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D E C I S I O N
of 22 October 2001

Case Number: T 1045/98 - 3.3.4

Application Number: 89311322.5

Publication Number: 0367596

IPC: A61K 39/395

Language of the proceedings: EN

Title of invention:
Antagonist to interleukin-5 for preventing or reducing eosinophilia

Patentee:
SCHERING CORPORATION

Opponent:
SmithKline Beecham plc, Corporate Intellectual property, SB House

Headword:
Eosinophilia/SCHERING

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no)"

Decisions cited:
T 0606/89, T 0241/95, T 0377/95, T 0158/96, T 0333/97

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1045/98 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 22 October 2001

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 25 August 1998 revoking European patent No. 0 367 596 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: L. Galligani
S. U. Hoffmann

Summary of Facts and Submissions

I. The appeal was lodged by the patent proprietors against the decision of the opposition division issued on 25 August 1998 whereby the European patent No. 0 367 596, which had been opposed by one party under Article 100(a) to (b) EPC, was revoked pursuant to Article 102(1) EPC.

Claim 1 as **granted** read:

"The use of an antagonist to human interleukin-5 in the manufacture of a pharmaceutical composition for preventing or reducing eosinophilia in a patient."

Dependent claims 2 to 6 concerned particular embodiments of the use according to claim 1.

The opposition division decided that, while the requirements of sufficiency of disclosure and novelty were met, none of the requests on file (a main request and three auxiliary requests) involved an inventive step, in particular in the light of the following documents:

(1) J. Immunol., Vol. 141, No. 5, September 1988, pages 1576 to 1581;

(2) J. Exp. Med., Vol. 167, January 1988, pages 219 to 224.

II. On 23 December 1998, with the statement of grounds of appeal, the appellants submitted a new main request and a first auxiliary request.

III. In reply to the statement of grounds of appeal the respondents (opponents) made written submissions with new documents, including the declarations of Professors C. J. Sanderson, A. B. Kay and A. F. Lopez.

IV. In reply thereto, the appellants filed additional documents including the declaration by Professor G. J. Gleich.

V. On 25 September 2001, the board issued a communication with an outline of the points to be discussed.

VI. Oral proceedings took place on 22 October 2001. A new main request and a second auxiliary request were filed. An amendment to the first auxiliary request already on file (cf Section II above) was introduced, namely the replacement of the expression "capable of" by the word "for".

Claim 1 of the **main request** read:

"The use of an antagonist to human interleukin-5 in the manufacture of a pharmaceutical composition for preventing eosinophilia in a patient."

Claim 1 of the **first auxiliary request** read:

"The use, in the manufacture of a pharmaceutical composition for preventing eosinophilia in a patient, of an antagonist of human interleukin-5 selected from a monoclonal antibody capable of blocking the biological activity of human interleukin-5, a fragment of a monoclonal antibody capable of blocking the biological activity of human interleukin-5, and a binding composition comprising the heavy-chain variable region

and light-chain variable region of a monoclonal antibody capable of blocking the biological activity of human interleukin-5."

Claim 1 of the **second auxiliary request** was identical to claim 1 of the first auxiliary request but it contained at the end the expression "by reducing the production of eosinophils and their accumulation in tissues".

VII. In addition to the documents already cited above, the following documents are referred to in the present decision:

(7) J. Exp. Med. Vol. 167, January 1988, pages 43 to 56;

(8) Proc. Natl. Acad. Sci. USA, Vol. 84, May 1987, pages 2761 to 2765;

(10) The New England Journal of Medicine, September 3, 1987, pages 593 to 598;

(11) "Eosinophils - A Comprehensive Review, and Guide to the Scientific and Medical Literature", C. J. F. Spry 1988, Oxford University Press, Oxford (GB), pages 10 to 28;

(21) Proc. Natl. Acad. Sci. USA, Vol. 84, October 1987, pages 6629 to 6633;

(35) Immunological Reviews, No. 102, 1988, pages 29 to 50;

(55) J. Exp. Med., Vol. 163, May 1986, pages 1085

to 1099;

(59) "The Cytokine Handbook", Chapter 7 "Interleukin-5", 1991, Academic Press Ltd., pages 149 to 167;

(60) Blood, Vol. 73, No. 6, May 1, 1989 pages 1504 to 1512.

