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) [ ] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 6 May 2008

Case Number: T 1370/04 - 3.3.04

Application Number: 96933862.3

Publication Number: 0873135

IPC: A61K 39/00

Language of the proceedings: EN

Title of invention:
Peanut allergens and methods

Applicant:
THE UNIVERSITY OF ARKANSAS

Headword:
Peanut allergens/UNIVERSITY OF ARKANSAS

Relevant legal provisions:
EPC Art. 123(2)

Relevant legal provisions (EPC 1973):
EPC Art. 56

Keyword:
"Main request - inventive step (no)"
"Auxiliary request 1 - inventive step (no)"
"Auxiliary requests 2-5 - added matter (yes)"
"Auxiliary request 6 and 7 - inventive step (no)"
"Auxiliary request 8 - added matter (no)", sufficiency, inventive step (yes)"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1370/04 **-** 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 6 May 2008

Appellant: THE UNIVERSITY OF ARKANSAS
2404 North University Avenue
Little Rock, AR 72207-3608 (US)

Representative: Pilkington, Stephanie Joan
Potter Clarkson LLP
Park View House
58 The Ropewalk
Nottingham NG1 5DD (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 2 July 2004 refusing European patent application No. 96933862.3 pursuant to Article 97(1) EPC 1973.**

Composition of the Board:

Chair: U. Kinkeldey
Members: B. Claes
G. Weiss

Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the examining division refusing European patent application 96 933 862.3, based on international patent application PCT/US96/15222 and which was published as WO 97/24139 with the title "Peanut allergens and methods".

Claim 32 of the application as filed read:

"32. A method of treating humans comprising the steps of isolating and identifying a protein or epitope binding IgE, mutating the protein or epitope so hat it no longer binds IgE, vaccinating a patient with the mutated protein or epitope."

II. Claim 1 of the main request before the examining division read:

"1. A method of altering the immunogenicity of an allergen comprising identifying one or more IgE binding epitopes of the allergen, and mutating the one or more IgE binding epitopes so that **pooled serum** IgE binding to the one or more IgE binding epitopes is reduced or **pooled serum** IgE binding to the allergen is reduced, wherein the allergen is a food allergen." (emphasis added)

Claims 1, 6 and 7 of the first auxiliary request before the examining division read:

"1. A method of altering the immunogenicity of an allergen comprising identifying one or more IgE binding

epitopes of the allergen, and mutating the one or more IgE binding epitopes so that IgE binding to the one or more IgE binding epitopes is reduced or IgE binding to the allergen is reduced, wherein the allergen is a food allergen."

"6. An allergen altered by the method of any one of Claims 1 to 5 for use in medicine."

"7. Use of an allergen altered by the method of Claim 1 to 5 in the manufacture of a medicament for treatment of an allergic individual wherein an effective amount of the medicament is administered to reduce an allergic reaction to the said allergen."

Claim 1 of the second auxiliary request before the examining division read:

"1. A method of altering the immunogenicity of an **anaphylactic** allergen comprising identifying one or more IgE binding epitopes of the allergen, and mutating the one or more IgE binding epitopes so that pooled serum IgE binding to the one or more IgE binding epitopes is reduced or pooled serum IgE binding to the allergen is reduced." (emphasis added)

Claim 1 of the third auxiliary request before the examining division read:

"1. A method of altering the immunogenicity of an **anaphylactic** allergen comprising identifying one or more IgE binding epitopes of the allergen, and mutating the one or more IgE binding epitopes so that IgE binding to the one or more IgE binding epitopes is

reduced or IgE binding to the allergen is reduced." (emphasis added)

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

(1) Burks *et al.* (1995), J. Clin. Invest., 96, pages 1715-1721;

(3) WO 94/20614.

IV. The examining division decided that claims 1 of the main request and second and third auxiliary request before them contravened Article 123(2) EPC, whereas the subject-matter of claims 1, 6 and 7 of the first auxiliary request lacked inventive step. The examining division reasoned its decisions in essence as follows:

– In the application as originally filed the binding of **pooled serum** IgE was only disclosed as being qualified as pooled serum IgE of "hypersensitive patients" and was only mentioned in the context of particular allergens, i.e. Ara h I and Ara h II. The generalisation in claim 1 of the main request of the binding of pooled serum IgE in the context of allergens other than the particular peanut allergens constituted therefore added matter.

