BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

Datasheet for the decision of 10 May 2012

Case Number: T 1328/08 - 3.3.08

Application Number: 01980473.1

Publication Number: 1322960

IPC: G01N 33/68

Language of the proceedings: EN

Title of invention:
Allergen-Microarray assay

Patent Proprietor:
Phadia Muliplexing Diagnostics GmbH

Headword:
Allergen-Microarray/PHADIA

Relevant legal provisions:
EPC Art. 53(c), 54, 56, 123(2)(3)
RPBA Art. 12(2), 13(1)

Keyword:
"Amended claims - admitted"
"Requirements of the EPC - met"

Decisions cited:
G 0002/88, G 0001/04, T 0263/05

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1328/08 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 10 May 2012

Appellant: (Patent Proprietor)
Phadia Multiplexing Diagnostics GmbH
Rennweg 95B
AT-1030 Wien (AT)

Representative:
Polz, Leo
Hoffmann Eitle
Patent- und Rechtsanwälte
Arabellastraße 4
D-81925 München (DE)

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 30 April 2008 revoking European patent No. 1322960 pursuant to Article 101(3)(b) EPC.

Composition of the Board:

Chairman: M. Wieser
Members: B. Stolz
C. Heath

Summary of Facts and Submissions

I. Three oppositions were filed against European patent No. 1 322 960 on the grounds of Article 100(a) EPC (lack of novelty and inventive step and lack of patentability pursuant to Article 53(c) EPC).

II. The opposition division decided that all requests before it lacked an inventive step and revoked the patent.

III. The patent proprietor lodged an appeal against the decision of the opposition division. With the statement of the grounds of appeal, the appellant submitted a new main request and an auxiliary request.

IV. All three opponents (respondents) withdrew their oppositions during appeal proceedings.

V. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA) annexed to a summons to oral proceedings, the board informed of its preliminary, non-binding opinion on some of the issues to be discussed at the upcoming oral proceedings, in particular issues concerning Articles 123(2) and 56 EPC.

VI. The appellant replied to the communication of the board and submitted new evidence in support of its argumentation. In response to a telephone conversation with a member of the board wherein appellant's attention was drawn to outstanding issues under Articles 56 and 53(c) EPC yet to be discussed at the

oral proceedings, the appellant submitted a new main request.

VII. Oral proceedings took place on 10 May 2012.

VIII. Appellant's **main request** consists of 33 claims. Independent claims 1, 24, 25 and 33 read as follows:

"1. A method for the detection of an IgE immunoglobulin which binds to an allergen in a sample, characterized in that one or more purified single allergens are immobilized on a microarray chip after which the sample is incubated with the immobilized allergens so that IgE immunoglobulins which are specific for the allergens bind to the specific allergen after which the IgE immunoglobulins which are bound to the specific immobilized allergens are detected."

"24. A method for in vitro diagnosis of allergies in a patient, characterized in that a serum sample from the patient is analysed for IgE immunoglobulins which bind to allergens, according to a method according to any one of claims 1 to 23, whereby a microarray chip is used on which at least 10, preferably at least 50, still preferred at least 90, different allergens are immobilized, after which a positive reaction between the sample and the immobilized allergens is diagnosed as an allergy."

"25. The use of a microarray chip on which one or more purified single allergens are immobilized for the detection of IgE immunoglobulins."

"33. The use of a kit for carrying out a method according to any one of claims 1 to 24, characterized in that it comprises a microarray chip on which one or more purified single allergens are immobilized and a first reagent comprising at least one immunoglobulin detecting reagent, preferably an anti-immunoglobulin antibody, preferably in a known concentration, and possibly a second reagent as a positive sample comprising at least one immunoglobulin which binds to an allergen."

Dependent claims 2-23 are directed to specific embodiments of the method of claim 1, while dependent claims 26 to 32 are directed to specific embodiments of the use of claim 25.