VIII. The appellants pointed out that, while treatment of eosinophilia in the prior art was based on the use of glucocorticosteroids, the patent in suit proposed treating patients with an antagonist of IL-5, which was a totally different approach. In their view, it was not proper to combine the knowledge of the previous drugs with that about IL-5 as there were no apparent links between eosinophilia and IL-5. The patent in suit reported results of an *in vivo* experiment which supported the feasibility of the proposed approach. There were no reports in the prior art of *in vivo* attempts to interfere with the activity of IL-5. A skilled person in 1988 did not consider it to be established which molecule was responsible for eosinophilia as a number of different factors were known to be involved in eosinophilopoiesis. Furthermore, no one would have thought that only one factor would be responsible (cf documents (7), (8), (10), (11), (35)). Document (35) stated, for example, in the conclusions (ibidem page 46, first paragraph) that the art was still a long way from understanding the control of eosinophilia. Thus, the knowledge existing in 1988 would have given no expectation that an IL-5 antagonist would have produced *in vivo* a drastic reduction in eosinophils as shown in the example of the patent in suit. The fact that IL-5 was a cytokine with a variety of important functions (B cell

growth, B cell differentiation, T cell differentiation, IL-2 receptor induction etc.) would have deterred the skilled person from administering an IL-5 antagonist to a patient. The neutralisation effect shown in document (7) was an *in vitro* effect. Based thereupon, the skilled person would not have been in the position of reasonably predicting that by specifically blocking *in vivo* IL-5 by administering eg a monoclonal antibody eosinophilia would be stopped. Later evidence (cf eg document (59)) confirmed the experiment reported in the patent in suit had illustrated the unique role of IL-5 in the control of eosinophilia in parasite infection (ibidem, page 157, last paragraph) and that this was a valuable contribution to the art (cf eg document (60)).

IX. The respondents argued that, the skilled person, in the light of the *in vitro* experiments reported in document (7), would have considered *in vivo* experiments in mice to be the next obvious step to try. There were no reasons not to proceed to such experiments and not to expect success as the selectivity of IL-5 for eosinophils (cf eg document (2)), and its recognised site of action at the final step of eosinopoiesis (cf eg documents (7), (35) and (55)) and its primary role in eosinophilia (cf eg documents (21) and (35)) made it the primary candidate for inhibition by way of antagonism, in particular with monoclonal antibodies, which were available in the prior art (cf document (1)).

X. The appellants requested that the decision under appeal be set aside and that the patent be maintained on the basis of either the main request filed during oral proceedings or on the basis of the first auxiliary request filed on 23 December 1998 where in claim 1 the

expression "capable of" was replaced by the word "for" during oral proceedings or on the basis of the second auxiliary request filed during oral proceedings.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

The main request

1. Although the respondents indicated at oral proceedings with reference to "reasons on record" that they had objections also as regards novelty and sufficiency of disclosure, the key controversial issue in the present case is that of inventive step.

2. The definition of the skilled person (or team) is not a controversial point as both parties consider that the expertise of an average person acquainted with work both in clinical practice and research has to be taken as a reference.

3. The definition of "eosinophilia" is also not controversial: it is a pathological condition characterised by an increased number of eosinophils in the blood and/or tissues (cf eg declaration of Prof Gleich dated August 2001, point 5, which was submitted by the appellants, and the declaration of Professor C. J. F. Spry dated 23 March 1998, page 3, last paragraph, which was submitted by the respondents).

4. Controversial is the question which prior art document should be used as a starting point for the evaluation of inventive step. The appellants are of the opinion that, in view of what is claimed, the closest prior art

is represented by the known use of glucocorticosteroids for the treatment of eosinophilia, no reference being made to any particular document. The respondents consider that both documents (2) and (35) are suitable springboards for an analysis of inventive step.

5. In line with the case law of the boards of appeal (cf eg T 606/89 of 18 September 1990; cf also Case Law of the Boards of Appeal, 3rd edition 1998, page 111 of the English version), the board considers that the most suitable starting point has to be a document which differs from the claimed subject-matter by a minimum number of structural and functional features, and is concerned with the same purpose or effect. As claim 1 at issue is essentially directed - in the form of a second (further) medical use type of claim - to the use of an antagonist to human interleukin-5 (IL-5) for preventing eosinophilia in a patient, in the board's judgement, document (7), which shows in a murine *in vitro* model that the dose-dependent eosinophilopoietic effect of IL-5 was neutralised specifically by anti-IL-5 antibody, represents the most appropriate starting point.

