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D E C I S I O N
of 26 July 1995

Case Number: T 0143/92 - 3.3.1

Application Number: 85304635.7

Publication Number: 0167366

IPC: C07H 21/00

Language of the proceedings: EN

Title of invention:
Accelerated nucleic acid reassociation method

Applicant:
GEN-PROBE INCORPORATED

Opponent:
-

Headword:
Hybridisation method/GEN-PROBE

Relevant legal provisions:
EPC Art. 54, 84, 111(1)

Keyword:
"Novelty (yes, after amendment)"
"Clarity (yes) - technical features defined by their function"
"Remittal for further prosecution"

Decisions cited:
T 0068/85; T 0409/91

Catchword:
-

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Case Number: T 0143/92 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 26 July 1995

Appellant: GEN-PROBE INCORPORATED
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Decision under appeal: **Decision of the Examining Division of the European Patent Office dated 7 August 1991 refusing European patent application No. 85 304 635.7 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. J. Nuss
Members: R. K. Spangenberg
J. A. Stephens-Ofner

Summary of Facts and Submissions

I. The appeal lies against the decision of the Examining Division of the EPO dated 7 August 1991, by which European patent application No. 85 304 635.7 was refused. This application was filed on 28 June 1985, claiming priority of 5 July 1984 from an earlier application in the United States, and was published as EP-A-0 167 366.

II. The decision under appeal was based on 2 sets of amended claims, one for the Contracting State IT and the other for the rest of the designated Contracting States.

III. The main ground of refusal was that the claimed method was not novel in view of the disclosure of some documents acknowledged in the description (see page 3, third paragraph, in combination with the content of Table 1 on pages 5 and 6 and page 11, lines 28 to 35), *inter alia*

Wetmur and Davidson, J. Mol. Biol., vol. 31(1968), 349-370 (hereinafter cited as D2), and

Orosz and Wetmur, Biopolymers, vol. 16(1977), 1183-1199 (hereinafter cited as D3)

In addition, the Examining Division considered that the above claim lacked clarity.

IV. In the statement of grounds of appeal the Appellant explained that the difference between the method disclosed in the above documents and the one disclosed in the patent application in suit was to be seen in the application of a concentration of the second single-stranded nucleic acid which was lower than that used in

D2 and D3. He further submitted that at high concentrations of the second single stranded nucleic acid the effect of the precipitation agent on the rate of hybridisation was different. In response to two communications of the Board the Appellant then submitted on 8 June 1995 two amended sets of 18 claims (one for Italy and one for the other Contracting States). Claim 1 for the Contracting States other than Italy reads as follows (the essential amendment in respect of the refused claim being shown in bold letters):

"1. An improved method for the formation of double-stranded nucleic acid molecules from separate single-stranded nucleic acid molecules wherein the rate of reaction is greatly increased over the standard reference condition reaction rate, said method comprising the steps of:

preparing an aqueous reaction solution containing

- a quantity of a first single-stranded nucleic acid molecule,

- a quantity of a second single-stranded nucleic acid molecule, said second single-stranded nucleic acid molecule having at least one segment of base sequences complementary to a corresponding segment of base sequences of said first single-stranded nucleic acid molecule, **the concentration of the second nucleic acid being such that at least a 100 fold increase in acceleration of rate of reaction is observed in the presence of 4 M LiCl compared with the rate of reaction observed with 0.18 M NaCl at 60°C;** and

- at least one nucleic acid precipitating agent, other than sodium phosphate or sodium sarcosinate, in a concentration sufficient to accelerate the rate of reaction of the said first and second single-stranded nucleic acid molecules at least about 100 times the rate of reaction in solution using 0.18 M NaCl at 60°C;

incubating said aqueous reaction solution at a temperature at which reassociation can occur; and

assaying said incubated aqueous reaction solution for the presence of double-stranded nucleic acid molecules."

Claim 1 for the Contracting State Italy differs from the above claim only by the absence of the disclaimer in the definition of the precipitation agent. This disclaimer was introduced during the examining proceedings in order to meet a novelty objection based upon

D1: WO-A-84/02721

(published 19 July 1984 and designating all Contracting States of the present patent application except Italy).

V. The Appellant requested that the decision under appeal be set aside and the application be further prosecuted on the basis of the sets of claims submitted on 8 June 1995.

Reasons for the Decision

1. The appeal is admissible.

2. The subject-matter of the amended independent claims is based upon the application documents as filed (see Claim 1 as filed in combination with the description as filed, page 4, line 13 to 24, page 11, line 19 to 24 and page 16, lines 6 to 12). The requirement of Article 123(2) EPC is therefore met by the amended Claim 1.

