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D E C I S I O N
of 3 March 2004

Case Number: T 1091/01 - 3.3.8

Application Number: 91119059.3

Publication Number: 0484961

IPC: G01N 33/74

Language of the proceedings: EN

Title of invention:
Method of measuring human c-peptide

Patentee:
Tosoh Corporation

Opponent:
BIO-RAD PASTEUR

Headword:
Human c-peptide/TOSOH

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main and first auxiliary requests - inventive step - no"

Decisions cited:
T 0207/94

Catchword:
-

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Case Number: T 1091/01 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 3 March 2004

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 17 July 2001 revoking European patent No. 0484961 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
V. Di Cerbo

Summary of Facts and Submissions

I. European patent No. 0 484 961 based on European patent application No. 91119059.3 with the title "Method of measuring human c-peptide." was revoked by the Opposition Division. The reason for this decision was lack of inventive step of claim 1 of the main request (granted claims) and, of claim 1 of the auxiliary request filed at oral proceedings on 28 February 2000, which claim requests are also those on appeal.

Granted claim 1 read as follows:

"1. A method of measuring human C-peptide which comprises the steps of (a) contacting a sample containing human C-peptide with a first antibody specifically recognizing human C-peptide and a second antibody specifically recognizing human C-peptide at a site thereof different from the site recognized by the first antibody, (b) separating the thus-produced immunoreaction product from the unreacted antibodies, and (c) determining the immunoreaction product or the unreacted antibodies."

Dependent claims 2 to 4 related to further features of the method as claimed in claim 1.

Claim 1 of the auxiliary request read as follows:

"1. A method of measuring human C-peptide which comprises the steps of (a) contacting a sample containing human C-peptide with a first **monoclonal** antibody specifically recognizing human C-peptide and a second **monoclonal** antibody specifically recognizing

human C-peptide at a site thereof different from the site recognized by the first antibody, (b) separating the thus-produced immunoreaction product from the unreacted antibodies, and (c) determining the immunoreaction product or the unreacted antibodies." (emphasis added by the Board in order to show the difference in respect of claim 1 as granted).

II. The Appellants (Patentees) filed an appeal against this decision, paid the appeal fee and submitted a statement of grounds of appeal.

III. The Respondents (Opponents) filed observations in reply to the statement of grounds of appeal.

IV. A communication under Article 11(1) of the Rules of Procedure of the Boards of Appeal presenting the Board's preliminary, non-binding opinion was sent to the parties together with the summons to oral proceedings.

V. Both parties answered this communication.

VI. The documents which are mentioned in the present decision are the following:

(2): Wu Congyuan et al., Acta Acad. Medic. Sinicae, Vol. 11, No. 1, 1989, page 51;

(3): Angelo, L. et al., Diabetes Res. and Clinical Practice, Vol. suppl. No. 1, abstract No. 46, 1985, pages 18 to 19;

(4): Bürgi, W. et al., Clin. Biochem., Vol. 21, 1988, pages 311 to 314;

(6): Madsen, O.D. et al., Diabetes, Vol. 33, 1984, pages 1012 to 1016;

(10): Certified English translation of Japanese Patent Application Laid Open (Kokai) H2-2935, published on 8 January 1990;

(15): Madsen, O.D. et al., Endocrinology, Vol. 113, No. 6, 1983, pages 2135 to 2144.

VII. The Appellants' arguments in writing and during oral proceedings may be summarized as follows:

Inventive step; claim 1 of the main and first auxiliary requests.

– At the priority date, it was known that the human C-peptide was a short molecule comprising a tertiary structure in the shape of a hairpin. The amount of C-peptide in a sample was measured by radio-immunoassay with either polyclonal or monoclonal antibodies (document (3)). Some anti-C-peptide monoclonal antibodies had been isolated and respectively characterised as recognizing the C- or N- terminal parts of the molecule (document (2)), as being highly sensitive (document (3)) or as recognizing a conformational epitope comprising 75% of the peptide sequence (document (6)). Sandwich immunoassays had already been developed for measuring insulin and angiotensin, a peptide hormone of small size (documents (4) and (10)).

Document (15) taught that an antibody had a molecular mass approximately 15 times greater than that of the C-peptide and also that a certain minimal distance was required between two different epitopes to allow the simultaneous binding of two antibody molecules.

