents:

D14 Clinical Chemistry, Vol. 32, No. 5, 1986, 887-890, Wians et al., "Evaluation of Simultaneous Measurement of Lutropin and Follitropin with the SimultROPIN™ Radioimmunoassay Kit"

D17 Clinical Chemistry, Vol. 33, No. 12, 1987, 2281 - 2283, Hemmilä et al., "Double Label Time Resolved Immunofluorometry of Lutropin and Follitropin in Serum"

D18 Clinical Chemistry, Vol. 29, No. 8, 1983, 1474-1479, Weeks et al., "Acridinium Esters as High Specific Activity Labels in Immunoassay"

III. In the decision under appeal, the opposition division was satisfied as to compliance with Article 83 EPC (disclosure of the invention - sufficiency) and Article 123 EPC (amendments - added subject matter). The division was also satisfied as to novelty of the claimed subject matter (Article 54 EPC) and did not find persuasive the arguments of the opponents with respect to inventive step (Article 56 EPC). However, of its own motion under Article 114(1) EPC, the division reached a negative view as to inventive step. The

approach taken was that the difference between a radio immunoassay described in document D14 and that claimed in independent claim 1 is that in the latter different chemiluminescent labels are coupled to the binding partners and that between steps (i) and (ii) the sample is treated to trigger simultaneously the chemiluminescent reactions. The problem to be solved is thus to provide a multichannel assay where the use of radioactive materials can be avoided. According to document D18, the universal application of chemiluminescent labels makes them a logical alternative to radioisotopes for immunoassays purposes. Since document D14 deals with multichannel assays, the skilled person would obviously realise the need for applying two chemiluminescent labels. In doing so, the subject matter of claim 1 would be arrived at without any inventive step.

IV. According to the appellant (=patentee), the solution to the problem is the provision of different chemiluminescent labels which are directly coupled to different binding agents in order to arrive at a method/assay which allows the simultaneous detection of multiple analytes in a sample without the use of radioactivity. The earlier document D18 merely discloses one chemiluminescent label, which means that only one specific acridinium molecule detailed in document D18 can be considered as an alternative label to one radioisotope. However, the solution requires at least two suitable chemiluminescent labels for which document D18 provides no motivation or suggestion. Thus even when combining the teachings of documents D14 and D18, the skilled person not only would not but could not have arrived at the claimed subject matter of the

patent. The skilled person conditioned by the prior art obviously did not enter the unpredictable area of chemiluminescent labels but accepted the disadvantages of radioactivity. In any case, later document D17 teaches a successful approach with simultaneous fluorescent labels for lutropin and follitropin, just like document D14, but of course avoiding radioactivity.

- V. According to respondent I (=opponent I), in relation to the supposed and imaginary contribution of the patent in dispute, the reality is merely that at least two (non-interfering) conventional assays are run at the same time, largely relying on the existing knowledge of those skilled in the art. The convenience of simultaneous assays in some situations had already been realised (document D14), but the use of radioactive labels had known disadvantages. Chemiluminescent labels (e.g. document D18) were an attractive alternative among a few available options, document D18 using the terms "universal", "logical" and "practical". In the present case, it can be said that the patent specification relies upon what a skilled person already knows and the common theme is a fishing trip. A sample is hooked, sometimes directly, sometimes indirectly and there are various labels for doing this, e.g. chemiluminescent, fluorescent and radioactive. Advantages and disadvantages of the labels are known, e.g. speed, light emission and radioactivity, and are traded off against one another according to the choice made. Dual labels were known for enzymes, radiolabels and fluorescence and it was only the use of two chemiluminescent labels together which was not known.

Sometimes, as in the present case, a problem does not mean that what is not said cannot be done but only that it has not been said, e.g. in the present case use "one" was not said in the prior art, the plural is used in relation to chemiluminescent labels. The skilled person thus had everything available if he wished to use more than one label. On the "could/would" question, the skilled person would use more than two chemiluminescent compounds if he wanted to as nothing is thereby made possible which was not possible before. There are not many possibilities and chemiluminescence is not precluded. Moreover there was an expectation of success as something which had already been done was being repeated. Hindsight cannot be considered involved as people always try to move forward, there are a number of reasons for doing, for example scientific curiosity. There is merely a tried and tested approach used, which results in nothing surprising, the patent is about no more than choosing "horses for courses".

VI. The appellant requests that the decision under appeal be set aside and the patent maintained on the basis of the main request submitted on 18 October 2002, or in the alternative on the basis of a first or second auxiliary request. Respondent I requests that the appeal be dismissed. Both the appellant and respondent I requested oral proceedings on an auxiliary basis, which were in consequence appointed by the board. In a communication attached to the summons to oral proceedings, the board observed it seemed the focus of the case was moving towards considering documents D14 and D18 in the context of inventive step. The parties would have a chance to elaborate on the contents of

their written submissions and it was intended to decide the case at the oral proceedings.

