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# D E C I S I O N
## of 21 May 1996

**Case Number:** T 0379/94 - 3.3.4

**Application Number:** 88300407.9

**Publication Number:** 0276120

**IPC:** A61K 37/66

**Language of the proceedings:** EN

**Title of invention:**
Treatment of certain leukemias with a combination of gamma interferon and alpha interferon

**Patentee:**
SCHERING CORPORATION

**Opponent:**
Boehringer Ingelheim International GmbH

**Headword:**
IFN γ+α/SCHERING

**Relevant legal provisions:**
EPC Art. 54, 56

**Keyword:**
"Inventive step (no)"

**Decisions cited:**
G 0006/88, T 0149/93, T 0249/88, T 0455/91

**Catchword:**
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**Case Number:** T 0379/94 - 3.3.4

**D E C I S I O N**
**of the Technical Board of Appeal 3.3.4**
**of 21 May 1996**

**Appellant:** (Opponent)
Boehringer Ingelheim
International GmbH
D-55216 Ingelheim (DE)

**Representative:**
-

**Respondent:** (Proprietor of the patent)
SCHERING CORPORATION
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**Representative:**
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**Decision under appeal:**
**Decision of the Opposition Division of the European Patent Office posted 17 February 1994 rejecting the opposition filed against European patent No. 0 276 120 pursuant to Article 102(2) EPC.**

**Composition of the Board:**

**Chairman:** U. M. Kinkeldey
**Members:** R. E. Gramaglia
J.-C. Saisset

## Summary of Facts and Submissions

I. European patent No. 0 276 120 with application No.88 300 407.9 was granted on the basis of claims 1 to 7.

II. An opposition was filed on the grounds, in Article 100(a), of lack of novelty and lack of inventive step having regard in particular to the following documents:

(1) W.R. Fleischmann, Intracellular Communications, vol. 2, pages 58-71 (1986)

(2) J.H. Schiller et al., Cancer Research, vol. 46, pages 483-488 (1986)

(3) H. Denz et al., J. Interferon Research, vol. 5, pages 147-157 (1985)

(4) C.W. Czarniecki et al., J. Virology, vol. 49, pages 490-496 (1984)

III. By its decision issued in writing on 17 February 1994, the Opposition Division rejected the opposition. Independent claims 1 and 2 read as follows:

"1. The use of recombinant human alpha interferon in the manufacture of a pharmaceutical composition for use in inhibiting the proliferation of susceptible human lymphoma derived B cell leukaemia cells by a combination therapy involving simultaneously or sequentially treating such cells with an effective amount of a combination of recombinant human alpha interferon and recombinant human gamma interferon."

"2. The use of recombinant human gamma interferon in the manufacture of a pharmaceutical composition for use in inhibiting the proliferation of susceptible human lymphoma derived B cell leukaemia cells by a combination therapy involving simultaneously or sequentially treating such cells with an effective amount of a combination of recombinant human alpha interferon and recombinant human gamma interferon."

Dependent claims 3 to 7 relate to specific embodiments.

IV. The Appellant (Opponent) filed a notice of appeal against this decision with the payment of the fee on the same day and filed a Statement of Grounds of Appeal. The Respondent (Proprietor of the patent in suit) filed counterarguments.

V. Oral proceedings took place at 21 May 1996. Because he considered that it was clarified in the summons which points will be dealt with in details at the oral proceedings, the Respondent informed the Board in due time that he will not be represented at the oral proceedings.

VI. During the opposition and written appeal proceedings the Appellant provided no detailed submission in relation to novelty. Yet a new line of argument mainly based on decision G 6/88 (OJ EPO 1990, 114) was submitted at the oral proceedings. Decision G 6/88 acknowledged the novelty of a use of a known compound for a particular purpose, which was based on a technical effect, provided that such technical effect had not previously been made available to the public. Claims 1 and 2 of the patent in suit, however, were concerned with a known use of a known composition relying on an effect that has been made available to the public. Therefore, the novelty had to be denied.