IX. The following documents are cited in the present decision:

D1: WO 01/27627

D2: WO 00/49412

D3: Valenta et al. (1999), Clin. Exp. Allergy 29: 896-904

D4: Ekins R.P. (1998), Clin. Chem. 44:2015-2030

D6: Mendoza et al. (1999), BioTechniques 27:778-787

D9: US-A-4 849 337

D14: Joos et al. (2000), Electroph. 21:2641-2650

D18: Ekins et al. (1998), Nanobiol. 4:197-220

D25: Chapman et al. (2000), J. Allergy Clin. Immunol. 106:409-418

D34: Mattson et al. (1997), NCCLS Vol. 17, No. 24, "Evaluation Methods and Analytical Performance Characteristics of Immunological Assays for Human Immunoglobulin E (IgE) Antibodies of Defined Allergen Specificities; Approved Guideline"

D35: Yman (1990), *in-vitro* Diagnostica Special Band 1, 2/1990: 18-22

D36: Yman (1991), JIFCC 3(5):198-203

X. The arguments of the appellant, in so far as they are relevant for the present decision, can be summarized as follows:

Admissibility of the main request

The request had been submitted to address the board's concerns with regard to inventive step and exclusion from patentability. Since there had been no substantive replies from any of the opponents to the statement of the grounds of appeal, the communications of the board had in fact been the only source drawing appellant's attention to outstanding issues. Previous amendments had been bona fide attempts to overcome the board's objections under Article 123(2) EPC, and the issue of inventive step in relation to IgE had not been perceived. Moreover, the amendment to claim 1 was merely the result of a combination of previous claim 1

with a dependent claim; no features from the description had been added.

Article 56 EPC

The closest prior art was document D9, which disclosed a method for identifying and quantifying allergen specific IgE levels in serum. The method of document D9 used allergen extracts. Using allergen extracts however had two major disadvantages: they might contain contaminants which impaired testing and they gave rise to a lack of reproducibility due to difficulties in standardizing the extracts. The present invention provided advantages over D9 in that the sample volume could be largely reduced and many allergens could be tested in parallel without any loss of sensitivity or reliability. This could not be derived from the prior art in any obvious way. Document D14 described an assay for the testing of IgG in the context of auto-immune diseases. The concentration of IgG in serum was however much higher than the concentration of IgE. Document D25 was speculative when it referred to the use of microarray chips and, if anything, speculated about the use of allergen cocktails on such chips.

XI. The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of its main request filed with letter of 30 April 2012.

Reasons for the Decision

Withdrawal of oppositions

1. Withdrawal of the oppositions by the respondents does not affect the appeal proceedings, in so far as the board has to re-examine the substance of the opposition division's decision. The board can set the appealed decision aside and maintain the patent as requested by the appellant only if the specification meets the requirements of the EPC. Although the appealed decision is not to be examined "by the Office of its own motion", but only as a result of the appeal and taking into account arguments and evidence cited by the opponent before the opposition was withdrawn (see Case Law Book, VII.C.2.1.2), the board nevertheless has an ex officio duty under Article 114 EPC to examine amended claims for their prima facie non-compliance with the EPC (decision T 263/05 of 28 June 2007, published in the Official Journal of the EPO OJ 2008, 329).

Main request

Admissibility

2. In the communication accompanying the summons to oral proceedings, the board set out some of the issues to be discussed. In detail it addressed issues under Articles 123(2) and 56 EPC. In its reply, the appellant repeated its arguments with regard to article 56 EPC and addressed the board's objections under Article 123(2) EPC.

3. In an attendance note submitted to the appellant on 25 April 2012, concerning a phone conversation between the Representative of the Appellant and a member of the Board, held on 25 April 2012, attention was drawn to the fact that the discussion on inventive step in the appellant's written submissions was focussed on the detection of IgE, while the claims included methods for the detection of IgG. Moreover, reference was made to an objection under Article 53(c) EPC that had been raised in opposition proceedings.

In reply to this attendance note the appellant, with letter dated 30 April 2012, filed its new request, consisting of claims 1 to 33.

4. Thus, the request has been filed only a couple of days before oral proceedings.

5. Article 12(2) of the Rules of Procedure of the Boards of Appeal (RPBA) lays down that "[t]he statement of grounds of appeal and the reply shall contain a party's complete case", while Article 13(1) RPBA leaves it to the board's discretion to admit any amendment to a party's case after it has filed its grounds of appeal or reply.

At the oral proceedings, the appellant argued credibly that it was convinced that the issue of inventive step was solved as a result of amendments made during the opposition procedure. Moreover, no information in this respect was available to the appellant from the former opponents, who had all withdrawn their oppositions. Likewise, despite the fact that the objection under Article 53(c) EPC had been raised by opponent 2 in its

notice of opposition, this issue had neither been addressed in the appealed decision, nor had it been mentioned in the communication accompanying the summons to oral proceedings before the board.