– Document (1) disclosed in the paragraph bridging pages 1719 and 1720, in the context of the peanut allergen Ara h I, that in order to be used in immunotherapy the recombinant allergen could be modified "in order to reduce the IgE binding capacity while retaining the T-cell reactivity".

For reducing this to practice the skilled person would inevitably have considered the identification and mutation of the IgE binding epitopes, without the exercise of inventive skill. The subject-matter of claims 1, 6 and 7 therefore lacked inventive step.

– Claims 1 of the second and third auxiliary request referred to an **anaphylactic** allergen. The application as originally filed did not refer to such allergens but only contained passages reciting that peanut allergy might result in systemic/fatal anaphylaxis. The reference to the sub-group of anaphylactic allergens constituted therefore added matter.

V. With letter dated 1 November 2004 the appellant filed a new main request and auxiliary requests 1 to 7.

Claim 1 of the main request read:

"1. A method of altering the immunogenicity of an allergen comprising identifying one or more IgE binding epitopes of the allergen, and mutating the one or more IgE binding epitopes so that binding of **pooled serum** IgE of **hypersensitive individuals** to the one or more IgE binding epitopes is reduced or binding of **pooled serum** IgE of **hypersensitive individuals** to the allergen is reduced, wherein the allergen is a food allergen." (emphasis added)

Claim 1 of auxiliary request 1 was identical to claim 1 of the first auxiliary request before the examining division (see section II above).

Claims 1 of auxiliary requests 2 and 3 corresponded to those of the main request and auxiliary request 1 and were directed to *a method of altering the immunogenicity of an* ***anaphylactic*** *allergen* (emphasis added), whereas claims 1 of auxiliary requests 4 and 5 were directed to *a method of altering the immunogenicity of an* ***anaphylactic food*** *allergen* (emphasis added).

Claim 1 of auxiliary request 6 corresponded to claim 1 of the main request whereby the claimed method was specified as *a method of altering* ***for medical use*** *the immunogenicity of an allergen*.

Claim 1 of auxiliary request 7 read:

"1. A method of altering the immunogenicity of an allergen comprising identifying one or more IgE binding epitopes of the allergen, and mutating the one or more IgE binding epitopes so that binding of **pooled serum** IgE of **hypersensitive individuals** to the one or more IgE binding epitopes is reduced or binding of **pooled serum** IgE of **hypersensitive individuals** to the allergen is reduced, **wherein the allergen is Ara h II, or Ara h I**." (emphasis added)

VI. Oral proceedings took place on 6 Mai 2008. During these oral proceedings the appellant filed auxiliary request 8 of which independent claim 1 read as follows:

"1. A method of altering the immunogenicity of an allergen comprising identifying one or more IgE binding epitopes of the allergen, and mutating the one or more

IgE binding epitopes so that binding of **pooled serum** IgE of **hypersensitive individuals** to the one or more IgE binding epitopes is reduced or binding of **pooled serum** IgE of **hypersensitive individuals** to the allergen is reduced, **wherein the allergen is a food allergen, and wherein only one amino acid mutation is made in the one or more IgE binding epitopes.**" (emphasis added)

Claims 2 to 5 were dependent on claim 1 whereas 6 and 7 of this request were identical to claims 6 and 7 of the first auxiliary request before the examining division.

VII. The appellant's arguments can be summarised as follows:

The main request

Article 123(2) EPC

– The application as filed presented results concerning the reduction of the binding of pooled serum IgE of **hypersensitive individuals** by using the peanut allergens Ara h I and Ara h I. These allergens were representative of allergens in general as could be taken e.g. from the disclosure at page 174, lines 1 to 8 and 14 to 19. The reference to the binding of pooled serum IgE of hypersensitive individuals in the context of food allergens did therefore comply with the requirements of Article 123(2) EPC.