6. In the light of the said prior art document, the underlying technical problem is the preparation of a pharmaceutical composition for the prevention of eosinophilia in humans.

7. As a solution, claim 1 proposes using an antagonist to human interleukin-5 in the manufacture of a pharmaceutical composition for preventing eosinophilia in a patient.

8. The patent in suit reports an *in vivo* experiment in

mice which shows that animals treated with an anti-IL 5 antibody had a reduced number of eosinophils in the blood and in the lung in comparison with untreated animals, this being indicative of a prevention of parasite-induced eosinophilia. It is an accepted principle of the case law that, for the purpose of patent protection of a medical application of a substance, a pharmacological effect or any other effect such as an effect observed either *in vitro* or on animal models is considered to provide sufficient evidence of a therapeutic application if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application (cf T 158/96 of 28 October 1998 and T 241/95, OJ EPO 2001, 103). Based upon the said principle, it can be accepted in the present case that, in the absence of any data on human patients, the *in vivo* experiment in mice renders plausible that the solution proposed in claim 1 solves the underlying technical problem as stated above.

9. The key question is in essence whether the skilled person, starting from document (7), would have reasonably expected - based on the knowledge of the biological effects of IL-5 on eosinophils in mice and humans - that the *in vivo* administration to mice of an anti-IL-5 antibody would have resulted in the prevention of eosinophilia. An affirmative answer to this question would automatically imply, based on the above stated principle, which is by the same token applicable also to prior art considerations, a reasonable expectation of the same effect also in humans.

10. As regards the effect of IL-5 on eosinophils, there were a number of indications in the prior art that,

although IL-5, G-CSF and IL-3 participated in eosinophilopoiesis, IL-5 supported the terminal differentiation and proliferation of eosinophil precursors (cf eg documents (2), (7), (35)). Document (7) itself stated inter alia: "IL-5 specifically facilitated the terminal differentiation and amplification of eosinophils. This mechanism of eosinophilopoiesis may be responsible for the urgent mobilization of eosinophils during helminthic infections and allergic responses" (ibidem page 53, third paragraph; see also Figure 4). Document (35) reported also the *in vivo* observation that in mice the development of eosinophilia was preceded by detectable levels of IL-5 (referred to as EDF) in serum, no IL-3 being detected in serum at any stage of the infection (ibidem page 34, Figure 1 and paragraph at the bottom). Document (2), which dealt with recombinant human IL-5 by measuring its function as an activator, also indicated in the discussion that it was the most likely factor responsible for the increase in eosinophil numbers (ibidem, page 222). Thus, although the role of other cytokines, in particular G-CSF and IL-3 in the cascade of events leading to eosinophil differentiation was recognised in the art (cf eg Figure 2.1 in document (11) as well as Figure 4 in document (7)), IL-5 was generally seen as **the** factor having a specific role in the final stages, in particular in the amplification phase, and, possibly a role, in the regulation of eosinophilia (cf document (21), in particular last sentence of the abstract).

11. The appellants emphasized that uncertainties in the prior art did not allow an unambiguous link between IL-5 and eosinophilia. In their view, for example, the results in Table V of document (7) did not exclude a

role of IL-3. Moreover, they submitted that from the report in document (35) of detectable levels of IL-5 in the serum of mice subjected to infection, no detectable levels of IL-3 being found, one would not have derived a specific role of IL-5 in eosinophilia because the determinations were done in serum, not in bone marrow where eosinophils are actually produced. The same document concluded that there could be other hemopoietic growth factors involved. As for document (2), it concerned the selective function of human IL-5 as an activator of the eosinophil function, not of their proliferation or amplification.

12. In the board's judgement, although there was no definite proof in the art that maturation of eosinophils did not require factors other than IL-5, there were sufficient indicia of a selective role of IL-5 in the process of terminal differentiation and proliferation of eosinophils so as to direct the skilled person's attention to this cytokine. None of the observations above (cf point 11) would have affected the skilled person's perception of the selective role played by IL-5.

13. In view of this, the skilled person, who knew from the disclosure of document (7) of the antagonist effect *in vitro* of an anti-IL 5 antibody on the eosinophilopoietic activity of IL-5, would have readily considered that the *in vivo* test in mice was the next experiment to try.