6. Appellant's new request of 30 April 2012 is considered to be a direct answer to the directions given by the board in one of its communications (the attendance note about a phone conversation); (see Article 12(1)(c) RPBA). In the light of this situation, the board, exercises its discretion under Article 13(1) RPBA and admits the request into the procedure. The claimed subject-matter has been restricted to the detection of an IgE immunoglobulin by combining a feature from a dependent claim with the features of the independent claims, and an amendment has been made to overcome the exclusion from patentability under Article 53(c) EPC.

Article 123(2)(3) EPC

7. Claim 1 results from the combination of originally filed claims 1 and 2. In addition, the appellant has indicated the last paragraph of page 10 of the application as filed as further basis. Claims 25 to 33 have all been directed to uses of products rather than to the products themselves as in the previous claims. According to the appellant, basis for these amendments can also be found on page 10, last paragraph. Additional basis for amended claim 33 can be found in original claims 36 and 37 in combination with claim 28.

8. The board agrees that the indicated passages of the application as filed constitute an appropriate basis

for the claims, which therefore meet the requirements of Article 123(2) EPC.

9. As regards Article 123(3) EPC, it is apparent that the scope of protection of claim 1, directed to the detection of IgE, has been further limited compared to that of the granted claims, directed to the detection of immunoglobulins in general. In relation to claims 25 to 33, appellant's arguments can be followed that, "an amendment of granted claims directed to "a compound" and to "a composition including such compound", so that the amended claims are directed to "the use of that compound in a composition" for a particular purpose, is not open to objection under Article 123(3) EPC" (decision G 2/88 of 11 December 1989,Headnote, point 2). Accordingly the request also fulfils the requirements of Article 123(3) EPC.

Article 53(c) EPC

10. In opposition proceedings, an objection under Article 52(4) EPC 1973 (Article 53(c) EPC 2000) was raised against claim 27 as granted because the claimed method of in vitro diagnosis included the steps of taking a sample from a patient, analyzing the sample and diagnosing an allergy.

Amended claim 24 is directed to a method for in vitro diagnosis of allergies in a patient characterized in that a serum sample is analysed for IgE immunoglobulins by one of the preceedingly claimed methods and a positive reaction is then diagnosed as an allergy.

11. According to Article 52(4) EPC 1973 (Article 53(c) EPC 2000), European patents shall not be granted in respect of methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body.

In order to fall under the prohibition of Article 52(4) EPC 1973 (Article 53(c) EPC 2000) a diagnostic method practised on the human or animal body has to include the features relating to: (i) the diagnosis for curative purposes stricto sensu representing the deductive medical or veterinary decision phase as a purely intellectual exercise; (ii) the preceding steps which are constitutive for making that diagnosis; and (iii) the specific interactions with the human or animal body which occur when carrying those out among these preceding steps which are of technical nature (Point 1 of the Headnote of Opinion G 1/04 of 16 December 2005). Furthermore, "in a diagnostic method under Article 52(4) EPC 1973, the method steps of a technical nature belonging to the preceding steps which are constitutive for making the diagnosis for curative purposes stricto sensu must satisfy the criterion "practised on the human or animal body"" (Point 3 of the Headnote of opinion G 1/04).

12. Claim 24 is directed to a method for in vitro diagnosis of allergies, with all the features listed in point 1 of the Headnote of decision G 1/04. It does however not encompass a method step that involves interaction with the human or animal body. Because it does not satisfy the criterion of point 3 of the Headnote of the opinion G 1/04, claim 24 does not fall under the exclusion of Article 53(c) EPC.

Article 54 EPC

13. In opposition proceedings, a novelty objection under Article 54(2) EPC was raised against claim 1 in view of document D14.

Novelty objections under Article 54(3) EPC were also raised in view of documents D1 and D2. Both of these prior art documents were cited as anticipating the subject matter of claims 1, 28 and 36 as granted.

14. Independent claims 1, 24, 25 and 33 are now restricted to methods and uses for the detection of IgE immunoglobulins characterized by the use of microarray chips onto which purified single allergens are immobilized.

15. Document D14 discloses the detection of autoantibodies against autoantigens. The assay involves the binding of autoantibodies to autoantigens which have been immobilised on a microarray. An ELISA is used to detect the bound autoantibodies. Rabbit anti-human IgG-peroxidase conjugate is used for the detection of bound autoantibodies (cf. page 2643, section "2.1 Antigens and antisera"). The test thus aims at the detection of IgG immunoglobulins and not at the detection of IgE immunoglobulins.