Inventive step

– Document (l) disclosed the expression of recombinant Ara h I, a peanut allergen, and its

recognition in immunoblot analysis using pooled serum IgE from patients with peanut hypersensitivity. Document (l) noted in the passage spanning pages 1719 and 1720 that: "*Another use of immunotherapy could be the modification of the molecular structure of the recombinant allergen in order to reduce the IgE binding capacity while retaining the T cell reactivity ...* .". The sentence continued with a further option: "... *or the production of specific T cell epitopes designed for immunotherapy*" which highlighted the speculative nature of the suggestion in document (l). Document (l) did not teach identification or modification of IgE epitopes. Document (l) neither described the nature of the IgE epitopes nor suitable mutations. There was even no suggestion in document (l), that "modification of the molecular structure of the recombinant allergen" should involve mutating the allergen, that such a mutation should be made within one or more of the IgE epitopes, and/or that a mutation within one or more IgE epitopes would reduce IgE binding across a population. Overall, the suggestion in document (l) was therefore, at the utmost, no more than a suggestion to try an unspecified modification.

– Peanut allergens were highly allergenic and like many other food allergens presented a significant risk of anaphylaxis to those allergic to them. Accordingly, even if document (l) had made a specific suggestion, prior to the inventive demonstration of the present application, one of ordinary skill in the art would have had no

reasonable expectation that such a modification would be successful.

– The examining division, in paragraph 22.5 of the decision, had considered that because "the person skilled in the art is well aware of the fact that antibodies bind to specific epitopes" and "identification of such epitopes (epitope screening) was also a routine procedure in the art" then "in order to reduce the binding of IgE, the skilled person would inevitably have considered the identification and mutation of the IgE binding epitopes, without the exercise of an inventive skill". It had however not provided evidence in support of these assertions. Even if it was true that both epitope identification and epitope mutation were routine and obvious at the time of the invention, it did not logically follow that the claimed methods were obvious. The method of claim 1 specified that the allergen was modified so that binding of pooled serum IgE of hypersensitive individuals to the one or more IgE binding epitopes was reduced or binding of pooled serum IgE of hypersensitive individuals to the allergen was reduced. Accordingly, this method could only be rejected as obvious if, at the time of the invention, it was also obvious that simple mutation of the IgE epitopes would actually reduce IgE binding and it was also obvious that simple mutation of the IgE epitopes would reduce IgE binding in a therapeutically relevant way (i.e. across a population of allergic individuals, as evidenced by reduced binding in pooled serum).

– Although the examining division had referred to document (3) as showing that making "small" modifications of epitopes was well known in the art, the referred to passages did not support this contention. In particular on page 16, lines 20 to 27, Document (3) indicated that "*It is possible to modify the structure of a peptide having an activity of Der p VII or Der f VII for such purposes as increasing solubility, enhancing therapeutic or prophylactic efficacy, or stability (e.g., shelf life ex vivo and resistance to proteolytic degradation in vivo). Such modified peptides are considered functional equivalents of peptides having an activity of Der p VII or Der f VII as defined herein. A modified peptide can be produced in which the amino acid sequence has been altered, such as by amino acid substitution, deletion, or addition, to modify immunogenicity and/or reduce allergenicity, or to which a component has been added for the same purpose.*". Document (3) suggested therefore lots of possible modifications, but none of which were the identification and mutation of the IgE binding epitopes.

– In contrast to the lack of any suggestion in the cited prior art even to try, let alone that it was feasible, to reduce IgE binding by mutation of IgE binding epitopes, the present application identified IgE binding epitopes and actually demonstrated that mutations in these epitopes was able to reduce IgE binding in pooled serum. Neither of documents (1) or (3) suggested that the skilled person would have contemplated seeking to

reduce IgE binding by identifying and mutating IgE binding epitopes, still less that there would be any expectation of success in following such a strategy. Still less would there be any expectation of success with food allergens. Food allergens in general, not just peanut allergens, were life-threatening allergens. In view of this the skilled person would have had no reasonable expectation of success that it would be possible to alter the immunogenicity of any food allergen in such a fashion that it could be used as a medicament.

Auxiliary requests 2 to 5 - Article 123(2) EPC

– The application as filed clearly presented the tested peanut allergens as examples of **anaphylactic** (food) allergens. A basis for the term "anaphylactic" to qualify the allergen could be found at page 1 of the application as originally filed.

