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D E C I S I O N
of 4 May 2005

Case Number: T 0142/03 - 3.3.8

Application Number: 91916537.3

Publication Number: 0548200

IPC: C12N 15/12

Language of the proceedings: EN

Title of invention:
Cloning and sequencing of allergens of dermatophagoides (house dust mite)

Patentee:
INSTITUTE FOR CHILD HEALTH RESEARCH

Opponent:
ALK-ABELLO A/S

Headword:
Mite allergens/INSTITUTE FOR CHILD HEALTH RESEARCH

Relevant legal provisions:
EPC Art. 56
RPBA Art. 10a, 10b

Keyword:
"Inventive step - main and first auxiliary requests (no)"
"No further requests admitted into the proceedings at a late stage"

Decisions cited:
T 0391/91, T 0694/92, T 0187/93, T 0296/93, T 0207/94, T 0794/94, T 0838/97

Catchword:
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Case Number: T 0142/03 - 3.3.8

D E C I S I O N
of the Technical Board of Appeal 3.3.8
of 4 May 2005

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 21 October 2002 revoking European patent No. 0548200 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: F. L. Davison-Brunel
S. C. Perryman

Summary of Facts and Submissions

I. European patent No. 0 548 200 with the title: "Cloning and sequencing of allergens of dermatophagoides (house dust mite)" was granted with 20 claims on the basis of the European application No. 91916537.3 corresponding to the international application No. PCT/AU91/00417 published as WO 92/04445.

II. An opposition was filed for lack of novelty and inventive step (Article 100(a) EPC) as well as lack of sufficiency of disclosure (Article 100(b) EPC). The patent was found to be lacking in all three respects and was revoked.

III. The appellant (patentee) filed an appeal, submitted a statement of grounds of appeal together with an auxiliary request and paid the appeal fee.

IV. The respondent (opponent) replied to the grounds of appeal.

V. The board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal, indicating its preliminary non-binding opinion.

VI. The appellant sent a further submission in answer to the board's communication together with a new main request to replace the requests on file.

Claim 1 of this request read as follows:

"1. Isolated DNA encoding Der fI protein allergen or a peptide comprising at least one B or T cell epitope of

Der fI protein allergen, which epitope is not cross reactive with Der pI."

VII. At oral proceedings which took place on 4 May 2005, the appellant submitted an auxiliary request.

Claim 1 of this request read as follows:

"1. Isolated DNA encoding Der fI protein allergen or a peptide comprising at least one B or T cell epitope of Der fI protein allergen, which epitope is not cross reactive with Der pI wherein the isolated DNA encodes all or a portion of the amino acid sequence represented in Figure 2."

Dependent claims 2 to 5 related to further features of the isolated DNA of claim 1. Claim 6 was directed to a method for producing an isolated Der fI allergen. Claim 7 was directed to an isolated Der fI protein allergen produced in an E.coli host and dependent claims 8, 9, 15 related to further features of the allergen of claim 7. Claim 10 to 12, 16, 17 and 20 were respectively directed to diagnostic reagent, therapeutic compositions comprising the Der fI allergen. Claims 13, 14, 18 to 20 related to variously formulated uses of the allergen.

VIII. The documents mentioned in the present decision are the following:

(6): Chua, K.Y. et al., Int.Arch.Allergy Appl.Immunol., Vol. 91, pages 118 to 123, February 1990;

(22): Thomas, W.R. et al., Advances in the Biosciences, Vol. 74, pages 139 to 147, 1989.

IX. The appellant's submissions in writing and during oral proceedings insofar as they are relevant to the present decision may be summarised as follows:

Article 56 EPC; inventive step
Main request; claim 1

In accordance with the case law, it must be remembered that a legitimate hope to succeed is not be confused with a reasonable expectation of success (T 296/93, OJ EPO 1995, 627, point 7.4.4, T 187/93 of 5 March 1997, point 21 and T 207/94, OJ EPO 1999, 273, point 31). In the present case, the problem to be solved was to provide allergen compositions useful in diagnosis. In order to do so, the inventors had faced a number of challenges which implied that there was no reasonable expectation of success to arrive at the claimed cDNA.