16. Document D1 discloses a test device suitable for a variety of assays, inter alia for the detection of a reagent present in a liquid (page 20, line 22). Antigen may be used as a capture reagent in the detection of an antibody (page 27, lines 14-17), and the bound antibody

may be detected for instance by addition of anti IgE (page 29, line 1). Document D1 does however not disclose the immobilization of purified single allergens. For this reason alone, document D1 does not anticipate the claimed subject matter.

17. Document D2 discloses immobilized combinatorial libraries of carbohydrates. The libraries can be immobilized on microparticles, beads or a flat platform, in a preferred embodiment on a chip (page 41, lines 19-30). Such a device can inter alia be used for the detection of new drug candidates (page 43, line 18), for the identification of carbohydrate receptors (page 44, line 19), for the mapping of antibodies (page 46, line 7) or for diagnosing a disorder characterized by self or non-self complex carbohydrate structures and elicitation of antibodies against them. In the latter case, the library is reacted with antibodies derived from a patient suspected of having a disease (paragraph bridging pages 43/44). A long list of possible disorders includes allergies (page 44, line 16). This document thus discloses several possible supports for immobilizing the carbohydrate structures and the use of such devices for different purposes, one of them the detection of allergies. There is however no direct and unambiguous disclosure of the specific combination of a microarray chip with immobilized single carbohydrates (allergens) for the detection of allergies.

18. The claimed subject matter is therefore novel.

Article 56 EPC

19. Independent claims 1, 24, 25 and 33 refer to methods and uses concerning the detection of IgE immunoglobulins characterized by the use of microarray chips onto which purified single allergens have been immobilized.

20. The closest prior art document for the assessment of inventive step is generally a document disclosing subject-matter conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (Case Law of the Boards of Appeal, 6th edition, 2010, I.D.3.1 and 3.2).

21. In the board's view, the closest prior art is represented by document D3 disclosing methods of diagnosing allergies by using recombinantly produced allergens. The document discusses the concept of component resolved diagnosis (pages 897 to 900) which requires the use of individual purified allergens. Figure 2 discloses assays, using grass pollen allergens, to demonstrate the feasibility of this concept. Serum IgE levels to grass pollen extract and to purified individual grass pollen allergens were determined using the Pharmacia CAP system. According to document D35, the Pharmacia CAP system provides a cellulose derived foam like support onto which allergens are immobilized. Thus, document D3 discloses the immobilization of purified individual grass pollen allergens on a solid support for the detection of IgE immunoglobulins.

22. The appellant in its written submissions as well as the opposition division considered document D9 to represent the closest prior art. Document D9 discloses the use of allergen cocktails immobilized on a solid support for the detection of IgE immunoglobulins. The method of detecting IgE is however based on the use of allergen extracts and not on the use of single purified allergens (see examples 1 through 46). Thus, although pursuing the same goal, the method of document D9 has less features in common with the claimed subject matter than the method of document D3.

23. Starting from document D3, the technical problem is defined as the provision of an improved method for the detection of allergen specific IgE immunoglobulins.

24. The solution proposed by the patent is a method for the detection of an IgE immunoglobulin with the features of claim 1.

25. As demonstrated by Examples 1 to 5 of the patent, the claimed method is operable. It is apparent from the patent that the claimed methods and uses have advantages over the methods of the prior art, including those of document D3 (see patent paragraphs [0023] to [0025]). The board is therefore satisfied that the above mentioned technical problem is solved.

26. It remains to be established if the claimed methods and uses could be derived in an obvious way, either from the disclosure of document D3 alone or upon combination with the disclosure of any other prior art document on file. In this respect the board notes that document D3 per se does not provide any hint or suggestion to use

microarray chips for performing component resolved diagnostics.

27. The person skilled in the art knows that the detection of IgE in serum samples is more difficult than the detection of IgG. Allergens cause not only an IgE but also an IgG response, and the concentration of the respective IgGs in serum samples is about 5 orders of magnitude higher than the concentration of IgEs (see e.g. document D34, page 11). Thus, in order to obtain a reliable estimate of the concentration of IgEs and in order to outcompete cross-reacting IgGs in patient sera, it is necessary to immobilize a vast excess of allergen molecules (cf. also document D36, page 201, last paragraph). To achieve this, a solid phase with a very high binding capacity is needed.