Auxiliary requests 6 and 7 - Inventive step

– In contrast to the lack of any suggestion in documents (1) and (3) even to try, let alone that it was feasible, to reduce IgE binding by mutation of IgE binding epitopes, the present application identified IgE binding epitopes and actually demonstrated that mutations in these epitopes were able to reduce IgE binding in pooled serum. This finding indicated that the changes in IgE binding were of general significance and were not restricted to a particular test individual. This

was very relevant when considering the therapeutic uses of the modified allergens. Although the examining division had commented that the method claims did not specify a therapeutic use, it had not identified any other motivation for the skilled person to want to modify allergens so that IgE binding, or binding of pooled serum IgE of hypersensitive individuals, was reduced.

Auxiliary request 8

Article 123(2) EPC

– The amendment that "only one amino acid mutation is made in the one or more IgE binding epitopes" found a basis in the application as originally filed on page 124, in particular in lines 14 to 15 and on page 157, in particular in lines 15 to 17.

Inventive step

– The combination of the teaching of documents (1) and (3) did not render obvious such methods and resulting modified food allergens wherein only one amino acid mutation is made in the one or more IgE binding epitopes. The subject-matter of these claims was therefore inventive.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or the auxiliary requests 1 to 7, all these requests filed with letter dated 1 November 2004 or, alternatively, on the basis of the auxiliary request 8 filed at the oral proceedings.

Reasons for the Decision

Main request

Article 123(2) EPC

1. The examining division decided that the application as originally filed disclosed merely the binding of **pooled serum** IgE of hypersensitive patients and was only mentioned in the context of particular allergens, i.e. Ara h I and Ara h II. The amendments introduced in claim 1 of the main request now before the board qualify the referred to pooled serum IgE as being of hypersensitive patients. The board notes furthermore that the passages referred to by the appellant on page 174 of the application as filed, i.e. at lines 1 to 8 ("*In accordance with the present invention, it is contemplated that the discovery or identification of particular peptides or epitopes which bind IgE and cause an IgE response by a person having an allergy or sensitivity to that particular protein, ...*") and lines 14 to 19 ("*Also in accordance with the present invention, similar peptides, epitopes and IgE binding proteins from other legumes, herbs, oil seeds, and the like, for example soybeans or wheat can be isolated and identified, mutated so that they do not bind IgE, and used ...*"), frame the invention in a context which is broader than that of the specifically exemplified peanut antigens.

2. The board furthermore notes that the general wording of the independent claims of the main request finds a basis in original claim 32 of the application (see

section I) in combination with the general passages on page 174 of the application as originally filed.

3. The board is therefore satisfied that claim 1 of the main request complies with the requirements of Article 123(2) EPC.

Inventive step

4. Claim 1 is directed to a method of altering the immunogenicity of a food allergen comprising identifying one or more IgE binding epitopes of the allergen, and mutating the one or more IgE binding epitopes so that binding of pooled serum IgE of hypersensitive individuals to the one or more IgE binding epitopes is reduced or binding of pooled serum IgE of hypersensitive individuals to the allergen is reduced.

5. For assessing whether or not a claimed invention meets the requirements of Article 56 EPC 1973, the boards of appeal apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art. In accordance with the established case law of the boards of appeal, the closest prior art is a teaching in a document 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 to arrive at the claimed invention.

6. In the present case document (1) qualifies as closest prior art in the sense of the case law. The content and

text of document (1), a publication by inventors of the present patent application, is in essence identical to that of the application as originally filed on pages 58, line 7 to page 84, line 9. The "Results" section discloses the cloning, the expression and the characterisation of the recombinant peanut allergen Ara h I. IgE binding thereto was detected in immunoblot analysis using *inter alia* serum IgE from a pool of patients with peanut hypersensitivity (see e.g. page 1717, right-hand column, lines 22 to 27). In the "Discussion" section it is stated that: "*We have demonstrated that the cloned Ara h I gene is capable of producing a protein product in procaryotic cells that is recognized by serum IgE from a large proportion of individuals with documented peanut hypersensitivity. These results are significant in that they indicate that some of the allergenic epitopes responsible for this reaction are linear amino acid sequences that do not include a carbohydrate component. These findings may provide the basis for the improving diagnosis and therapy of persons with food hypersensitivity.*" (see page 1719, right-hand column, lines 5 to 13). The succeeding two paragraphs deal with the prospects of improving the diagnosis and, more relevantly, with immune therapy of these persons. Concerning the latter the document states that in case of peanut hypersensitivity immunotherapy with specific recombinant allergen epitopes rather than the crude allergen mixture could prove to be an effective treatment modality for down-regulating the specific IgE response and continues that: "***Another use of immunotherapy could be the modification of the molecular structure of the recombinant allergen in order to reduce the IgE binding capacity while***

retaining the T cell reactivity or the production of specific T cell epitopes designed for immunotherapy." (emphasis added).

