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D E C I S I O N
of 28 March 2000

Case Number: T 0457/95 - 3.3.4

Application Number: 85105105.2

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Language of the proceedings: EN

Title of invention:
Immunoassay for the detection of ligands

Patentee:
ABBOTT LABORATORIES

Opponent:
Dade Behring Marburg GmbH

Headword:
Immunoassay/ABBOTT LABORATORIES

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (yes) - reformulation of the problem"

Decisions cited:
T 0013/84, T 0386/89, G 0002/88, T 0184/82

Catchword:
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Case Number: T 0457/95 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 28 March 2000

Appellant: (Opponent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 29 March 1995 rejecting the opposition filed against European patent No. 0 160 900 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
C. Holtz

Summary of Facts and Submissions

I. The appeal lies against the decision of the opposition division rejecting the opposition against European patent No. 0 160 900 (application No. 85 105 105.2) which was granted on the basis of 10 claims. The patent in suit relates to an immunoassay for the detection of ligands. Claim 1 as granted read as follows:

"1. An immunoassay for detecting a ligand comprising:

a) immobilizing a ligand-specific binding material onto a solid phase;

b) reacting the solid phase with a test sample;

c) reacting the solid phase with a biotin-labelled ligand-specific binding material;

d) reacting the solid phase with antibiotin labelled with a marker;

e) separating unreacted reagents from the solid phase; and

f) measuring the presence of the marker in the solid phase or in the unreacted reagents to detect the amount of ligand present in the sample.

Dependent claims 2 to 10 related to specific embodiments of the immunoassay of claim 1.

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

(1) US-A-4,228,237;

(2) Langer-Safer P.R. et al., Proc. Natl. Acad. Sci. USA vol. 79, pages 4381-4385 (1982);

(3) Brigati D.J. et al., Virology, vol. 126, pages 32-50 (1983);

(4) Mushahwar I.K. et al., J. Virol. Methods, vol. 16, pages 45-54 (1987);

(5) Bayer E. A. et al., Methods of Biochemical Analysis, vol. 26, pages 1-45 (1980);

(6) Wilcheck M. et al., Immunology Today, vol. 5 (No. 2), pages 39-43 (1984) and R.E. Morris et al, ibidem, vol. 5 (No. 5), page 127 (1984);

(7) Diponkar Banerjee, S.P, J. Clin. Path., vol. 7, pages 223-225 (1981);

(9) Declaration of Dr Isa Mushahwar dated October 1987 and

(10) Guesdon, J-L, et al., J. Histochem. Cytochem., vol. 27, pages 1131-1139 (1979).

III. The submissions provided by the appellant can be summarized as follows:

- The opposition division had made a reformulation of the problem to be solved as being that of avoiding a specific binding of avidin to endogenous biotin or biotin-like substances. This was not in conformity with the rationale of

decisions T 13/84 (OJ EPO 1986, 253) and T 386/89 of 24 March 1992 (Case Law of the Boards of Appeal of the EPO, 3rd edition, page 42), which required that the redefined problem had to be deducible from the application as filed. In the present case, there was no disclosure in the application as filed of the problem of aspecific binding of avidin to endogenous biotin or biotin-like substances and the technical effect achieved by avoiding aspecific binding of avidin to endogenous biotin could not be derived from the application as filed. The problem to be solved was instead that of avoiding problems that arose from the non-specific binding of avidin to components in the immunoassay of document (1).

- The use of antibiotin was known for another purpose, namely for minimizing aspecific binding of labelled avidin to negatively charged components such as chromatin (see documents (2) to (6)). Thus, even by assuming that the problem to be solved by the immunoassay of claim 1 were actually to avoid binding of labelled avidin to endogenous free biotin, the solution proposed in claim 1 to this problem would have to be considered as a "second indication" invention in the sense that it is based on a new technical effect. However, the technical effect on which said "second indication" was based was not disclosed in the patent in suit, contrary the requirements set out in decision G 2/88 (OJ EPO 1990, 93).

IV. The submissions provided by the respondent can be summarized as follows:

- The technical problem underlying the claimed immunoassay was overcoming the drawbacks arising from endogenous avidin-binding activity as well as non-specific avidin binding to non-biotin components (patent in suit, column 1, lines 30 to 33).