14. The question here is whether the skilled person would have envisaged any obstacles, difficulties or pitfalls which would have made *in vivo* experiments either impossible to carry out or so uncertain in their

outcome that any expectation of success would be abandoned.

15. As a factor which would have deterred the skilled person from making the *in vivo* test in mice, the appellants referred to the fact that, as IL-5 is a cytokine with a variety of biological activities (eg as a B-cell growth factor has an effect on the immune system), the skilled person would have expected, for example, the administration of IL-5 *in vivo* to induce defects in B and T cell functions. Moreover, they submitted that the skilled person would have considered such a test as unpromising and would have had strong reservations about its outcome because, in view of the multiplicity of factors involved in eosinophilia, one would not have expected that just acting on one factor would have prevented eosinophils from accumulating in tissues.

16. In the board's judgement, the skilled person, although knowing that IL-5, as an endogenous humoral factor, was involved in a number of complex biological processes of activation and regulation, and although aware that any interference which such phenomena could result in adverse responses by the organism, would not have been deterred from testing in an *in vivo* animal model the activity of an antagonist which had been shown by document (7) to have a dose-dependent effect in an *in vitro* model. In bio-medical sciences, studies *in vitro* wherein a given product is shown to have a biological effect, are normally, and logically, followed by experiments *in vivo* in an animal model where the effect can be tested in the more complex context of a living organism. One of the purposes of such animal models, from the simplest to the more complex, is indeed to

serve as an intermediary step before clinical testing in patients, thus as a sort of barrier between potentially harmful products and human exposure. Thus, as already stated, far from being deterred, the skilled person would have considered the *in vivo* testing in mice as being the next logical step. The question here is rather whether this test would have been approached by the skilled person with scepticism, with a neutral attitude or with some expectation of success.

17. Although - as stated eg in document (35) - the control of eosinophilia was not completely understood at the date of the invention and an univocal link between eosinophilia and IL-5 was not yet demonstrated, the skilled person had good indications from the prior art (cf points 10 and 12 above) that IL-5, being involved in the final stages of eosinophilopoiesis, was **the** factor likely to be responsible for the increase in eosinophil numbers in response to infection. Although knowing that *in vitro* experiments cannot mimic the *in vivo* settings and that *in vitro* results are not always confirmed upon *in vivo* testing, the skilled person would have perceived the experiment reported in document (7) which showed *in vitro* dose-dependent neutralisation of the eosinophilopoietic effect of IL-5 by anti-IL-5 antibody as being encouraging, also in view of the raised IL-5 levels observed *in vivo* in mice infected with a parasite (cf document (35)). Thus, in spite of the understandable uncertainties which always characterise biological experiments, the skilled person had no reasons to adopt a sceptical attitude. He or she would have had either some expectations of success or, at worst, no particular expectations of any sort, but only a "try and see" attitude, which - as pointed out eg in decisions T 333/97 of 5 October 2000 and T 377/95

of 24 April 2001 - does not equate with an absence of a reasonable expectation of success.

18. For these reasons, claim 1 is found to lack an inventive step and thus the request of which it is part is not allowable under Article 56 EPC.

The first auxiliary request

19. Claim 1 of this request differs from claim 1 of the main request in that the nature of the antagonist is specified as being a monoclonal antibody capable of blocking the biological activity of human interleukin-5, a fragment of a monoclonal antibody capable of blocking the biological activity of human interleukin-5, and a binding composition comprising the heavy-chain variable region and light-chain variable region of a monoclonal antibody capable of blocking the biological activity of human interleukin-5.

20. Since the antagonist used in document (7) was an anti-IL-5 monoclonal antibody, and monoclonal antibodies capable of blocking the activity of human IL-5, including the one used in the patent in suit, were known in the art (cf document (1)), no inventive step can be acknowledged to this request for the same reasons given above in relation to the main request. The request is therefore not allowable under Article 56 EPC.

The second auxiliary request

21. Claim 1 of this request differs from claim 1 of the first auxiliary request only in that it contains as an additional feature at the end of the claim the

expression "by reducing the production of eosinophils and their accumulation in tissues".

22. The added feature is merely the definition of eosinophilia (cf point 3 above) and as such cannot contribute to inventive step. Thus, for the reasons already given, this request lacks an inventive step and is not allowable under Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairperson:

P. Cremona U. Kinkeldey