7. Accordingly, like the claimed invention, document (1) deals with altering the immunogenicity of a food allergen, in particular by reducing the IgE binding capacity of the allergen, whereby the IgE is *inter alia* pooled serum IgE of hypersensitive individuals to the allergen, an this in the context of immunotherapy.

In view of the fact that the closest prior art in document (1) lacks any technical experimental detail on how to reduce to practice the theoretically disclosed teaching, the board considers the technical problem to be solved by the present invention to be the factual provision of an altered food allergen having reduced IgE binding.

8. It therefore needs to be established whether the claimed solution to this problem, i.e. a method comprising **identifying** one or more IgE binding epitopes of the allergen, and **mutating** the one or more IgE binding epitopes so that binding of pooled serum IgE of hypersensitive individuals to the one or more IgE binding epitopes is reduced or binding of pooled serum IgE of hypersensitive individuals to the allergen is reduced as well as the resulting products, was rendered obvious to the skilled person by the prior art.

9. The board considers that the skilled person, in the present case a molecular immunologist specialised in allergies, when looking for a solution for the problem as stated above in the prior art and inevitably be

aware of document (3), which had been published in the same technical field and which deals with the identification of allergenic proteins and peptides from house dust mites and therapeutic compositions thereof which avoid the drawbacks of treatment of patients with sensitivity to house dust mites by administration of increasing doses of house dust extracts, such as potential anaphylaxis (see document (3), page 2, lines 10 to 15).

In the paragraph bridging pages 2 and 3, document (3) describes peptides which can be used in compositions suitable for pharmaceutical administration or diagnostics having at least one biological activity of Der p VII or Der f VII, which are the relevant studied dust mite allergen proteins. Preferred peptides are described as having "*the ability to induce a T cell response, which may include T cell stimulation (...) or T cell nonresponsiveness (i.e., contact with the peptide or a complex of the peptide with an MHC molecule of an antigen presenting cell induces the T cell to become unresponsive to stimulatory signals or incapable of proliferation)*." Exemplified are *inter alia* peptides which, either apart from or in addition to the ability to induce a T cell response, have the ability to bind the dust mite specific IgE of dust mite-allergic subjects, which peptides are said to be useful in diagnosing sensitivity to dust mite in a subject as well as other peptides which "*either apart from or in addition to the ability to induce a T cell response, have a significantly reduced ability to bind dust mite-allergic IgE.*" (see document (3), page 3 lines 4 to 9 and page 5, lines 26 to 31). Document (3) continues on page 15 by stating that: "*In yet another*

embodiment, peptides having a Der p VII or Der f VII activity are identified (emphasis added) *by IgE binding activity. For therapeutic purposes, peptides of the invention preferably do not bind IgE specific for a dust mite allergen, or bind such IgE to a substantially lesser extent (e.g., at least 100-fold, less, more preferred at least 1000-fold less) than the corresponding purified native dust mite allergen binds such IgE.*" (see page 15, lines 5 to 9). Similarly, "*If a peptide having an activity of Der p VII or Der f VII binds IgE, and is to be used as a therapeutic agent, it is preferable that such binding does not result in the release of mediators (e.g., histamines) from mast cells or basophils*." (see document (3), page 16, lines 1 to 3).