3. *Novelty*

3.1. Although D1 does not only disclose that sodium phosphate and sodium sarcosinate are able to accelerate the rate of renaturation of **Legionella** R-RNA more than 100 fold compared with the rate measured with 0,72 M NaCl at 76°C (see page 36, lines 1 to 13 and page 84, lines 1 to 15), but, in addition states on page 36, lines 13 to 16, that other salts can also be used to effect this hybridisation rate acceleration, and that these salts include "most sodium, ammonium, rubidium, potassium, cesium, and lithium salts", the Board is satisfied, that the claimed subject-matter is novel. In the Board's judgment, the expression "most" used in the above part of D1 shows that there is no unambiguous disclosure of particular chemical entities other than sodium phosphate and sodium sarcosinate which can be used in order to obtain the desired acceleration of the rate of hybridisation. In addition, this document does not contain any technical teaching as to how to find an appropriate RNA concentration for performing the desired reaction at the desired accelerated reaction rate.

3.2. It is true that D2 and D3 each disclose the use of various inorganic salts as precipitation agents which are capable to accelerate the precipitation rate (precipitation, and renaturation are only different expressions indicating that hybridisation - or reassociation - has occurred). This is acknowledged in the description. However, the observed rate acceleration is much less than the 100 fold increase in rate required by the present claim. The explanation given by the Appellant for this failure to observe high rate accelerations is that a high acceleration in reaction rate is only observed at low concentrations of at least one of the two single stranded nucleic acids which are to be hybridised. Such low concentrations have obviously been inadvertently chosen in the experiments described in D1, whereas the experiments reported in D2 and D3 were obviously performed at higher concentrations of single stranded nucleic acids, where the effect of the precipitation agent is low. At present, there is no evidence available to the Board which would not be in agreement with the Appellant's explanations. Since the amended Claim 1 now contains a limitation of the concentration of the second nucleic acid which excludes concentrations which are such that only slight effects of the precipitation agent can be observed, the Board is satisfied, on the balance of probabilities, that the concentration of the second single stranded nucleic acid required by the present Claim 1 differs from the concentrations used according to D2 and D3. Therefore, in the Board's judgment, the novelty objection raised in the decision under appeal cannot be maintained in respect of the present Claim 1.

4. *Clarity*

It is true that the present Claim 1 according to both sets of claims continues to contain technical features which are defined mainly by a technical result, e.g the concentration of the second single stranded nucleic acid, the chemical nature as well as the necessary amount of the precipitating agent, the reaction temperature and the method for assaying the presence of double-stranded nucleic acid molecules. The above concentrations can, however be readily determined by a skilled person, who can also easily observe whether or not a given chemical compound causes precipitation of double stranded nucleic acids. In view of the Appellant's submissions and in the absence of any evidence to the contrary the Board further accepts that this precipitation can be observed by applying any known assaying method, so that the present Claim 1 determines the subject-matter for which protection is sought in a sufficiently clear manner (see also T 68/85, OJ EPO 1987, 228, points 8.4.3 and 8.4.4 of the reasons).

5. The grounds which led to the refusal of the present patent application are thus no longer applicable to the amended Claim 1. The decision under appeal can therefore be set aside.

6. However, the Examining Division had not yet had the opportunity to consider the other requirements of the EPC, including the question whether or not the present Claim 1 is sufficiently supported by the description.

6.1 In this respect the Board observes that the requirements of clarity and support by the description of a claim containing technical features which are defined by their function are not identical. Thus, although in the present case the Board is satisfied that e.g. the

expression "precipitation agent" is sufficiently clear, it remains to be decided whether the description supports this broad definition or whether it only supports the use of precipitation agents having certain essential structural features (see also decision T 409/91, OJ EPO 1994, 653). In the Board's judgment, the relevant facts for deciding this question have not yet been established.

6.2. Similarly, the Examining Division has not yet considered whether the disclosure in the application documents as filed enables the skilled person to perform the claimed method under reaction conditions other than those mentioned in Claim 14 as filed (now Claim 13). Therefore the question of sufficiency (Article 83 EPC) may also arise (concerning the link between the requirement of support by the description and that of sufficient disclosure see again T 409/91).

6.3. In addition, the Examining Division has not yet had the opportunity to consider the question of inventive step on the basis of the present amended claims.

7. For these reasons, the Board of Appeal deems it appropriate, after having settled the questions of clarity and novelty of the claimed subject-matter, to remit the case to the Examining Division for further prosecution on the basis of the amended sets of claims.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Examining Division for further prosecution on the basis of the sets of Claims for Italy and the other designated Contracting States submitted on 8 June 1995.

The Registrar: The Chairman:

P. Martorana A. Nuss