There existed at the time three cDNA cloning strategies. Screening an expression library with an antiserum containing anti-Der fI antibodies was one of them. However, one could not be sure that this would work as the recombinant form of the other major allergen Der pI itself was not detectable by an immunological assay. Furthermore, antibodies to Der fI were not available at the time of filing and anti-Der pI antibodies would not necessarily be cross-reactive with Der fI.

Alternatively, the cDNA library could be probed with short probes. Yet, because of the degeneracy of the

genetic code, relevant short probes could not be devised with any certainty on the basis of the known amino terminal end of Der fI.

Finally, one could use long oligonucleotide probes from Der pI cDNA to identify the clones carrying Der fI cDNA. This was the approach taken by the appellant in view of the fact that Der fI and Der pI were known to be 80% homologous. However, this protein-protein homology did not mean at all that the same degree of homology existed at the DNA level because of codon degeneracy. The inventors had clearly demonstrated an inventive step in selecting the correct hybridisation conditions. The risks included that if the stringency conditions were too high, no cDNAs would be identified. For this reason, it would have been tempting to use low stringency conditions but, then, the cDNAs encoding cysteine proteases known to be related to Der pI would have equally hybridized, leaving the skilled person at a loss as to which of the clones which positively responded, were, in fact, the ones encoding Der fI.

For these reasons, the subject-matter of claim 1 enjoyed inventive step.

The present case was analogous to that dealt with in the decision T 694/92 (OJ EPO 1997, 408, points 28.5 to 28.7) where inventive step was acknowledged to the achievement of detectable levels of phaseolin expression in a dicotyledonous plant cell. The then competent board had concluded that, although the prior art taught that the experiment leading to this expression was in progress, the skilled person was

nonetheless not in a position to reasonably predict its successful conclusion.

Auxiliary request; claim 1

Claim 1 was directed to the DNA encoding Der fI allergen as defined by its amino acid sequence. The arguments presented in relation to claim 1 of the main request, namely that the skilled person had no reasonable expectation of success when cloning the Der fI cDNA equally applied to claim 1 of the first auxiliary request. Furthermore, the sequence of the Der fI protein sequence was clearly different from that of Der pI in the central region where the T cell epitopes were found. This had the unexpected advantages for making species specific reagents for diagnostics and therapy. The Der fI sequence was also advantageous for the construction of synthetic peptides containing T or B cell epitopes.

Admissibility of further auxiliary requests

Further auxiliary requests ought to be admitted because the appellant had already indicated in writing its intention to file such requests if the board was minded to decide that the requests already on file were not allowable.

Allowing further requests at oral proceedings was a common practice at the European patent office and there was no reason to depart from this practice in the present case.

X. The respondent's submissions in writing and during oral proceedings insofar as they are relevant to the present decision may be summarised as follows:

Article 56 EPC; inventive step
Main request; claim 1

The closest prior art was document (22) which described the cloning of the DNA encoding Der pI protein allergen starting from a cDNA library established in λgt11 and using a combination of plaque immunoassay with a specific rabbit anti-Der pI antibody and of oligonucleotide hybridisation with probes based on amino acid sequences obtained from the N-terminal and tryptic peptides of faecal Der pI. This document also disclosed that the overall homology between the Der pI and Der fI allergens was 80% (passage bridging pages 143 and 144). Finally, it was emphasized that the difference in structure between Der fI and Der pI was of interest for further work relating to mite allergy. This last statement gave the skilled person an incentive to produce the Der fI allergen, ie to clone the cDNA encoding it.

Starting from the closest prior art, the problem to be solved could be defined as providing Der fI cDNA.