10. Accordingly, in the context of recombinant house dust mite allergens and with a view to provide therapeutically relevant compounds, document (3) teaches the skilled person to provide particular peptides comprised within the allergen which do not bind IgE or which bind IgE to a substantially lesser extent than the corresponding purified native dust mite allergen binds such IgE. The board notes that, from a technical point of view, this teaching is equivalent to the identification of IgE binding in the allergen and consequently the **identification** of one or more IgE binding epitopes (which however does not necessarily require characterisation) and the subsequent mutation of one or more of those epitopes by deleting (**mutating**) them as a whole from the allergen, by providing only such part of the allergen which does not bind IgE or which binds IgE to a substantially lesser extent than the corresponding allergen. Accordingly, the board

considers that the skilled person, when looking for a solution in the context of food (peanut) allergens is taught by document (3), to provide such allergen parts which do not bind IgE or which bind IgE to a substantially lesser extent than the corresponding allergen.

11. The board notes that the wording of claim 1 of the main request does not exclude the defined mutation step to consist of deleting the IgE binding parts from the food allergen thereby reducing IgE binding. The method as rendered obvious by the combination of the teaching in documents (1) and (3) is therefore encompassed by the subject-matter of claim 1 of the main request.

12. The appellant has argued that even if it was true that both epitope identification and epitope mutation were routine and obvious at the time of the invention, it did not logically follow that the claimed methods were obvious. The method of claim 1 could only be rejected as obvious if, at the time of the invention, it was also obvious that simple mutation of the IgE epitopes would actually reduce IgE binding and it was also obvious that simple mutation of the IgE epitopes would reduce IgE binding in a therapeutically relevant way (i.e. across a population of allergic individuals, as evidenced by reduced binding in pooled serum).

The board observes however that, as was concluded in point 11 above, the combination of the teaching of document (1) and (3) would lead the skilled person to provide a method for the production of such compounds which consist of only a part of the peanut allergen which does not bind IgE or which binds IgE to a

substantially lesser extent than the unmodified allergen. Although admittedly such modification may not be considered as "simple", the board repeats that such compounds and methods for their production are encompassed by the subject-matter of claim 1 of the main request.

13. The appellant has furthermore argued that peanut allergens were highly allergenic and like many other food allergens presented a significant risk of anaphylaxis to those allergic to them. Accordingly, prior to the inventive demonstration of the present application, one of ordinary skill in the art would have had no reasonable expectation that such a modification in food allergens would be successful.

Claim 1 of the main request is directed to a method for altering the immunogenicity of a food allergen in general by modifying one or more of IgE epitopes. The board considers that the appellant has not put forward any serious technical reason why the skilled person would or could be hampered from believing that modifying the IgE epitopes (or even deleting) in a food allergen in general would not enable the reduction of the binding of pooled serum IgE of hypersensitive patients. For this reason the argument must fail.

14. The appellant has also argued that there was no mention in the passage in document (3) on page 16, lines 20 to 27, related to the production of modified peptides of identifying or modifying, let alone mutating, one or more IgE epitopes in the house dust mite allergens, despite document (3) setting out a multitude of possible modifications on pages 16 to 18 such as,

modified T cell epitopes (page 16, line 28, to page 17, line 14); modified disulfide bonds (page 17, lines 15 to 18); modified side chains (page 17, lines 18 to 19); cyclisation (page 17, line 19); polymorphisms (page 17, line 21); non-natural amino acids, etc (page 17, line 23); pegylation (page 17, lines 25-28); reduction and alkylation (page 17, line 29); chemical coupling (page 17, line 31); formalin treatment (page 17, line 33); addition of a histidine tag (page 18, lines 1 to 4); addition of endoprotease sites (page 18, line 6); addition of amino acids that increase the solubility of the peptide (page 18, lines 7 to 12); and addition of canonical protease sites (page 18, lines 13 to 19).

However, as elaborated on in point 13 above, document (3) in combination with the disclosure in document (1) renders the subject-matter of claim 1 of the main request obvious as it specifically indicates one route for arriving at a method which falls under the claimed method. The argument of appellant must thus fail.

15. For the above reasons the board considers that the subject-matter of claim 1 of the main request was rendered obvious to the skilled person and consequently lacks inventive step.

Auxiliary request 1 - Inventive step

16. The subject-matter of claim 1 of the main request is embraced by claim 1 of auxiliary request 1. Accordingly, the subject-matter of the latter also lacks inventive step.

