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Datasheet for the decision of 3 June 2008

Case Number: T 0414/07 - 3.3.08

Application Number: 97938467.4

Publication Number: 0870025

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Reagents and methods useful for detecting diseases of the breast

Applicant:
ABBOTT LABORATORIES

Opponent:
-

Headword:
Diseases of the breast/ABBOTT

Relevant legal provisions:
EPC Art. 56, 84, 123(2)

Relevant legal provisions (EPC 1973):
EPC Art. 54(3)

Keyword:
"Main request: added matter (no)"
"Clarity (yes)"
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
G 0010/93

Catchword:
-

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Case Number: T 0414/07 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 3 June 2008

Appellant: ABBOTT LABORATORIES
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 10 August 2006 refusing European application No. 97938467.4 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chairman: L. Galligani
Members: T. J. H. Mennessier
C. Rennie-Smith

Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division dated 10 August 2006, whereby the European patent application No. 97 938 467.4 with publication number 0 870 025 was refused. The application, entitled "*Reagents and Methods Useful for Detecting Diseases of the Breast*", originated from an International application published as WO 98/07857.

II. The application had been refused by reason of non-compliance with the requirements of Article 56 EPC in view of document D2 (see Section IX infra) taken as the closest prior art, the basis for the refusal being claims 1 to 33 of the request filed on 12 August 2005.

III. Together with the statement setting out the grounds of appeal dated 18 December 2006 the appellant submitted a main request corresponding exactly to the request on which the decision was based and an auxiliary request.

IV. The examining division did not rectify its decision and referred the appeal to the Board of Appeal (Article 109 EPC).

V. On 1 February 2008 a communication under Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) presenting some preliminary and non-binding views of the board was sent to the appellant. In its communication the board expressed in particular some concerns regarding the compliance of certain claims of the main request then on file with Articles 84 EPC and 123(2) EPC.

VI. In reply to that communication, the appellant filed further observations in a letter dated 2 May 2008, which was accompanied by an amended main request (claims 1 to 27) as well as three (first, second and third) auxiliary requests to replace the previous requests then on file.

VII. The main request consisted of 27 claims. It was derived from claims 1 to 27 of the previous main request, previous claims 28 to 33 being removed.

Claim 1 read as follows:

"1. A purified polynucleotide, wherein said polynucleotide has a sequence selected from the group consisting of SEQUENCE ID NOS 1-4, and the full length complementary sequences thereof."

Claim 2 was dependent on claim 1 and directed to a particular embodiment thereof.

Claim 3 was directed to a recombinant expression system comprising a nucleic acid sequence as defined in claim 1.

Claim 4 was directed to a cell transfected with the recombinant expression system of claim 3.

Claim 7 was directed to a test kit useful for the diagnosis of breast cancer comprising a container containing at least one polynucleotide having a sequence as defined in claim 1. Claim 8 was dependent

on claim 7 and directed to a particular embodiment thereof.

Claim 16 was directed to a method of detecting breast cancer in an individual comprising contacting a test sample with at least one polynucleotide having a sequence as defined in claim 1. Claim 17 was dependent on claim 16 and directed to a particular embodiment thereof.

Claims 18 and 21 were directed to an amplification-based method of detecting breast cancer in an individual wherein use was made as primers of oligonucleotides with a sequence as defined in claim 1 or having at least 90% identity therewith (claim 21 only). Claims 19 and 20 were dependent on claim 18 and directed each to a particular embodiment thereof. Claims 22 to 24 were dependent on claim 21 and directed each to a particular embodiment thereof.

Claim 5 read as follows:

"5. A polypeptide having an amino acid sequence selected from the group consisting of SEQUENCE ID NOS 16-22."

Claim 9 was directed to a test kit for determining the presence of an antigen or antibody in a test sample comprising a container containing a polypeptide as defined in claim 5. Claims 10 and 11 were dependent on claim 9 and directed each to a particular embodiment thereof.

Claim 15 was directed to a method for producing a polypeptide which was an amino acid sequence selected from the group consisting of SEQUENCES ID NOS 16, 19, 21 and 22 or which comprised an amino acid sequence selected from the group consisting of SEQUENCE ID NOS 17, 18 and 20.