One solution to this particular problem provided by document D9 consists of immobilizing allergen extracts onto the large surface area of individual microtiter wells.

Another solution, known from the prior art, which also addresses this particular problem, is the Pharmacia CAP system (documents D35 and 36). According to this technology , the solid support consists of an activated cellulose foam which, due to its three dimensional organization, provides a high and specific binding capacity and low non-specific interference in a small volume.

28. Obviously, the prior art methods for the detection of IgE immunoglobulins pointed the skilled person to solutions providing large binding capacities by either

providing large surface areas or by providing a three dimensional matrix. The board is therefore convinced by appellant's argument that the skilled person would not have had a reasonable expectation of success to apply single purified allergens to a microarray chip because this solution implied the use of vastly reduced surface areas and thus pointed in a totally different direction than the prior art discussed above.

29. Without doubt, the use of microarray chips for miniaturized ligand binding assays and immunoassays in general was known in the art (cf. e.g. documents D4, D6 or D18). However, all these prior art documents disclosed different assay formats wherein antibodies were bound to a substrate in order to capture analytes (see Figure 5 of document D4, Figure 1 of document D6, Figure 3 of document D18).

Therefore, based on document D3 and its general knowledge as represented for instance by the disclosure of documents D4, D6 and D18, the skilled person would not have arrived at the claimed subject-matter in an obvious way.

30. The opponents, moreover, relied on document D25, a review article concerning recombinant allergens and their use in the diagnosis of allergies, i.e. for the determination of IgE immunoglobulins. It contains an explicit statement that "exciting new developments are possible with recombinants in microchip technologies or rapid screening for allergy diagnosis" (page 414, last paragraph).

This statement is however found in a section entitled "Allergen cocktails for Diagnosis - in vivo and in vitro", beginning on page 413 and ending on page 415. This section discusses the use of recombinant allergens to prepare "cocktails" such that "By careful allergen selection and careful formulation of the "cocktail", the allergenic activity of the natural product could be completely reproduced with recombinant allergens" (page 413, last four lines). Furthermore, within the same section on page 414, right column last lines, the following is stated: "For all the main sources of allergens (...) recombinant allergens can be identified that could be used in cocktails for diagnostic purposes (...). It is envisaged that recombinants would initially be used in in vitro tests, where interference or nonspecific binding by non-allergen proteins in natural products is a particular problem. Here recombinants have advantages because they can be loaded with greater efficiency onto capture supports because they are pure proteins. Recombinants would also provide greater specificity and fewer problems with spurious cross-reactivities than would natural allergen extracts."

Thus, the use of cocktails of recombinant allergens for the detection of IgE is clearly envisaged and expected to provide advantages over the prior art methods. As mentioned above, document D25 also states that "Exciting new developments are possible with recombinants in microchip technologies or rapid screening tests for allergy diagnosis." (page 414, last line). However, this passage, when read in the context of the preceding lines and the header of the whole section, relates clearly to the use of allergen

cocktails and does not suggest to immobilize single purified allergens on a microchip.

Therefore, even when combining the teachings of D3 and D25 the skilled person would not have arrived at the claimed solution in an obvious way. In order to do so, he/she still would have had to modify the teaching of document D25 by replacing the allergen "cocktails" disclosed by purified single allergens. Such a further modification can only be derived in an obvious way by using hindsight.

31. Finally, reference was made to document D14, which has been cited by the opposition division as disclosing microchip assays for the detection of IgE immunoglobulins.

As already indicated in point 15 above, document D14 does not disclose the detection of IgE but pertains to the detection of IgG in the context of auto-immune diseases. Therefore, also the combination of document D3 with document D14 would not have rendered the claimed solution obvious.

32. Accordingly, the board decides that the subject-matter of claims 1 to 33 involves an inventive step according to Article 56 EPC.

Adaptation of the description

33. At oral proceedings before the board, the description has been amended to bring it into conformity with the scope of the 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 in following version:

   – Claims 1 to 33 of the main request filed with letter of 30 April 2012,

   – description pages 2, 4-9, 14 as filed during oral proceedings,

   – description pages 3, 10-13 as granted, and

   – Figures 1-4c as granted.

The Registrar: The Chairman:

A. Wolinski M. Wieser