VII. The appeal and statement setting out the grounds of appeal were notified by the registry to opponent II with communications dated 19 February 2003 and 23 April 2003, respectively. A summons dated 25 November 2004, a notification of modification of date dated 10 December 2004 were like wise notified to opponent II. In response to the summons to oral proceedings, a letter was received informing the board that (a) bioMérieux B.V. had purchased AKZO NOBEL N.V. activities in the diagnostic field, (b) bioMérieux should replace AKZO NOBEL as Opponent II in the ongoing procedure and (c) there would be no participation in the oral proceedings scheduled.

VIII. The wording of the independent claims according to the main request is as follows.

All contracting states

"1. A method for the assay, detection, quantification, location or analysis of a sample containing at least two substances of interest comprising the steps of
i) reacting said sample with a mixture comprising at least a first reagent and a second reagent that form at least a first complex and a second complex wherein said first complex comprises one of said substances or a respective associated substance and said first reagent, and wherein said second complex comprises another said substance and said second reagent, wherein at least said first reagent and second reagent each comprise

- a) a binding partner for binding or otherwise linking with one or more of said substances, and
- b) a different chemiluminescent molecule exhibiting distinguishable emission characteristics, wherein said chemiluminescent molecule is chemically or physically coupled to said binding partner;
- ii) subsequently treating said sample comprising said first and second complexes to cause a first and second chemiluminescent reaction to occur, wherein said chemiluminescent reactions are simultaneously triggered, and
- iii) observing, sensing, measuring and/or recording the emissions of each of said chemiluminescent reactions."

All contracting states except ES

"17. A luminescent reagent which comprises a mixture of at least two reagents, wherein said reagents each comprise

- a) a binding partner for binding or otherwise linking with respective substances of interest; and
- b) a different chemiluminescent molecule exhibiting distinguishable emission characteristics, chemically or physically coupled to the binding partner."

The wording of claims according to the auxiliary request of the appellant is not given as this is not subject of the present decision (see point 5 of the reasons below).

IX. Opponent II was not represented at the oral proceedings, at the end of which the board gave its decision.

Reasons for the Decision

1. The appeal complies with the provisions referred to in Rule 65(1) EPC and is therefore admissible.
2. During the appeal proceedings, the board has not been presented with any reason for diverging from the position of the opposition division in relation to sufficiency, added subject matter or novelty. Inventive step on the other hand, insofar as relating to the negative view reached by the opposition division of its own motion, has been considered extensively in the appeal proceedings.

3. *Prior Art*

3.1 Document D14

This document relates to radioimmunoassay and involves Lutropin (LH) and follicle stimulating hormone (FSH) being simultaneously quantified, the assay kit exploiting the difference in scintillation energies produced by ^{57}Co and ^{125}I labelled tracers and the ability of gamma counters to discriminate between radioactivity due only to ^{57}Co or ^{125}I in tubes containing both ligands.

3.2 Document D17

This document relates to a procedure for the simultaneous immunofluorimetric assay of lutropin and follitropin in human serum, based on the use of monoclonal antibodies and of fluorescent lanthanides Eu^{3+} and Tb^{3+} . The α -chain specific antibody was used

as a common capture antibody on the surface of monotitration strips. The anti- β -follitropin antibody was labelled with Tb. the anti- β -lutropin antibody with Eu³⁺. After the immunoreactions had taken place, the bound fractions of the labels were dissociated in a fluorescence enhancement solution of pivaloyltrifluoroacetone, trioctylphosphine oxide, and Triton X-100 surfactant. In this solution both lanthanides can be measured successively with a time-resolved fluorometer. Results were said to correlate well with those by commercial immunofluorometric assays and radioimmunoassays.

3.3 Document D18

According to this document various acridinium salts can be stimulated to produce light in the presence of dilute alkaline hydrogen peroxide (Figure 1) in the absence of a catalyst (6). Such compounds include derivatives of acridine possessing a quaternary nitrogen centre and derivatized at the 9 position to yield a labile phenyl ester moiety. Further, the electronically excited molecule of N-methylacridone (II) formed in the reaction is resistant to quenching before radiation. Synthesis of a stable chemiluminescent acridinium ester derivative is reported that is capable of covalent association, under mild conditions, with antibodies to yield stable, immunoreactive derivatives of high specific chemiluminescence activity. With this compound, proteins can be labelled reproducibly to predetermined specific activities. Proteins so labelled can be detected at lower concentrations than can the corresponding ¹²⁵I derivatives. It is remarked that the universal application of chemiluminescent labels makes

them a logical alternative to radioisotopes for immunoassay purposes.