Auxiliary requests 2 to 5 - Article 123(2) EPC

17. During the appeal proceedings, the appellant has referred to a passage at page 101, lines 5 to 8, of the application as filed as supporting the wording "**anaphylactic** (food) allergen", i.e. "*Individuals sensitive to peanuts may experience symptoms ranging from mild urticaria to severe, systemic anaphylaxis.[1] In food-induced, fatal anaphylaxis, peanuts are the food most commonly implicated in causing the reaction.[2,3]*".

18. Inspection of the application as originally filed reveals that the description contains, besides in titles of referenced journal articles (as e.g. references 2 and 3 referred to in the above quote), a few further passages which mention anaphylaxis. On page 1, lines 16 to 22, it is stated that "*The ingestion of peanuts is a common cause of food hypersensitivity reactions. Symptoms can vary from mild abdominal discomfort to severe anaphylaxis. In a recent report ... four of seven patients who experienced fatal anaphylaxis died after peanut ingestion*.". On page 12, lines 25 to 27, the application refers to "*Nine patients (mean age 4.2 years) with AD and a positive immediate prick skin test to peanut had either a positive DBPCFC or a convincing history of peanut anaphylaxis.*" (this passage is virtually identical to the passages at page 29, lines 7 to 12, page 61, lines 3 to 8) whereas similarly on page 102, lines 13 to 19, reference is made to: "*Twelve patients with atopic determatitis and a positive immediate prick skin test response to peanut had either a positive response to double-blind placebo-controlled food challenge (DBPCFC) or a convincing history of peanut anaphylaxis (the allergic reaction was potentially lifethreatening,*

that is with laryngeal edema, severe wheezing, and/or hypotension)" (similar passages can also be found on page 120, lines 3 to 9 and page 140, lines 3 to 7). On page 59, lines 8 to 11 there is a reference to "*Peanut hypersensitivity reactions often tend to be quite severe in nature, sometimes resulting in episodes of fatal anaphylaxis (3,4).*" (this passage is virtually identical to the passage on page 113, lines 1 to 5). Similarly, on page 71, lines 2 to 5, the application refers to "*Peanuts are one of the most allergenic foods (25). Sensitive individuals may experience symptoms ranging from urticaria to anaphylaxis (25). Multiple cases of fatal anaphylaxis have been reported (4).*" and on page 148, lines 2 to 5: "*Peanuts are one of the most common food allergens in both children and adults. In addition, peanut hypersensitivity is less likely to resolve spontaneously and more likely to result in fatal anaphylaxis*." On page 118, lines 5 to 10 it is stated that: "*Allergic reactions to peanuts can produce symptoms ranging from urticaria to anaphylaxis in patients with peanut hypersensitivity. Several reports (4,5) have detailed fatal and near-fatal anaphylactic reactions occurring in adolescents and adults following the ingestion of peanuts or peanut products*." (this passage is similar to those on page 158, line 29 to page 159, line 1 and on page 160, lines 4 to 6). On page 138, lines 9 to 11 it is stated that: "*In addition, peanut allergy is more likely to cause fatal anaphylaxis than any other food allergy.*" whereas on page 150, lines 10 to 14 the application states that "*The elucidation of the major IgE binding epitopes on Ara h 2 may enable us to design better therapeutic options for the prevention of anaphylaxis as a result of peanut hypersensitivity.*" In the context of wheat

allergic patients the application refers on page 93, lines 15 to 18, to "*Seven wheat-allergic patients (ages: 1-17 yr. median 2 yr.) confirmed by prick skin tests, blinded challenges and/or convincing histomes of anaphylaxis after wheat ingestion were studies* (sic)."

19. The above quoted parts of the application as filed show that (peanut) allergy might result in anaphylaxis and the board concurs with the finding of the examining division that the application as originally filed did not refer to a particular class of allergens in the context of the invention, i.e. anaphylactic allergens. An amendment to the claims which limits the claimed subject-matter to such methods of altering the immunogenicity of an allergen to such of "anaphylactic" antigens introduces subject-matter which goes beyond what was clearly and unambiguously derivable from the application as filed and therefore constitutes added matter.

20. Accordingly, claims 1 of auxiliary request 2 to 5 infringe the requirements of Article 123(2) EPC.

Auxiliary request 6 - Inventive step

21. Claim 1 of auxiliary request 6 corresponds to claim 1 of the main request whereby the claimed method is specified as "a method of altering <u>for medical use</u> the immunogenicity of an allergen" (emphasis added).