At the priority date, there existed at least three methods which could be used in a routine manner to clone this cDNA: screening an expression library with antibodies, screening with short specific DNA probes, screening with longer DNA probes. The first of these approaches was cautioned against in document (6) (passage bridging pages 122 and 123). The appellant was

thus left with the two other approaches and, in view of the known homology between Der fI and Der pI, it took no inventive step to choose the long probe approach. This much was acknowledged in the patent itself, column 13, section [0052].

The appellant argued that the skilled person had no reasonable expectation of success to isolate Der fI cDNA using the long probe approach because the screening of the positive clones required that proper hybridisation conditions be set up; in particular, cDNAs encoding related proteases would be isolated if the stringency of hybridisation was too low. This argument was not convincing since setting up the right hybridisation conditions could take time but would be done as a matter of routine in 1990, and the cDNAs encoding other proteases could be discarded on the basis that the proteins they encoded would not hybridize to anti-Der fI antibodies.

It also had to be kept in mind that no problems were encountered during the cloning.

For these reasons, the subject-matter of claim 1 lacked inventive step.

Auxiliary request; claim 1

This claim related to the DNA encoding Der fI allergen characterised by its ability to encode the protein defined by its sequence (that given in Figure 2). The arguments presented with regard to obtaining the cDNA remained the same as given in relation to claim 1 of the main request. Furthermore, no inventive step could

be seen in the particular amino acid sequence, as no unexpected advantages were derivable from the specific chain of amino acids.

Admissibility of further claim requests

The board had already accepted the filing of one auxiliary request at oral proceedings after the main request had been refused. It would be an abuse of procedure if the appellant was allowed to tailor its requests at will in order to comply with what seemed the board's current thinking. Thus, further auxiliary requests should be found inadmissible.

XI. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the sets of claims filed as main request on 5 April 2005 or as first auxiliary request at the oral proceedings on 4 May 2005, and further requested permission to file a further auxiliary request or requests and time in which to formulate these.

The respondent requested that the appeal be dismissed.

Reasons for the decision:

Main request
Article 56 EPC; inventive step

1. The closest prior art is document (22) which is concerned with an analysis and the expression of cDNA clones coding for house dust mite allergens. The introductory part of the document describes the

advantages which may result from producing them in recombinant form. The three main causative agents of allergic diseases are identified as Dermatophagoides pteronyssinus, Dermatophagoides microceras and also Dermatophagoides farinae. On page 140, the desirability of obtaining a panel of cloned allergens which could be used in vitro or in vivo, ie of obtaining workable amounts of the allergens, is expressed. The data produced in this framework describe the cloning in λgt11 of the cDNA encoding the D. pteronyssinus major allergen: Der pI. The homology between Der pI and D. farinae major allergen Der fI is disclosed on page 144:

"Previous published comparison of Der p I and Der f I homology shows only 11/20 homologous residues in the N-terminal [12,16]. Further data for Der f I [17] shows that most of the non-homologous residues were in extreme N-terminal and ***the overall homology will be about 80%*** *(Chapman et al., unpublished)."*(emphasis added by the board)

In the passage bridging pages 144 and 145, future perspectives associated with developing products from the cloning of mite allergen cDNAs are discussed.

2. Starting from the closest prior art, the problem to be solved can be defined as the provision of a further allergen in workable quantities.

3. The solution provided in claim 1 is the cDNA encoding Der fI. At the priority date, it was a matter of common general knowledge that the best route to producing a protein in workable quantities was the recombinant route and, besides, this had been the route used for

producing Der pI. Thus, the cDNA cloning was obvious to try. The question which remains to be answered is whether or not the task would be viewed as achievable with a reasonable expectation of success, and whether there was any serious reason to doubt that the task would routinely be completed successfully.