Claim 26 was directed to a method of detecting breast cancer in an individual, wherein a test sample was contacted with a polypeptide containing at least one epitope from an amino acid sequence having at least 90% identity to an amino acid sequence selected from the group of SEQUENCE ID NOS 15, 16-22 and 23. Claim 27 was dependent on claim 26 and directed to a particular embodiment thereof.

Claim 6 read as follows:

"6. An antibody which specifically binds to at least one epitope from an amino acid sequence selected from the group consisting of SEQUENCE ID NOS 16-22".

Claim 12 was directed to an assay kit comprising an antibody which was defined as in claim 6. Claims 13 and 14 were dependent on claim 12 and directed each to a particular embodiment thereof.

Claim 25 was directed to a method of detecting breast cancer in an individual comprising contacting a test sample with an antibody which was defined as in claim 6 or a fragment thereof.

VIII. Oral proceedings took place on 3 June 2008.

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

(D1) Malcolm Parker et al., Nature, Vol. 298, 1 July 1982, Pages 92 to 94

(D2) Mark A. Watson and Timothy P. Fleming, Cancer Research, Vol. 56, 15 February 1996, Pages 860 to 865

(D3) WO 97/34997 (no claimed priority; international filing date: 21 March 1996; publication date: 25 September 1997)

X. The submissions made by the appellant with respect to the main request, insofar as they are relevant to the decision, may be summarised as follows:

Requirements of Article 123(2) EPC

The expressions "full-length complementary sequences" (see claims 1, 3, 7, 16, 18 and 21, "one epitope from an amino sequence selected from the group" (see claim 6), and "A method of detecting breast cancer in an individual" (see claims 16, 18, 21, 25 and 26) had support in the application as filed (see WO 98/07857). The reference to oligonucleotides which "have at least 90% identity to a sequence selected from the group consisting of SEQUENCE ID NOS 1-4" in claim 21 and to an amino acid sequence "having at least 90% identity to an amino acid sequence selected from the group consisting of SEQUENCE ID NOS 15-23" in claim 26 had a counterpart in WO 98/07857 in the passage from line 26

to line 28 on page 23 and in the passage from line 12 to line 15 on page 13, respectively.

Clarity (Article 84 EPC)

The term "amplicon" as employed in claim 18 was a term commonly used in the technical field of biotechnology at the relevant filing date. It referred to a piece of DNA that has been synthesised using amplification techniques. The expression "having at least 90% identity to" was to be read in connection with page 11, lines 7 to 17 of the application which provided an unambiguous definition of the term "identity". It meant an exact nucleotide to nucleotide or amino acid to amino acid correspondence.

Novelty of claim 6 of the main request over document D3 (Article 54(3) EPC 1973)

The antibodies covered by claim 6 were to be regarded as a selected population of antibodies directed against individual segments of the protein not disclosed in document D3.

Inventive step of the main request (Article 56 EPC)

In view of document D2 which represented the closest state of the art, the technical problem to be solved was the provision of an alternative polypeptide that could be used for the management of breast cancer. There was absolutely nothing in document D2 that would have suggested the claimed polypeptides to the skilled person. There was no guarantee at all of finding any further marker of high specificity within acceptable

time limits. The chance of finding useful polypeptides for the detection of breast cancer in an individual was perceived as low at the relevant filing date of the application in issue. Due to difficulties regarding protein expression, there was considerable uncertainty that the "BU101" protein was indeed expressed in an individual such that it could be used as a marker for detecting breast cancer.

XI. The appellant requested that the decision under appeal be set aside and a patent be granted on the basis of either the main request or first, second or third auxiliary requests all filed on 2 May 2008.