22. The board considers that, like the claimed invention, document (1) deals with altering the immunogenicity of a food allergen, in particular by reducing the IgE binding capacity of the allergen, whereby the IgE is

inter alia pooled serum IgE of hypersensitive individuals to the allergen in the context of immunotherapy. The amendment to the preamble of claim 1 over claim 1 of the main request does therefore not influence the selection of the closest prior art nor the formulation of the objective technical problem or its solution. Accordingly, the subject-matter of claim 1 of the auxiliary request 6 lacks inventive step.

Auxiliary request 7 - Inventive step

23. As compared to the subject-matter of claim 1 of the main request, claim 1 of auxiliary request 7 specifies the food allergen to be the specific peanut allergens Ara h I or Ara h II. Also in the context of auxiliary request 7 the closest prior art is represented by document (1), which discloses altering the immunogenicity of a food allergen, in particular by reducing the IgE binding capacity of the allergen, whereby the IgE is *inter alia* pooled serum IgE of hypersensitive individuals to the allergen whereby the recombinant allergen is the Ara h I allergen. Therefore, the reasoning as for claim 1 of auxiliary request 6 applies *mutatis mutandis* and the subject-matter of claim 1 of auxiliary request 7 lacks inventive step.

Auxiliary request 8

Article 123(2) EPC

24. On page 124, in particular in lines 14 to 15, and on page 157, in particular in lines 15 to 17, the application as originally filed discloses in the context of the IgE biding characteristics of mutated

peanut allergens Ara h I and II, that "Clearly, a single amino acid substitution has dramatic effects on the IgE binding characteristics of that peptide." and that "Mutational analysis of these immunodominant epitopes indicate that single amino acid changes result in loss of IgE binding.", respectively. The board is satisfied that the amendment in claim 1 over the main request that "only one amino acid mutation is made in the one or more IgE binding epitopes" constitutes no added matter and complies with the requirements of Article 123(2) EPC.

Sufficiency of disclosure and novelty

25. In its decision to refuse the application the examining division has not objected to the novelty and or sufficiency of disclosure of the claimed subject-matter. Also the board sees no reason for doing so.

Inventive step

26. Claim 1 of auxiliary request 8 is directed to a method of altering the immunogenicity of a food allergen corresponding to claim 1 of the main request **wherein only one amino acid mutation is made in the one or more IgE binding epitopes**.

27. As analysed in point 13 above, document (3) teaches the skilled person looking for a solution to the stated technical problem to provide particular peptides comprised within the allergen which do not bind IgE or which bind IgE to a substantially lesser extent than the corresponding purified native allergen binds such IgE, which is equivalent to the identification of IgE

binding in the allergen and consequently the **identification** of one or more epitopes (which however does not necessarily require characterisation) and the subsequent mutation of one or more of those epitopes by deleting (**mutating**) them as a whole from the allergen, i.e. by providing only a part of the allergen which does not bind IgE or which binds IgE to a substantially lesser extent than the corresponding allergen.

28. The board notes however that the method as referred to above does not concern methods of altering the immunogenicity of a food allergen wherein only one amino acid mutation is made in IgE binding epitopes and which thus only consist of minor or "simple" mutations of the original food allergen. Moreover, none of the other cited document reflecting the prior art relevant for the invention describe methods of the reduction of the immunogenicity of allergens by single amino acid mutation in one or more IgE binding epitopes.

29. In view of the above considerations therefore the subject-matter of claim 1 of auxiliary request 8 is not rendered obvious by a combination of the disclosure in document (1) and (3). Neither is it in fact rendered obvious by any other prior art document on file. A similar consideration applies to the products of this method. Therefore, the subject-matter of independent claims 6 and 7 directed to medical uses of allergens altered in accordance with claim 1 likewise involves an inventive step.

30. Accordingly, the subject-matter of claims 1, 6 and 7, as well as dependent claims 2 to 5 of auxiliary request 8 involves an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to grant a patent on the basis of the auxiliary request 8 filed at these oral proceedings and a description yet to be adapted thereto.

The Registrar: The Chair:

P. Cremona U. Kinkeldey