4. *Patentability*

- 4.1 The appeal proceedings have focused on document D14 as representing the closest prior art document. This document relates to radioimmunoassay and does not involve chemiluminescent labels as in the patent in dispute. The approach of the opposition division in relation to the problem to be solved can thus be considered reasonable, i.e. to provide a multichannel assay where the use of radioactive materials can be avoided.
- 4.2 While document D18, published three years before document D14, does not relate to a multichannel approach, it can be considered to illustrate that there were a number of analysis options open to the skilled person, for example enzyme, fluorescent and chemiluminescent probes as indicated in the left column on page 1478 (first paragraph of the discussion). Document D18 is particularly concerned with acridinium salts which can be stimulated to produce light in the presence of dilute alkaline hydrogen peroxide. Although the words "labels" and "radioisotopes" are used in the plural in document D18, the actual use taught is no more than one at a time with for example the antibodies in Table 1. In a more general way, the document also explains that little work had been reported on the use of chemiluminescent labels in the immunoassay of polypeptides. The major reason is said to be difficulty in developing immunoassays with sensitivity and precision equivalent to that offered by ¹²⁵I based

techniques. At the beginning of the document, it is also explained that various derivatives of luminol and isoluminol had been used for chemiluminescent labelling of proteins, but even the most recent work had yielded labelled proteins of low specific activity. Problems are said to have been that quantum yield of emission often decreases on coupling to proteins and the requirement for a catalyst leads to high chemiluminescent background. It can therefore be concluded that document D18, in the terminology it uses, teaches that use of a chemiluminescent label is a logical alternative to use of a radioisotope, in particular, ^{125}I , but indicates that use of chemiluminescence in general is not straightforward.

4.3 Turning to a document which does involve a multichannel approach, document D17, published a year after document D14, it is reported at the beginning of the discussion on page 2283 that the fluorescent lanthanides are ideal candidates for double label or even multiple parameter assays. This document also relates to lutropin and follitropin, as does document D14. Moreover, towards the end, the document indicates the assay sensitivities were considerably higher than those obtained with commercial double label radioimmunoassays. The board therefore considers it more likely that, starting from document D14, a skilled person would have been expected to use the approach of D17 than D18 in pursuing a multichannel approach.

4.4 The link in the reasoning of the opposition which is weak or indeed missing in the prior art is therefore that the skilled person would obviously have realised the need for applying two different chemiluminescent

labels in a mixture. The board did not find anything in the arguments of the respondent which could provide this link and strengthen the argument, for example "scientific curiosity" and "moving forward" can often be cited in a general way against inventive step, but are not specific enough to present a successful challenge in the present case. The board does not accept there was an expectation of success in view of the numerous references in document D18 which point to difficulties with chemiluminescence. Moreover, the argument that what has already been done is repeated is not persuasive as running two non interfering assays at the same time, relying on the knowledge of the skilled person, need not be to the point, since separate chemiluminescent runs would not amount to reagents with a different chemiluminescent molecule being in a mixture. The argument that multichannel assays were known for enzymes and fluorescent labelling but not for chemiluminescent labelling even goes against the respondent as no reason has been presented why it does not indicate choosing one of the former two would have been the obvious step or to use the language of respondent I the horse for the course.

- 4.5 Looking at the prior art as a whole, including the time line of the documents, i.e. D18, D14 then D17, the board was not therefore able to find a convincing chain of reasoning to reach a conclusion of lack of inventive step in the light of documents D14 stepping back to document D18 yet still not reaching all the claimed features and thus does not agree with the opposition division. Accordingly, the board has no reason to conclude the subject matter of claim 1 cannot be

considered to involve an inventive step within the meaning of Article 56 EPC.

4.6 Since claim 17 is directed to a luminescent reagent which comprises a mixture of at least two reagents with the (a) and (b) features of claim 1, considerations corresponding to those taken into account for claim 1 apply in considering inventive step of the subject matter of claim 17 in the light of documents D14 and D18.

4.7 The remaining claims of the main request are in dependent form and therefore are also directed to subject matter which can be considered to involve an inventive step.

5. *Auxiliary Requests*

Since the board was satisfied as to inventive step of the subject matter of the claims according to the main request, there was no reason to consider the auxiliary requests in the present decision.

6. Opponent II

There was no reaction from opponent II to the appeal. The appeal and the summons to oral proceedings were correctly served on opponent II and the company claiming to replace the respondent company indicated responsive to the summons that it did not intend to attend the oral proceedings. Only the appellant and respondent I participated in the oral proceedings, which went ahead according to Rule 71(2) and gave the parties present an opportunity to elaborate on their

written submissions. As it was clear from the behaviour of opponent II and the company claiming to replace it that no input bearing on the decision could be expected, there was no reason for not following the course of action indicated in the summons to oral proceedings and accordingly taking a final decision on the appeal at the oral proceedings.

7. *Remittal*

The first instance should ensure that in the patent specification the prior art documents D14 and D18 are appropriately evaluated and there is consistency between the specification and claims.

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 maintain the patent on the basis of:
 - claims 1 to 29, claims 1 to 16 (for the contracting state ES), all as filed on 18 October 2002 (main request)
 - description to be adapted
 - drawings as granted.

The Registrar:

The Chairman:

P. Martorana

A. G. Klein