Reasons for the Decision

Main request

Requirements of Article 123(2) EPC

1.1 The amendments contained in the main request are allowable under Article 123(2) EPC. In particular, the replacement of the term "complements" by the expression "full-length complementary sequences" (see claims 1, 3, 7, 16, 18 and 21) is supported by the sentence on page 22, lines 15 to 16 of WO 98/07857 (the published form of the application as filed). The expression "one epitope from an amino sequence selected from the group" which no longer includes the term "derived" before "from" as used in claim 6 still has support in the sentence bridging pages 6 and 7 in WO 98/07857, in the light of the passages from lines 22 to 26 on page 10 and from lines 18 to 22 on page 16. Specifying in the

claims directed to a method of detecting (see claims 16, 18, 21, 25 and 26) that it is intended to detect breast cancer in an individual is reflected by the passage from line 18 to line 22 on page 11 of WO 98/07857. It is also agreed that, as argued by the appellant, the reference to oligonucleotides which "have at least 90% identity to a sequence selected from the group consisting of SEQUENCE ID NOS 1-4" in claim 21 and to an amino acid sequence "having at least 90% identity to an amino acid sequence selected from the group consisting of SEQUENCE ID NOS 15-23" in claim 26 have a counterpart in WO 98/07857 in the passage from line 26 to line 28 on page 23 and in the passage from line 12 to line 15 on page 13, respectively. Thus the main request complies with Article 123(2) EPC.

Clarity requirement of Article 84 EPC

2. The board is satisfied that, in view of the newly filed amendments, in particular the removal of the indefinite term "BU101" throughout the claims and the deletion of the unambiguous term "derived" formerly used in the expression "one epitope derived from an amino acid sequence" in the claim directed to an antibody (see claim 6), the main request meets the clarity requirement of Article 84 EPC. The explanations provided by the appellant in its letter of 2 May 2008 with respect to the term "amplicon" as used in claim 18 are accepted. They convincingly show that it was commonly used in the field of biotechnology at the relevant filing date to refer to a piece of DNA that has been synthesised using amplification techniques. As argued by the appellant, the expression "having at least 90% identity to" is clear in view of the

unambiguous definition given to the term "identity" on page 11, lines 7 to 17, of the application, namely "identity" meaning in the context of the claims exact nucleotide to nucleotide or amino acid to amino acid correspondence.

Novelty (Article 54(3) EPC 1973)

3. At the oral proceedings the board exercising its discretionary power (see decision G 10/93 (OJ EPO, 1995, 172; see the Order) has on its own motion questioned whether an antibody according to claim 6 may be regarded as new over document D3.

4. Document D3 is a Euro-PCT application published as WO 97/34997. It was filed on 21 March 1996, i.e. before the earliest priority date of the application in issue, which is 19 August 1966, and published, after this latter date, on 27 September 1997. WO 97/34997 entered the European regional phase on 21 October 1998. The designation and filing fees provided for in the EPC were duly paid. Ten of the Contracting States, namely AT, BE, CH, DE, ES, FR, GB, IT, LI, NL, designated in respect of the European application were the same as those designated in respect of the application in issue. Therefore, WO 97/34997 has to be considered as comprised in the state of the art under Article 54(3) EPC 1973 for the novelty assessment of the application in issue.

5. Document D3 describes *inter alia* three polypeptides, referred to therein as hESF I, II and III, hESF II having a 90 amino acid sequence named SEQ ID NO:4 which is represented in Figure 2 (Drawing 2/10). That

sequence corresponds exactly with the sequence of the "BU101" polypeptide of the application in issue (see the sequence SEQ ID NO: 15).

6. Document D3 contains two sections entitled "*Polypeptide assays*" and "*Antibodies*", respectively, in which antibodies in relation with the hESF polypeptides are referred to (see pages 40 to 42).

7. The question to be answered is whether the subject-matter of claim 6 (see Section VII, *supra*) is disclosed in pages 40 to 42 of document D3.

8. The "*Antibodies*" Section provides a very general disclosure. Antibodies specifically directed to hESF II are not mentioned. A skilled person cannot derive therefrom any relevant information as to the characterising features of those antibodies. The "*Polypeptide assays*" Section reports on diagnostic assays in which antibodies specific to any of hESF I, hESF II and hESF III may be used. Antibodies specifically directed to hESF II are not described.