- The affinity of avidin for biotin was known before the priority date of the patent in suit (see reference to "Pillarisetti et al., 1983" at the bottom of page 52 of later document (4)) to be one million times greater than the affinity of an antibody for its antigen. Thus the skilled person would not have expected that an immunoassay based on biotin-antibiotin would have been as sensitive as the classical one based on avidin-biotin.

- The claimed immunoassay could not be considered as a "second indication" because it did not involve a known use of the enzyme-labelled antibiotin in a known process.

V. The appellant requested that the decision under appeal be set aside and that the patent be revoked.
The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Technical problem and solution

2. The patent in suit is concerned with a biotin-antibiotin solid-phase immunoassay (column 1, lines 5 to 8). It is stated in the patent in suit that a particular problem arises with the conventional biotin-avidin solid-phase immunoassay because "the highly basic avidin carries a high positive charge and can non-specifically adsorb to any negatively-charged biological component in the assay" (see column 1, lines 30 to 33). To avoid this disadvantage, avidin is replaced with antibiotin.

3. The parties agree, and so does the board, that the closest prior art is represented by document (1) because it discloses an immunoassay as in claim 1 of the patent in suit, with the difference that the prior art immunoassay is based on the conventional biotin-avidin interaction instead of the biotin-antibiotin interaction (antibiotin is an antibody against biotin).

4. It is the precise statement of the technical problem arising from the disclosure of document (1) that is the main issue of the appeal proceedings. The appellant objects to the reformulation of the technical problem made by the opposition division as being that of avoiding aspecific binding of avidin to endogenous biotin. It is argued that there is neither a disclosure in the application as filed of the problem of aspecific binding of avidin to endogenous biotin nor it is possible to derive therefrom the technical effect achieved by avoiding aspecific binding of avidin to

endogenous biotin. In view of this incorrect reformulation of the technical problem, the appellant requests in the Statement of Grounds of Appeal that the patent be revoked, without citing any Articles or Rules of the EPC. The board assumes that the appellant maintains the arguments submitted before the opposition division that once the "correct" technical problem is identified (avoiding problems that arose from non-specific binding of avidin to components in the immunoassay of document (1)), the use of antibiotin in the immunoassay of claim 1 would be obvious in the light of the prior art.

6. On the basis of established case law, the proper yardstick for defining a problem is **what is actually achieved vis-à-vis the closest prior art**, namely the ultimate technical effect. This follows from Rule 27(1)(c) EPC, according to which the description of an application should "disclose the invention, as claimed, in such terms that the technical problem (even if not expressly stated as such) and its solution can be understood, and state any advantageous effects of the invention with reference to the background art". This yardstick may change according to which art is known at the time the assessment is made.

7. Consequently, it is considered appropriate at this point that the board establishes what technical effect the immunoassay of claim 1 actually achieves vis-à-vis the closest prior art represented by document (1), disclosing the conventional biotin-avidin immunoassay. It is stated on page 3, lines 13 to 17 of the application as filed that "According to the invention, a direct or inhibition-type biotin-antibiotin immunoassay is provided which is not subject to the disadvantages of biotin-avidin immunoassay", "this immunoassay is more specific and sensitive than

previous biotin-avidin assays" (page 8, lines 2 to 4) and "the inventive assay gives well-defined readings of positive and negative samples and offers better quantification of unknown ligands" (page 8, lines 20 to 22). In order to clarify the above information given in the original description, the respondent submitted before the opposition division a test report (annexed to document (9)), wherein Table 1, inter alia, compares the background noise of a negative control incubated for two hours at 40°C with I^{125}-avidin versus a negative control incubated under the same conditions with I^{125}-antibiotin. The count rate was 3-4 fold lower with I^{125}-antibiotin (claim 1) than with I^{125}-avidin (document (1)). In the board's view, this is a valid comparative test indicative of improved sensitivity and specificity of the claimed immunoassay over the one disclosed by document (1) since the conditions used (temperature, incubation time, negative control) are the **same** for both I^{125}-antibiotin and I^{125}-avidin: there is thus no reason to assume that the conditions used would bias one of the two labelled ligands, more so as the incubation conditions of two hours at 40°C are those disclosed by Example II of the patent in suit.