– The closest prior art was document (3) which disclosed measuring the concentration of human C-peptide in a sample by a competitive radio-immunoassay. Starting from this document, the problem to be solved could be defined as providing an alternative method for determining the concentration of said peptide. The solution given was that of developing a sandwich immunoassay. In accordance with the case law, assessing whether this solution was inventive required an evaluation of whether or not the skilled person had a reasonable expectation to succeed when attempting to develop a sandwich immunoassay for the C-peptide.

– The prior art did not suggest the use of sandwich assays for measuring the concentration of the C-peptide. Said peptide would have been considered as an unsuitable target for this kind of assays. Indeed, document (6) taught that a secondary structure in the form of a â turn was present at positions 47-50 which brought the C- and N-terminal parts of the molecule near each other. A rigid structure was, thus, created which would be expected to act as a steric hindrance to the simultaneous binding of antibodies. Furthermore, the skilled person would be aware of the teachings

of document (15) relative to the existing limitations to the binding of more than one antibody to the same molecule.

– The teachings of document (10) would not have been taken into account because the size of angiotensin was quite different from that of the human C-peptide. The fact that, like the C-peptide, angiotensin contained a Pro residue did not mean that the two molecules would necessarily adopt the same conformation. Thus, the fact that a sandwich immunoassay could be carried out with angiotensin did not allow the skilled person to make any predictions that it could also be carried out with the human C-peptide. The same conclusion equally applied in relation to the sandwich immunoassay performed on insulin (document (4)) because of the difference in the structures of insulin and peptide C.

– For these reasons, the skilled person would have had no reasonable expectation of success when attempting to develop a sandwich immunoassay for the human C-peptide. The method as claimed in claim 1 of both the main request and the auxiliary request was inventive.

VIII. The Respondents' arguments in writing and during oral proceedings may be summarized as follows:

Inventive step; claim 1 of the main and first auxiliary requests.

– The invention was in the field of developing diagnostic immunoassays for diabetes. The closest prior art, the problem to be solved and its solution were as defined by the Appellants.

– At the priority date, sandwich immunoassays were an obvious alternative method to radio-immunoassays as was shown in documents (4) and (10). The skilled person would have been very motivated to use a sandwich assay considering that several monoclonal antibodies against the C-peptide had already been obtained which specifically recognized epitopes in different regions of the molecule (document (2)) or its tertiary conformation (document (6)). There was no reason why other antibodies could not be obtained. In the patent in suit, it was mentioned that isolating them and setting up the method was merely a matter of routine work.

– The Appellants' arguments relating to the alleged inability of the C-peptide to bind more than one antibody at a time were mere assumptions which had not been demonstrated to be true. Indeed, there was no evidence that the C-peptide was not flexible. It was described in document (6) as having a flexible glycine-rich central portion and it contained a Pro residue. In contrast, it did not contain any S-S bridges. Even if, for the sake of argument, it was accepted that its structure was somewhat rigid, this did not necessarily imply that it could not bind two antibodies.

– The skilled person would be aware from document (15) that a minimum distance had to exist between two epitopes to obtain the simultaneous binding of two antibodies. Yet, he/she would also be aware of the teachings in document (10) describing a sandwich immunoassay involving angiotensin, a much smaller molecule than the human C-peptide. Thus, he/she would not refrain from attempting to set up this assay with the C-peptide.

– There were no reasons to doubt that the sandwich immunoassay could be successfully developed with the human C-peptide. Inventive step had to be denied. This conclusion applied to claim 1 of both requests since they only differed by the fact that claim 1 of the main request comprised the use of monoclonal antibodies whereas claim 1 of the auxiliary request was limited to said use, and monoclonal antibodies were the tools routinely used for the sandwich immunoassay.

IX. The Appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims as granted or of the auxiliary request filed on 28 February 2001.

The Respondents requested that the appeal be dismissed.

Reasons for the Decision

Main and auxiliary requests

1. The issue to be decided is that of inventive step in relation to the subject-matter of claim 1 (both requests, see Section I, supra).