9. The skilled person having read document D3 is left with a lack of crucial information especially as regards the localisation of the relevant epitopes. He/she is not in a position to derive therefrom that epitopes - conformational or not, and generally consisting from 3 to 10 amino acids (see page 16, lines 18 to 22 in the application in issue) to which antibodies can specifically bind - are to be found in the partial sequences of the polypeptide referred to in the application in issue as SEQ ID NO:16 (amino acids 22 to 36), SEQ ID NO:17 (amino acids 37 to 51),

SEQ ID NO:18 (amino acids 45 to 59), SEQ ID NO:19 (amino acids 54 to 68), SEQ ID NO:20 (amino acids 69 to 83), SEQ ID NO:21 (amino acids 69 to 90) and SEQ ID NO:22 (amino acid 46 to 90). Individual antibodies, whether polyclonal or monoclonal, capable of specifically binding to those epitopes as such are not described in document D3. In contrast, such antibodies have been prepared and tested in the experiments reported in the application in issue (see Examples 14 to 17, including Table 2 on page 83).

10. In view of the above remarks, the board considers that, in agreement with the submissions by the appellant, antibodies according to claim 6 represent groups of antibodies selected within a larger population of antibodies known from document D3.

11. Thus, claim 6 is novel. The board is satisfied that the rest of the claims are also new over the relevant state of the art and concludes that the main request as a whole meets the requirements of Article 54 EPC.

Inventive step (Article 56 EPC)

12. Claim 5 which is directed to a number of selected polypeptides or peptides (see Section VII, *supra*) is chosen as the starting point for the assessment of inventive step.

13. Document D2, which is considered to represent the closest state of the art, describes *inter alia* a protein, designated mammaglobin, a mammary-specific member of the uteroglobin gene family, which is overexpressed in human breast cancer and believed to be

a clinically useful marker for managing patients with breast cancer (see the "Discussion" on pages 864 to 865).

14. In view of that closest state of the art, the technical problem is regarded as the provision of a further marker for the management of human breast cancer, the solution thereto being the polypeptides according to claim 5, as well as methods and means for using or making them.

15. The question to be answered is whether at the relevant filing date the skilled person would have found in the state of the art all the necessary guidance to discover without undue burden a polypeptide according to claim 5 and characterise it as a putative marker for the management of human breast cancer.

16. The only other prior art document on file, as identified by the examining division, is document D1 which reports on the isolation of cDNA clones specific for each of the mRNAs which code for a rat protein, referred to as prostatic steroid binding protein, and for which no application is foreseen in the document as a marker for cancer, let alone as a marker for breast cancer. Thus, it is obvious that document D1 which deals with a totally unrelated subject-matter (even if an hindsight analysis may reveal that the rat protein and the BU101 polypeptide with the sequence SEQ ID NO:15 are partially homologous in terms of their amino acid sequences; see page 53, lines 25 to 28, in the application in issue) would have been ignored by the skilled person facing the aforementioned objective technical problem. In the absence of any other prior

art document, the only possible conclusion is that the skilled person would simply not have arrived at the said polypeptides without the exercise of inventive skill.

17. Similarly, at the relevant filing date, the skilled person would not have predicted that a polynucleotide according to claim 1 coding for the BU101 polypeptide with the sequence SEQ ID NO:15 or parts thereof, such as the polypeptides according to claim 5, might exist. Therefore, the polynucleotides of claim 1 also involve an inventive step.

18. The conclusive remarks made with respect to both claims 1 and 5 apply *de facto* also to the rest of claims as they are directly or indirectly dependent thereupon or their subject-matter is defined with a reference to polynucleotides having a sequence represented by SEQ ID NO:1 to 4 (see claims 2 to 4, 7, 8 and 16 to 24) or polypeptides encoded by those polynucleotides or portions thereof (see claims 6, 9 to 15 and 25 to 27). This leads to the conclusion that the claimed invention as a whole involves an inventive step. Thus, the main request meets the requirements of Article 56 EPC.

19. As the board is satisfied that the other requirements of the EPC are also meet, the main request may form a basis for the grant of a patent.

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 grant a patent on the basis of claims 1 to 27 of the main request filed on 2 May 2008 and a description and figures to be adapted thereto.

The Registrar: The Chairman:

A. Wolinski L. Galligani