As regarded the inventive step issue, the Appellant's position can be summarized as follows:

It was strongly contested that the man skilled in the art could not predict that the combination of interferon-α and interferon-γ would have shown a synergistic effect on human lymphoma derived B cell leukaemia cells. Firstly, documents (1) to (4) already disclosed the synergistic effect the patent in suit relied on. In particular, document (3) showed the synergistic effect of a combination of interferon-α and interferon-γ in inhibiting the proliferation of the lymphoma B cell line U 266 and of lymphoma T-cells MOLT 4.

Therefore the man skilled in the art could reasonably have drawn the conclusion that the combination of interferon-α and interferon-γ exhibited a synergistic inhibition of the proliferation of lymphoma leukaemia cells in general. Secondly, obviousness was not only at hand when the results were clearly predictable, but also when there was a reasonable expectation of success and it was only necessary to confirm experimentally that the highly probable result was in fact obtained. This position was confirmed by Boards of Appeal decisions T 149/93 of 23 March 1995 and T 249/88 of 14 February 1989 (both not published in the OJ EPO) and T 455/91 (OJ EPO 1995, 684).

VII. The Respondent argued that at the priority date of the patent in suit it could not have been forecast with any reasonable expectation of success that the claimed treatment of B cell leukaemia cells with a combination of interferon-α and interferon-γ would have been a synergistic and effective treatment for this particular type of blood malignancy. None of the prior art documents disclosed or rendered obvious (either alone

or in combination with other documents) the use of a synergistic composition comprising interferon-α and interferon-γ (to be used either simultaneously or sequentially) for inhibiting the proliferation of human derived lymphoma B cell leukaemia cells. Document (1) was concerned with investigations on the effects of a mixture of interferon-α and interferon-γ upon mouse P388 cells, which were lymphocytic leukaemia cells. These cells belonged to a macrophage cell line. Therefore they had nothing to do with B cells. B cells and macrophages were two distinct types, the former being of lymphoid origin while the latter were of myeloid origin. As regarded cell line U266 of document (3), Figure 6 thereof did not show a synergistic effect of interferon-α and interferon-γ. The results for cancer cells other than human lymphoma B cell leukaemia cells were inconclusive. The Appellant had not made credible that the results obtained with lymphoma T-cell could be extrapolated to leukaemia B-cells. It could not be taken for granted that T-cells and B-cells exhibited on their surface the same receptors, and even if this was the case, that the intracellular response would have been the same. For instance, document (1) showed activation of P388 macrophages by interferons but inhibition of natural killer cells (NK). If one took into account a mixture of two cytokines, it had to be expected that the effect thereof on a cell line was even less predictable.

VIII. The Appellant requested that the decision of the Opposition Division be set aside and that the patent be revoked. The Respondent requested in his written statement filed on 26 August 1994 that the decision of the Opposition Division of 17 February 1994 be confirmed and that the patent be maintained as granted and that the appeal be dismissed.

## Reasons for the Decision

1. The appeal is admissible.

*Novelty (Article 54 EPC)*

2. The Appellant based the opposition in his opposition brief on Articles 54 and 56 EPC and the Opposition Division dealt in its contested decision with both issues. In the written proceedings before the Appeal Board the Appellant filed no detailed observations in relation to novelty. During oral proceedings the novelty question was raised again with a completely new line of arguments. Whether or not this is admissible in view of the fact that the Respondent was not represented at oral proceedings and, consequently has not had an opportunity to present counterarguments, may be left aside in the light of the Board's finding on inventive step (see section V above and points 3 to 11 hereinafter).

*Inventive step (Article 56 EPC)*

*Closest prior art*

3. Documents (1) to (4) illustrate the potentiation of the antitumour activity of interferon-γ used together with interferon-α on cell lines of various histogenesis. Document (1) shows this effect on a murine lymphocytic leukaemia cell line P388 (see Section 3.2.2 on page 59). Document (2) discloses the same effect, **inter alia**, on seven cancer cell lines of human origin (see page 483, "Abstract" and page 486, "Discussion"). A further passage (see page 483, r-h column, first paragraph) discloses that a synergistic antiproliferative effect by application of interferon-α

and interferon-γ has been observed for mouse leukaemic L-1210 cells and mouse B16 melanoma cells. In document (3) the above synergistic effect is shown for hematologic malignancy cell line U 937 and marginally for the T-cell line MOLT 4 (see page 147, "Abstract"). Document (4) shows the synergistic effect of a combination of interferon-α and interferon-γ in inhibiting the proliferation of human Hs294T melanoma cells. A proper starting point for a problem to be solved seems to be a disclosure which relates to a synergistic antiproliferative effect when applying interferon-γ and interferon-α to cell lines of human hematologic malignancy. In the Board's view this is represented by document (3).