4. Amongst the three methods for cloning cDNA acknowledged by both parties as having been available at the priority date, the inventors chose the one which involved the screening of positive recombinant clones by long probes consisting of DNA encoding parts of the Der pI protein. In the patent in suit (col.13, section [0052]), it is explained that "*this approach was adopted because amino acid sequencing had shown high homology (80%) between these two allergens.*" (meaning Der pI and Der fI). Thus, it can be said that in addition to giving an incentive to clone the Der fI cDNA, document (22), which had in fact shown such homology, also pointed to the one of the three available methods which might be the most appropriate and provided the tool necessary for screening the recombinant clones.

5. The appellant argued that inventive step lay in the choice of the conditions for hybridisation between the Der pI cDNA-derived long probes and the clones potentially containing Der fI cDNA. Yet, at the same time, it informed the board of the rules recommended in the prior art to calculate optimal conditions for hybridisation as a function of the degree of homology of the corresponding proteins. Determining an initial set of conditions for hybridisation will, thus, have been obvious. At this point, it must be said that the

further argument that the skilled person would have been discouraged from trying Der pI- Der fI (ie cross-species) cDNA hybridisation by the fact that there was more than 30% difference in the N-terminal ends of the two proteins is not convincing. Indeed, it is the principle of the "long probe method" that it makes use of a probe which is longer than any small specific portion of DNA (as the one encoding the N-terminal end). For the board, the skilled person aware of the relative heterogeneity at the N-terminal end would, as a matter of course, turn to either a probe covering much more than that region or to a probe which did not include it.

6. If the chosen conditions are not stringent enough, it may be that recombinant clones show up positive when the D. farinae cDNA they contain encodes a protein which is not Der fI, for example, another protease having some homology to Der pI. Yet, the skilled person as defined in the case law (eg T 838/97 of 14 November 2000 or T 391/91 of 22 November 1994) seeing too many positive recombinant clones - as compared with the theoretical number of clones to be expected - would be capable as a matter of routine to make those conditions more stringent. Additionally, murine anti-Der fI antibodies were available at the priority date (patent in suit, column 6, section [0027] and document (6), introduction) which enabled the identification of Der fI protein. The argument was raised in this respect that one could not predict the "immunogenic behaviour" of recombinant Der fI because document (6) taught that recombinant Der pI could not be detected in an assay using IgE immuno-screening. This argument, however, is not convincing insofar as the human allergic serum used

in document (6) for the IgE radioimmunoassay has nothing in common with a mouse monoclonal antibody.

7. Finally, the board will also remark that the concern of isolating cDNAs encoding other proteases than Der fI cannot have been too strong since in the patent specification no experiments are described which would have been carried out to ascertain that the positive clones recovered by hybridisation contain nothing else than Der fI cDNA, whereas, of course, it could not have been possible to foresee that the hybridisation conditions used would only "highlight" the cDNA encoding the Der fI protein.

8. For the above reasons, the board believes that the skilled person would have considered it obvious to solve the problem by identifying the cDNA encoding Der fI, would have known what to do, would have embarked on this task with a reasonable expectation of success and would have succeeded by way of routine measures. Inventive step thus cannot be acknowledged on the basis of the process used to obtain the Der fI cDNA.

9. The appellant also made reference to the case law to the effect that one should not confuse a legitimate hope to succeed with a reasonable expectation of success (cf. T 296/93, T 187/93, T 207/94, supra). This is undeniably true, however, on the basis of the above reasoning, it must be concluded that in the present case both were present.

10. The present situation was also compared with that dealt with in the earlier decision T 694/92 (supra). The subject-matter which was then assessed for inventive

step was a method for genetically modifying a dicotyledonous plant so that it expressed a detectable level of phaseolin, comprising transforming said plant with a vector carrying the phaseolin gene under the control of its own promoter. The board decided in favour of inventive step because, although the vector was known from the prior art and an announcement had been made that the experiment was in progress, said prior art also warned that *"a number of people had already tried and nobody had shown a functional gene when one includes the endogenous promoter"*. The board is unable to see any similarity between this earlier case and the present one, taking into account on the one hand that the two technical situations are quite different and on the other that, here, the prior art reported the successful cloning of a gene equivalent to the Der fI gene, namely Der pI.

11. The main request is refused for failing to fullfil the requirements of Article 56 EPC.

Auxiliary request; claim 1

12. Having informed the parties of its decision relating to the main request and succinctly explained the reasons therefor, the board allowed the appellant to prepare and file an auxiliary request. As claim 1 of the main request, claim 1 of this auxiliary request (section VII) is to a DNA encoding the Der fI protein, the difference being that the protein is now defined by its specific sequence.

13. The entire reasoning which led to the finding that the skilled person had a reasonable expectation of success

of cloning Der fI cDNA is precisely based on the sequence homology of the Der pI and Der fI proteins. Mentioning the specific sequence of Der fI in the claim, thus, does not affect this finding. Three further arguments were presented: firstly recombinantly produced Der fI had reduced binding to IgE compared to native Der fI, secondly the T cell epitopes of Der pI were found in the central, non-conserved region between Der fI and Der pI which was advantageous for making species specific reagents for diagnostics and therapy, and thirdly the knowledge of the Der fI cDNA sequence was helpful for the construction of synthetic peptides for immunotherapy.

14. The board is not convinced that any of these arguments could reverse the conclusion on inventive step. It must first be emphasized that the subject-matter of claim 1 is the Der fI cDNA and not the recombinant Der fI protein. This protein may have an IgE binding capacity which is different from that of natural Der fI. Yet, this property does not depend on its primary structure (amino acid sequence) which remains the same as for natural Der fI, as the encoding DNA is the same for natural and recombinant Der fI. It is rather a consequence of the type of organism in which the cDNA is expressed, and that is not a claimed feature.

15. It was known from the state of the art that the Der fI and Der pI sequences were dissimilar to a certain extent, and thus the proteins would have been expected to have different immunogenic properties if the heterogeneous regions were in any way implied in the immunoreactions. In the same manner, knowing the sequence of a DNA encoding a given protein will be

expected to render easier the task of producing small peptides comprised within the protein. Thus, while the availability of the Der fI protein may bring advantages, it remains that these advantages are not unexpected and, therefore, that they do not contribute to inventive step.

16. The auxiliary request is rejected for failing to fulfil the requirements of Article 56 EPC.

Allowance of further auxiliary requests into the proceedings

17. The principles applicable to the admission into the proceedings of new requests filed at a late stage have long been established, and a three page review of these is to be found in decision T 794/94 of 17 September 1994, points 2.1.1 to 2.2.4. To summarize these briefly: appeal proceedings are essentially a written procedure in which alternative claims should be put forward as early as possible. Where the appellant is the patentee this is with the grounds of appeal (see also the amended Rules of Procedure of the Boards of Appeal (OJ EPO 2003, 60) in force since 1 May 2003, Articles 10a and 10b). Submission of alternative claims at oral proceedings is likely to disrupt the procedure, as the opposing party and the board are likely to be taken by surprise, and though the board has a discretion to accept such late requests it will only do so in exceptional circumstances. Such exceptional circumstances may exist in particular where from the discussion at oral proceedings of the requests already on file, it becomes clear that some claims, or parts of claims, meet the requirements of the EPC, but other claims do not.

18. In the present case, however, already discussion of claim 1, a fairly narrow claim directed to the core of the disclosed contribution to the art, led to the board confirming the decision under appeal that the subject matter of this claim lacked inventive step. As the other claims on file prima facie did not avoid all grounds of invalidity (the decision under appeal having held them invalid on a variety of grounds) the board was already generous in exercising its discretion to allow the appellant even a single opportunity to file a further request at such a late stage. Once this single new request too was found invalid, the board considered it would not be a proper exercise of its discretion to allow any further requests and accordingly refused to grant the appellant further time to prepare and submit such request(s).

Order

For these reasons it is decided that:

1. The request to allow further auxiliary requests into the proceedings is refused.

2. The appeal is dismissed.

The Registrar: The Chairman:

A. Wolinski L. Galligani