8. The skilled person would recognize that the original formulation of the technical problem as "preventing non-specific binding of the highly basic avidin to any negatively-charged biological component in the assay" stated in the application as filed and in the patent in suit (column 1, lines 30 to 33; see point 2 supra) is a possible explanation of the advantage invoked by the respondent (technical effect). Also the alternative formulation of the technical problem as "avoiding aspecific binding of avidin to endogenous biotin or biotin-like substances" (opposition division) is merely another possible explanation among others (eg binding of avidin to lectins: see document (6), page 42, right-

hand column) of the technical effect established above. The skilled person would also recognize that all these formulations or explanations fall under the more general concept of "avoiding problems that arise from non-specific binding of avidin". Therefore, since the advantage invoked by the respondent (technical effect) is already implied in the original problem, nothing prevents a more exact definition of the original problem from being given, even in the course of the appeal proceedings, provided it is supported by the original disclosure (cf decision T 184/82, OJ EPO 1984, 261, 263, points 3 to 5 of the Reasons). Thus, in the board's opinion, a precise formulation of the technical problem derivable from the technical effect disclosed in the application as filed is that of "avoiding problems that arise from non-specific binding of avidin".

9. In order to provide an immunoassay devoid of the drawbacks of avidin, the latter is replaced according to claim 1 of the patent in suit with antibiotin. In view of the findings emphasized under point 7 supra, the board is satisfied that the technical problem has been solved.

Inventive step

10. As for the issue of inventive step, it is necessary to establish whether the skilled person, starting from document (1), would have replaced avidin with antibiotin in the reasonable expectation of solving the problem set out above, namely providing an immunoassay devoid of the drawbacks of avidin.

11. In the board's view, even assuming that results obtained in the field of immunohistology can be extended to immunoassays, as the appellant maintains, replacement of biotin with antibiotin was not the sole

solution offered to the skilled person in order to obviate the drawbacks of avidin. In fact, document (7) ("Summary") teaches that an increase in sensitivity can be obtained with the addition of 1% avidin and 0.01% biotin or by dilution (page 225, left-hand column). An increase in sensitivity can also be achieved by increasing the spacer arm length of the biotin-substituted probes (document (3), page 45, top of left-hand column and document (2), page 4385, end of left-hand column), by using streptavidin or anti-avidin antibodies (see document (6), page 42, bottom of right-hand column) or increasing the degree of biotinylation (document (10), bottom of right-hand column). Therefore, the conclusion cannot be drawn that the skilled person, faced with the problem of avoiding the drawbacks of avidin, would of necessity have considered antibiotin in preference to other known and easy to apply solutions for arriving at the claimed immunoassay.

12. Furthermore, the success of the conventional immunoassays of document (1) is based on the high sensitivity of this assay due to the exceptionally strong biotin-avidin interaction ($K_D = 10^{-15}$ M^{-1})(see document (6), page 39, left-hand column: "the high affinity ($K_D = 10^{-15}$ M^{-1}) of avidin for biotin serves as an aid in **amplifying the sensitivity** of immunoassays..." (emphasis added). The affinity of an antibody for its corresponding antigen in immunoassays is, however, of the order of $K_D = 10^{-9}$ M^{-1}, ie about one million time lower. This finds support in the reference to "Pillarisetti et al., 1983" at the bottom of page 52 of later document (4). Thus the skilled person would have reasonably expected that replacement of avidin with antibiotin, leading to an immunoassay based on biotin-antibiotin, ie a common antibody-antigen interaction with $K_D = 10^{-9}$ M^{-1}, would have represented a worsening of the assay performance of the

biotin-avidin assay of document (1). Yet this is rather the opposite of solving the problem of avoiding the drawbacks of avidin.

13. In summary, having regard to the state of the art, the solution of the technical problem in this case does not present itself in an obvious way for the skilled person. The subject-matter of claim 1 and depending claims 2 to 10 therefore involves an inventive step.

14. The appellant also maintains that the claimed immunoassay has to be considered as a kind of "second medical application" if it were assumed that the problem to be solved by the immunoassay of claim 1 were actually to avoid binding of labelled avidin to endogenous free biotin (see paragraph VI supra). However, since the board does not agree with this formulation of the technical problem to be solved (see point 8 supra), no need arises to consider this objection further.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

A. Townend U. M. Kinkeldey