2. The closest prior art is document (3). It teaches a radioimmunoassay for detecting the presence of human C-peptide, said peptide (31 amino acids) being present in serum in an amount equimolar to that of insulin and serving, like insulin, for the diagnosis of diabetes. The monoclonal antibody used in this assay (PeP-001) is obtained by the conventional Köhler and Milstein method. It is characterized as "highly sensitive".

3. Starting from document (3) the problem to be solved can be defined as providing an alternative immunomethod for determining the amount of human C-peptide in a sample.

4. The solution provided in claim 1 (both requests) is a sandwich immunoassay to be carried out with two antibodies recognizing different epitopes on the C-peptide molecule.

5. Document (3) which is a short abstract does not suggest the possibility of detecting the C-peptide by another method than a radio-immunoassay. Yet, both parties agree that at the priority date, it was common general knowledge that sandwich immunoassays could advantageously replace radio-immunoassays, if only because they avoided the problems inherent to the application of radioisotopes (document (4)).

Furthermore, a sandwich assay had already been described as a rapid and convenient means to measure insulin for the diagnosis of diabetes (document (4), page 311). The concept of developing the same assay with the C-peptide ie with the other molecule used for the diagnosis of the same disease cannot, thus, be inventive per se.

6. In the patent in suit (page 2, lines 33 to 45, page 3, lines 3 and 4), it is disclosed that the anti-C-peptide antibodies and the radio-immunoassay can be produced/carried out by known processes with the help of conventional reagents. Thus, inventive step cannot be acknowledged on the basis of unexpected difficulties encountered when trying to put the claimed invention into practice.

7. *Prima facie*, it seems that all which needed to be done when attempting to resolve the above mentioned problem was to try a well-known assay on a well-known molecule and see if it worked. The Appellants argued that the skilled person would not have had a reasonable expectation of success in doing so because of the unique structure of the C-peptide which would have been considered as preventing the simultaneous binding of two antibodies.

8. The approach to inventive step which involves assessing whether or not the skilled person had a reasonable expectation of success was developed in the case law in relation to biotechnology cases to take into account the real difficulties which could have been foreseen in performing the necessary experimental steps at the priority date. In decision T 207/94 of 8 April 1997,

for example, it is stated: "*In order to be considered, any allegation of features putting in jeopardy reasonable expectation of success must be based upon technical facts*" (see Headnote). When using this approach for other biological inventions such as here, the same rationale must apply.

9. In the present case, it is not disputed that the structure of the C-peptide was known to the skilled person at the priority date. However, no technical evidence is provided that the presence of a â turn in its middle portion would have been considered as resulting in a rigid conformation of the molecule. It was also not shown that the â turn would cause such a spatial, tri-dimensional arrangement that the N- and C-terminal parts of the molecule would be found face to face, nor that if this occurred, it would prevent the binding of antibodies specific for one or the other of these ends (document (2)), or, for that matter, of any other antibodies.

10. The statement in document (15) that "*a minimal distance must be required between two different epitopes to allow the simultaneous binding of two antibody molecules*" concerns the binding of antibodies to antigens in general. Yet it is not presumptive of the fact that no two epitopes would be available at the same time on the human C-peptide molecule.

11. The Board accepts the Appellants' argument that being able to carry out a sandwich immunoassay on smaller molecules than the human C-peptide such as angiotensin (document (10)) and insulin (document (4)) would not necessarily have been considered by the skilled person

at the priority date as an **evidence** that the same assay would be workable with the C-peptide since the structure of these three molecules is different. Nonetheless, document (10) provides the teaching that two antibodies can simultaneously bind to as small a peptide as angiotensin (8 amino acids). The method whereby this is achieved is also described in detail. In the Board's judgment, the skilled person aware of this knowledge could only feel encouraged that a molecule like the C-peptide which is about four times bigger may also accommodate two antibodies, especially since, as just above discussed, no factual evidence existed as to the C-peptide having a tertiary structure likely to prevent the dual binding.

12. For these reasons, it is considered that there existed a reasonable expectation of success for the skilled person attempting to set up a sandwich assay for the human C-peptide. Consequently, the subject-matter of claim 1 of the main and auxiliary requests which comprises/relates to performing the sandwich immunoassay according to the conventional technique of using two monoclonal antibodies recognizing different epitopes of the molecule is found to lack inventive step. The requirements of Article 56 EPC are not fulfilled.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani