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D E C I S I O N
of 7 January 2004

Case Number: T 0182/00 - 3.3.4

Application Number: 89300872.2

Publication Number: 0327283

IPC: A61K 39/395

Language of the proceedings: EN

Title of invention:
Method of reducing immunoglobulin E responses

Patentee:
SCHERING CORPORATION

Opponent:
SmithKline Beecham plc

Headword:
IgE response/SCHERING

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - main and auxiliary requests (no)"

Decisions cited:
G 0001/92, G 0009/92, G 0004/93, T 0381/87, T 0482/89, T 0327/92, T 0792/92, T 0163/93, T 0348/94, T 0750/94, T 0473/98

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0182/00 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 7 January 2004

Appellant: (Proprietor of the patent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 9 December 1999 revoking European patent No. 0327283 pursuant to Article 102(1) EPC.

Composition of the Board:

Chairwoman: U. Kinkeldey
Members: A. Marie
R. Moufang

Summary of Facts and Submissions

I. European Patent EP-0 327 283 claiming priority from US 151413 (2 February 1988) was granted on the basis of ten claims for the Contracting States AT, BE, CH, DE, FR, GB, IT, LI, LU, NL and SE, claims 1 and 8 of which read:

"1. A pharmaceutical composition for reducing an immunoglobulin E response in humans comprising an effective amount of an antagonist to human interleukin-4 and a pharmaceutically acceptable carrier."

"8. Use of an antagonist to human interleukin-4 for the preparation of a therapeutic composition useful in reducing an immunoglobulin E response in humans."

II. The patent was opposed on the grounds of Article 100(a)(b) EPC and its revocation was requested for lack of novelty (Article 54 EPC), inventive step (Article 56 EPC) and industrial application (Article 57 EPC) and because the invention was not described in a manner sufficiently clear and complete for it to be carried out by a skilled person (Article 83 EPC).

III. The opposition division revoked the patent in suit pursuant to Article 102(1) EPC because the subject-matter of the claims as granted and of the claims of the auxiliary request submitted during oral proceedings did not fulfil the requirements of Article 56 EPC in view of the teaching of documents (28) and (38) (*cf* infra, section IV) considered together.

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

(4) Dorland's Illustrated Medical Dictionary, twenty-sixth edition, W.B. Saunders Company, page 85

(5) F.D. Finkelman et al., Proceedings of the National Academy of Sciences USA, 1986, Vol. 83, pages 9675 to 9678

(9) E. Maggi et al., La Ricerca Clin. Lab., 1987, Vol. 17, pages 363 to 367

(12) W.E. Paul and J. Ohara, Ann. Rev. Immunol., 1987, Vol. 5, pages 429 to 459

(28) WO 87/02990

(38) 44th Meeting of The American Academy of Allergy and Immunology , March 11-16 1988, Anaheim, California in J. of Allergy and Clin. Immunology, January 1988, abstracts 539, 540 and 542

(39) Affidavit of Mr Arthur J. Levine and Certificate of Copyright Registration Form SE

(42) Statutory declaration of Ms Thompson dated 30 March 2000

(43) Declaration of Ms McKenzie dated 13 April 2000

(44) Statutory declaration of Mr Ritter dated 5 December 1997

(45) Letter of Ms Trumbold dated 25 March 1998

V. The patentee lodged an appeal against the decision of the opposition division and in his statement of grounds of appeal only argued on the publication date of document (38) and asked the Board to make an interim decision on this issue.

VI. The respondent in his response to the statement of grounds of appeal also considered solely the availability to the public of document (38) before the priority date of the patent in suit.

VII. The Board issued a communication pursuant to Article 11(1) of the Rules of procedure of the Boards of appeal and indicated that the availability to the public of document (38) before the priority date appeared to be a major issue and that the Board did not intend to make an interlocutory decision on this issue. Further, the Board invited the appellant and the respondent to submit their arguments in view of the conclusions reached by the opposition division on Articles 83, 54 and 56 EPC.

VIII. Neither the appellant nor the respondent answered the communication of the Board.

IX. Oral proceedings were held on 7 January 2004 in the sole presence of the appellant who filed again the auxiliary request that had already been considered by the opposition division, claims 1 and 7 of which read:

"1. A pharmaceutical composition for reducing an immunoglobulin E response in humans comprising an effective amount of an antagonist to human interleukin-4 and a pharmaceutically acceptable carrier, said antagonist to human interleukin-4 being selected from a monoclonal antibody capable of blocking the immunoglobulin E enhancing activity of human interleukin-4, a fragment of a monoclonal antibody capable of blocking the immunoglobulin E enhancing activity of human interleukin-4, and a binding composition comprising the heavy chain variable region and light chain variable region of a monoclonal antibody capable of blocking the immunoglobulin E enhancing activity of human interleukin-4."

"7. Use of an antagonist to human interleukin-4 for the preparation of a therapeutic composition useful in reducing an immunoglobulin E response in humans, said antagonist to human interleukin-4 being selected from a monoclonal antibody capable of blocking the immunoglobulin E enhancing activity of human interleukin-4, a fragment of a monoclonal antibody capable of blocking the immunoglobulin E enhancing activity of human interleukin-4, and a binding composition comprising the heavy chain variable region and light chain variable region of a monoclonal antibody capable of blocking the immunoglobulin E enhancing activity of human interleukin-4."

X. (a) The appellant submitted that since the patentee, as the sole appellant, was not to be placed by the decision of the Board in a situation worse than that

decided by the opposition division, the appeal was to be restricted to issues which were not decided in favour of the appellant, i.e. to issues relating to the availability of document (38) to the public (prohibition of *reformatio in peius*).

(b) As far as the availability to the public of document (38) was concerned the appellant essentially argued that, according to decision T 381/87 (EPO OJ 1990, 213), a document was made available to the public only by its delivery to the addressee. However, as shown by documents (42) and (43) none of the libraries contacted in USA, France, Germany and England had received document (38) at a date earlier than 8 February 1988. In document (44) an inquiry to the publishers of document (38) showed that there was no record of the precise date of mailing of this document to the subscribers. The date "January 12 1988" mentioned under the heading "Date and nation of first publication of this particular issue" in the "Certificate of Copyright Registration" annexed to document (39) only referred to the date at which certain internal procedures for publication were completed at the publishers. This date had no bearing on any date of receipt of document (38). Finally, in document (45), "12 January 1988" was indicated as publication date, but was not supported by any documentary evidence.

(c) The appellant defined the technical problem underlying the patent in suit as the provision of an alternative to the already existing compositions containing glucocorticoid steroids for the treatment of IgE disorders and argued that the skilled person was

not led to the solution claimed in the main and auxiliary requests by the disclosure of document (9), since the last paragraph on page 366 on the role of IL-4 in the induction of IgE synthesis was formulated in a cautious and dissuasive manner and it was not excluded from the teaching of Figure 1 on page 365 that IL-4 was acting in concert with other undefined substances to stimulate IgE synthesis. However, without the knowledge of a clear causal link between IL-4 and the stimulation of IgE synthesis, the skilled person would have had no reasonable expectation of success and no motivation to prepare a pharmaceutical composition containing an antagonist to IL-4. Furthermore, interferon-γ used in document (9) to inhibit the action of IL-4 was not an antagonist in the sense of the patent in suit, since it was not specific for IL-4.

Since the monoclonal antibody "11B11" disclosed in document (5) was not specific for IL-4, but cross-reacted with another molecule unrelated to IL-4, the skilled person did not know whether the inhibition of the stimulation of IgE synthesis caused in mice by IL-4 was due to the binding of the antibody to IL-4 or to the unrelated cross-reacting molecule and was not led to the solution defined in the claims of the auxiliary request.

XI. (a) The respondent in his answer to the statement of grounds of the appellant only focused on the availability to the public of document (38) and argued that it was a common practice of publishers to supply local subscribers before overseas subscribers, so that it was not surprising that document (42) showed that none of the libraries contacted in Europe had received

document (38) before 4 March 1988. In addition, the transit time of post between US and Europe could reasonably be expected to be considerably longer than that for post within the US. Furthermore, document (39), to which the certificate of copyright registration (Form SE) for document (38) at the US Copyright Office was annexed, mentioned "12 January 1988" as the date of first publication", the term "publication" being defined in "Exhibit Q" of document (39) as "the distribution of copies ... of a work... or the offering to distribute copies ... to a group of persons...".

(b) In their opposition arguments an objection under Article 57 EPC was raised.

(c) During the opposition procedure, the respondent argued in view of Article 56 EPC that document (9) showed the role of IL-4 in induction of human IgE synthesis *in vitro* and the antagonistic effect of interferon-γ. In view of the need for an effective treatment of allergic disorders in humans, free from side-effects related to the use of glucocorticoid steroids, the skilled person would have considered it worthwhile to derive from the teaching of document (9) a pharmaceutical composition and its expectation of success would have been high relative to the effort required. Even more, since document (28) provided him with a purified recombinant human IL-4 which would have enabled him to verify the teaching of document (9). Moreover, the skilled person would have been comforted in this attitude by the result obtained in mice where the effect of IL-4 on IgE synthesis was antagonized by murine monoclonal antibody "11B11" (document (5)). The fact that this antibody cross-reacted with a 14 kD

peptide was irrelevant, since said peptide was, as shown in document (12) unrelated to IL-4 and hence did not interfere with the stimulation of IgE synthesis.

XII. The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted (main request) or on the basis of the auxiliary request submitted in the oral proceedings.

XIII. The respondent implicitly requested that the appeal be dismissed.

Reasons for the Decision

Availability to the public of document (38)

1. Document (38) consists of three abstracts of contributions for a scientific conference which was held on March 11-16, 1988 in Anaheim, California. The abstracts were published in the January issue (= issue No. 1) of 1988 of the Journal of Allergy and Clinical Immunology. Since the precise date of the publication of this issue is in dispute, the board has to evaluate the relevant evidence submitted by the parties.

2. The main piece of evidence on which the opponent relies is a certificate of copyright registration submitted as annex A to document (39) (the "Levine affidavit"). The certificate uses the Form SE of the US Copyright Office and relates to the January 1988 issue of the above mentioned journal. It states under No. 2 that this particular issue was first published on 12 January 1988. The certificate is signed by A. J. Freeland as

authorised agent of the publisher, the "C.V. Mosby Company". The application for copyright registration was received on 1 March 1988 by the Register of Copyright.

3. It follows from the "Levine affidavit" that, according to US copyright law (17 U.S.C. § 410(c)), the certificate of a registration made before or within five years after first publication of the work shall, in all judicial proceedings, constitute *prima facie* evidence of the validity of the copyright and of the facts stated in the certificate. Furthermore, 17 U.S.C § 506(e) makes any person who knowingly makes a false representation of a material fact in the application for copyright registration subject to a fine of up to $ 2500.

4. The Board takes the view that also in proceedings before the EPO a US certificate of copyright registration may generally be considered to constitute *prima facie* evidence of the facts stated therein. However, it follows from the principle of free evaluation of evidence (see T 482/89, OJ EPO 1992, 646, point 2.1) that even *prima facie* evidence may lose its probative force in the light of serious counter-evidence. It has also been held in US patent proceedings that the *prima facie* evidence of a certificate of copyright registration may be rebutted (see decision of 31 January 1989 of the Board of Patent Appeals and Interferences of the USPTO, *Ex parte* Research and Manufacturing Co. Inc., 10, USPQ2d 1657).

5. The appellant has submitted documents (42) and (43) which show surveys of inquiries made at libraries in

the United States, France, United Kingdom, Germany and Switzerland concerning the dates of receipt of the January 1988 issue of the Journal of Allergy and Clinical Immunology. According to these surveys, 41 libraries (out of 127 contacted) have kept a record of the date of receipt. The earliest date recorded is the 8 February 1988, i.e. six days after the priority date of the patent in suit. The appellant has further filed document (44) reporting a statement of an employee of the publishers of document (38) according to which in 1988 the journals were generally sent out to subscribers at the very end of the month.

6. The respondent has not submitted any evidence relating to a concrete example of a library or of an individual member of the public having received document (38) before the priority date of the patent in suit. Document (45) is a short letter of 25 March **1998** by a vice-president of the publishers who confirms the 12 January **1988** as date of first publication of document (38). However, the letter does not indicate any supporting facts as basis for the confirmation.

7. In ascertaining the facts relating to the public availability of an alleged prior art document, to an alleged prior oral disclosure or to an alleged prior use, a strict standard of proof has to be applied (see T 782/92 of 22 June 1994, point 2.2; T 348/94 of 21 October 1998, point 3.2; T 750/94, OJ EPO 1998, 32, point 4). A European patent should not be refused or revoked unless the grounds for refusal or revocation are fully and properly proved (T 750/94, point 4).

8. In the present case the evidence on file is not sufficient to prove beyond reasonable doubt that document (38) was publicly available before 2 February 1988. The *prima facie* evidence of the certificate of copyright registration according to which the relevant issue of the Journal was published on 12 January 1988 is rebutted by the counter-evidence submitted by the appellant. The surveys contained in documents (42) and (43) show that none of the more than forty libraries which have kept records of the receipt of the issue and which were predominantly libraries located in the United States, i.e. within the country of the publishers, have indicated receipt of the issue before 2 February 1988. The earliest recorded date according to the surveys was 8 February 1988, i.e. almost a month after the publication date stated in the certificate of copyright registration.

9. Thus it can be assumed that the date on which the January issue of the journal was sent to the subscribers of the journal was considerably later than the alleged publication date. Although this does not wholly exclude the theoretical possibility that some member of the public may in fact have received the issue earlier than normal subscribers, serious doubts are cast on the correctness of the publication date as stated in the certificate of copyright registration. In the absence of any evidence from the respondent relating to a concrete example of a member of the public having gained access to document (38), the Board comes to the conclusion that this document does not constitute prior art under Articles 54(2) and 56 EPC.

Principle of prohibition of reformatio in peius

10. The opposition division held that, if document (38) were not regarded as state of the art, the subject-matter of the claims as granted and of the auxiliary request would meet the requirements of the EPC. The appellant has argued that the principle of prohibition of *reformatio in peius* precluded the Board from challenging this finding of the opposition division.

11. According to the established case law of the boards of appeal, if a revocation decision of an opposition division is appealed by the proprietor, the opponents or the Board may challenge those findings in the decision which were favourable to the proprietor (T 169/93 of 10 July 1996, point 2.6; T 473/98, OJ EPO 2001, 231, point 2.6). In such cases the overall position of the appellant cannot be worsened since the patent has already been revoked by the first instance. Thus the doctrine of prohibition of *reformatio in peius* does not apply separately to each point decided by the opposition division (see T 327/92 of 22 April 1997, point 1.3). Otherwise, the procedural rights of the opponent would be seriously restricted as he is not adversely affected by a revocation decision and cannot file an appeal against it in view of Article 107, first sentence, EPC (see T 169/93, point 2.2; T 473/98, point 2.2).

12. The Board is thus free to examine whether the subject-matter of the claims as granted and of the auxiliary request meets the requirements of the EPC.

Article 57 EPC (Industrial applicability)

13. The opponents have raised in their opposition statement an objection that the subject-matter of the patent in suit was not industrially applicable because it firstly only stated a problem without providing a solution; secondly that there existed significant areas of inoperability and thirdly that there was an absence of requirement for a therapeutic effect. The Opposition Division in their reasoning did not refer to these objections at all. The Board considers none of these objections as falling under Article 57 EPC but rather concludes that these objections fell either under Articles 56 EPC (problem not solved) or 83 EPC (inoperability or lack of a therapeutic effect) respectively.

Article 54 EPC (Novelty) and Article 83 EPC (Sufficiency of disclosure)

14. The reasons given by the Opposition Division as to why they considered the requirements of these Articles to be fulfilled (pages 8 to 9 and pages 15 to 16 of the decision) appear to be convincing. However, since the claims of both requests before the Board fail for another ground (see below), the Board will not give detailed reasons in these respects.

Article 56 EPC (Inventive step)
Main Request

15. According to the first paragraph of the specification of the patent in suit the invention relates generally to a method for treating immune disease associated with

excessive production of immunoglobulin E (IgE). It was generally known that the "normal" immune response of IgE is triggered by and directed against an infection by parasites but there are about 10% of humans which suffer from an IgE response which has nothing to do with an infection by parasites and causes what is called an allergy (patent in suit, page 2, column 1, lines 35 to 40). This can be considered as common general knowledge.

16. Since the claims are directed to a pharmaceutical composition, the Board agrees with the appellant to consider the already existing pharmaceutical preparations containing glucocorticoid steroids mentioned in column 2, lines 35 to 58 of the patent in suit as the closest prior art. They have deleterious side-effects on the health of the patients and the technical problem to be solved can be defined as the provision of an alternative pharmaceutical composition for the treatment of immune disorders associated with excessive IgE production in humans.

17. The Opposition division has based their finding of lack of inventive step on the combined disclosure of document (28) and (38). Since, contrary to the view of the first instance, the Board does not consider the latter document to have been publicly available at the priority date of the patent in suit (see points 1 to 9 above), it will in the following be examined whether or not the technical teaching of any other document on file, be it separately or in combination with common general knowledge, makes obvious the subject-matter of claim 1 of this request.

18. The skilled person being confronted with the problem of allergy caused by the production of IgE without an infection by parasites (see above point 15) would be aware of document (9) which discloses the role of IL-4 in the induction of human IgE synthesis and the antagonistic effect of interferon-γ. In Figure 1 on page 365, the supernatants of T cell clones are shown to be able to induce IgE synthesis in human B cells *in vitro* and, on page 366 (last sentence of the first full paragraph), in commenting on Figure 1, IL-4 is said to always be present in supernatants active in IgE synthesis, whereas it is virtually undetectable from inactive supernatants. Even if, as argued by the appellant, the last sentence on page 366 ("*Experiments are now in progress to establish whether IL-4 is acting alone or in concert with other lymphokines in the induction of IgE synthesis*") may indicate that the mode of action of IL-4 in the stimulation of IgE synthesis was still to be investigated, the skilled person is, nevertheless, provided by document (9) with the crucial teaching of the existence of a causal link between IL-4 and IgE synthesis in humans by the penultimate sentence on page 366 stating that "*Taken together, these data suggest that IL-4 probably plays an important role in the induction of IgE synthesis by TCC SN and that its IgE helper activity is modulated by IFN-g*". Furthermore, the addition of interferon-γ to B cell cultures is shown in document (9) on page 366 (second full paragraph and Table 2) to induce a dose-dependent inhibition of the IL-4 induced IgE synthesis. Interferon-γ is hence an antagonist of IL-4 within the meaning of this term given in document (4), a medical dictionary reflecting the common general knowledge of the skilled person, as

"*a substance which tends to nullify the action of another substance*".

19. The teaching of document (9) in combination with common general knowledge is hence an incentive for the skilled person to prepare pharmaceutical compositions containing interferon-γ as an alternative to those already available and containing glucocorticoid steroids to antagonize the effects of IL-4 on IgE synthesis in humans and leads in an obvious manner to the subject-matter of claims 1 and 8 of the main request which does not meet the requirements of Article 56 EPC.

Auxiliary request

20. Claim 1 of the auxiliary request results from the introduction into claim 1 as granted of the subject-matter of claim 2 and identifies the antagonist to IL-4 as a monoclonal antibody to IL-4, a fragment thereof or a binding composition comprising the heavy chain variable region and light chain variable region thereof.

21. The closest prior art and the problem to be solved remain, in the Board's judgement, the same as for the main request and it has to be examined whether or not it makes a difference for the answer to the question of inventive step that the claims now define as an antagonist to IL-4 a monoclonal antibody, a fragment thereof or binding composition of heavy variable or light variable chains of it.

22. As in the case of the main request, the skilled person is provided by the disclosure of document (9) with the

knowledge of the causal correlation between IL-4 and the stimulation of IgE synthesis and of an antagonistic effect by interferon-γ. An immediate consequence of this is the knowledge that any kind of inhibitory (or antagonistic) action on IL-4 will result in a disappearance of its stimulating effect on IgE synthesis. It is part of the basic knowledge of the skilled person in the field of immunology and treatment of allergic disorders that a possible antagonist for a given molecule is the corresponding antibody.

23. Furthermore, in document (28), which describes the preparation and characterisation of recombinant murine and human IL-4 from page 26 (second paragraph) to page 28 (first two lines), antibodies raised against murine or human IL-4 are said to be antagonists of these molecules. Thus the combined teaching of documents (9) and (28), which enables the skilled person to identify IL-4 as a causal factor involved in the stimulation of IgE synthesis in humans and to envisage the use of antibodies to IL-4 as antagonist, leads in an obvious manner to the subject-matter of claim 1 of the auxiliary request.

24. The skilled person is also re-affirmed in reaching this conclusion by the teaching of document (5) on the antagonistic effect of monoclonal antibody "11B11" on the stimulation of IgE synthesis in mice by murine IL-4, thus defining a similar system in which an antibody to IL-4 antagonizes the stimulating effect of IL-4 on IgE synthesis. The argument submitted by the appellant that this antibody cross-reacts with a 14 kD molecule is not relevant in the context of the **stimulation** of IgE synthesis by IL-4 or of its **inhibition** by antibodies

directed to IL-4, since said 14 kD fragment is shown in document (12) from page 430 (last paragraph) to page 431 (first paragraph) to be structurally and functionally unrelated to IL-4, and, in particular, this fragment is said to fail to inhibit the binding of IL-4 to its receptor (page 430, last full sentence), so that said fragment does not interfere with the IL-4 caused stimulation of IgE synthesis.

25. In view of the foregoing, the Board concludes that the subject-matter of claim 1 of the auxiliary request can be deduced in an obvious manner from the combined teaching of documents (9) and (28) and thus does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona U. Kinkeldey