*Problem to be solved and its solution*

4. In the light of the disclosure of document (3), the problem to be solved lies in the effective inhibition of the proliferation of human lymphoma derived B cell leukaemia cells responsible for one type of human leukaemia. Its solution is provided by the simultaneous or sequential administration of a synergistic combination of interferon-γ and interferon-α. Having regard to Table III of the patent in suit, the Board is satisfied that the claimed use solves the above problem.

5. The Parties' approach (see Sections VI and VII **supra**) to the inventive step question as a matter of "reasonable (or not reasonable) expectation of success", is agreed by the Board and thus it has to be decided the issue of whether the skilled person would have expected a combination of interferon-α and interferon-γ to exhibit a synergistic effect in inhibiting the proliferation of a cell line of

hematologic malignancy, the human lymphoma derived B cell leukaemia, having regard to the prior art.

6. From documents (2) and (3) the skilled person could deduce a rough rate of success in synergistically inhibiting the proliferation, when a pattern of cells never previously subjected to a combined interferon treatment, is subjected to said treatment. Document (2) (see point 4 above) establishes synergistic effects on 7/7 cell lines tested, while document (3) shows the same effects on 2/7 cell lines tested (see page 156, line 8 from the bottom) and the two susceptible cell lines originated from hematologic malignancies. The Board observes that this success rate is roughly comparable with the one that can be deduced from the patent in suit, wherein 3/8 of the cell lines tested showed a synergistic effect (see page 3, lines 29 to 34 and Table III on page 7).

7. The Board further observes that as to the synergistic effect in reducing malignant cell proliferation by a combination of interferon-α and interferon-γ, there was a consensus before the priority date of the patent in suit that the interferon combination therapy for combatting cancer was worth being tried in general, as for example stated in document (4), page 495, last passage: "...there is now established a rational optimism for the use of combination IFN preparations in antiviral and antitumour therapy.". For the skilled person, said optimism is derivable not only from the finding that said synergistic effect turned up in quite a number of malignant cell lines of various histogenesis (see point 4 **supra**), but also from the finding that the rate of success was reasonably high.

8. Having regard to the score of success, the Board has to define as being reasonable the expectation of success by the skilled person that a combination of interferon-α and interferon-γ would have exhibited a synergistic effect in inhibiting the proliferation of another cell type of hematologic malignancy, namely human lymphoma derived B cell leukaemia.

9. The Respondent did not submit arguments aiming at showing a possible general conviction by the skilled person that cells from hematologic malignancies and in particular leukaemia cells were resistant to the combined interferon therapy. The Board rather arrives at the opposite conclusion, once the prior art literature (see point 4 **supra**) is borne in mind: at least four cells responsible for hematologic malignancies were known to be synergistically inhibited by application of a combination of interferon-α and interferon-γ, namely mouse leukaemia cells P388 and L-1210 as well as human cell lines U 937 and MOLT 4.

10. The Board concedes that any particular tumour cell's reaction to a combination treatment of various interferons, here interferon-α and interferon-γ, cannot be predicted with certainty and that the effect of any cytokine on a particular cell depends not only on the presence or absence of receptors for that cytokine on the cell surface, but also on the type of signal generated intracellularly if the receptor for that cytokine is present. However, it is not the certain predictability that leads the skilled person to try to apply a teaching of the prior art to something different, but rather the reasonable expectation of success. This is given.

11. The Board has thus to conclude that the subject matter of independent claims 1 and 2 does not fulfil the requirements of Article 56 EPC.

## Order

**For these reasons it is decided that:**

1. The decision under appeal is set aside

2. The patent is revoked

The Registrar: The Chairwoman:

L. McGarry U. Kinkeldey