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D E C I S I O N
of 12 October 2000

Case Number: T 0400/99 - 3.3.4

Application Number: 84308710.7

Publication Number: 0146354

IPC: C12N 15/23

Language of the proceedings: EN

Title of invention:
Recombinant gamma interferons and pharmaceutical compositions containing them

Patentee:
GENENTECH, INC.

Opponent:
Amgen Inc.

Headword:
Gamma Interferons/GENENTECH

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
"Novelty (yes): claimed subject-matter not directly and unambiguously derivable from the prior art"
"Inventive step (yes)"

Decisions cited:
T 0181/82, T 0296/87, T 0197/86

Catchword:
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Case Number: T 0400/99 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 12 October 2000

Appellant: (Opponent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 21 January 1999 concerning maintenance of European patent No. 0 146 354 in amended form.**

Composition of the Board:

Chairman: U. M. Kinkeldey
Members: R. E. Gramaglia
C. Holtz

Summary of Facts and Submissions

I. The appeal lies against the decision of the opposition division maintaining European patent No. 0 146 354 (application No. 84 308 710.7) on the basis of the claims of the first auxiliary request comprising 26 claims for all designated Contracting States, except AT (non-AT States) and 21 claims for the Contracting State AT. Claim 1 for the non-AT States read as follows:

"1. A gamma interferon polypeptide consisting of the amino acid sequence, extending from the N-terminus:

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X-Y-ASP-PRO-TYR-VAL-LYS-GLU-ALA-GLU-ASN-LEU-LYS-LYS-TYR-PHE-
  1  2   3   4   5   6   7   8   9   10  11  12  13  14  15
ASN-ALA-GLY-HIS-SER-ASP-VAL-ALA-ASP-ASN-GLY-THR-LEU-PHE-LEU-
 16  17  18  19  20  21  22  23  24  25  26  27  28  29  30
GLY-ILE-LEU-LYS-ASN-TRP-LYS-GLU-GLU-SER-ASP-ARG-LYS-ILE-MET-
 31  32  33  34  35  36  37  38  39  40  41  42  43  44  45
GLN-SER-GLN-ILE-VAL-SER-PHE-TYR-PHE-LYS-LEU-PHE-LYS-ASN-PHE-
 46  47  48  49  50  51  52  53  54  55  56  57  58  59  60
LYS-ASP-ASP-GLN-SER-ILE-GLN-LYS-SER-VAL-GLU-THR-ILE-LYS-GLU-
 61  62  63  64  65  66  67  68  69  70  71  72  73  74  75
ASP-MET-ASN-VAL-LYS-PHE-PHE-ASN-SER-ASN-LYS-LYS-LYS-ARG-ASP-
 76  77  78  79  80  81  82  83  84  85  86  87  88  89  90
ASP-PHE-GLU-LYS-LEU-THR-ASN-TYR-SER-VAL-THR-ASP-LEU-ASN-VAL-
 91  92  93  94  95  96  97  98  99 100 101 102 103 104 105
GLN-ARG-LYS-ALA-ILE-HIS-GLU-LEU-ILE-GLN-VAL-MET-ALA-GLU-LEU-
106 107 108 109 110 111 112 113 114 115 116 117 118 119 120
SER-PRO-ALA-ALA-LYS-THR-Z
121 122 123 124 125 126
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wherein X is a methionine residue, Y is a glutamine residue and Z consists of n amino acids in the sequence 127-143 depicted in Fig. 1 hereof where n is zero or an integer of 1 to 17, but excluding as an isolated polypeptide the Lys^{78} variant polypeptide having the above-recited sequence where X = methionine,

Y = glutamine, and

Z = Gly-Lys-Arg-Lys-Arg-Ser-Gln-Met-Leu-Phe-Arg-Gly-Arg-Arg-Ala-Ser-Gln,
127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143

or the Gln^{137} variant thereof; or X is hydrogen, Y is either a glutamine or pyroglutamate residue and Z consists of n amino acids in the sequence 127-143 depicted in Fig. 1 hereof where n is zero or an integer of from 1 to 16; or a modification or allelic variation of said amino acid sequence which (modification or variation) exhibits biological activity equivalent to or greater than that of gamma interferon of the amino acid sequence 1-143 depicted in Fig. 1 hereof, but excluding those of the said modifications or variations which contain any gamma interferon amino acid sequence contiguously upstream of Y or contiguously downstream of Z."

Dependent claims 2 to 26 related to specific embodiments of claim 1. Claims 1 to 21 for the Contracting State AT were drafted as corresponding process claims.

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

(A1) WO-A-83/04053;

(A2) Alton K. et al., The Biology of the Interferon System, De Maeyer and Schellekens Editors, Elsevier Science Publishers B.V., pages 119-128 (1983).

III. Oral proceedings were held on 12 October 2000.

IV. The submissions by the appellant can be summarized as follows:

Added subject-matter (Article 123 (2) EPC)

- The claims extended beyond the content of the application as filed.

Novelty (Article 54 EPC)

- Document (A1) directly and unambiguously disclosed the compound Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-IFN-γ variant covered by claim 1 of the patent in suit, wherein X = Met, Y = Gln and n = 17, for the following reasons:

  The passage bridging pages 48 and 49 of document (A1): "Other classes of IFNγ analogs consists of polypeptides wherein the [Trp^{39}] residue is replaced by [Phe^{39}], and/or wherein one or more of the methionine residues at amino acid positions 48, 80, 120 and 137 are replaced by, e.g., leucine, and/or wherein cysteines at amino acid positions 1 and 3 are replaced by, e.g., serine or are completely eliminated."

  showed that the generic classes of modifications to be made on human IFN-γ were designed to be carried out either alone or in conjunction with another class of modification (cf "and/or"). As one class of modifications, the passage of document (A1) on page 49, lines 1 to 3 mentioned "..and/or wherein cysteines at amino acid positions 1 and 3 are replaced by, e.g., serine or are completely eliminated". This cysteine replacement/deletion class was illustrated by three examples on page 49, line 33 to page 50, line 13, one of which was the Met^{-1}, des-[Cys^1-Tyr^2-

Cys^3]-Lys^{81}-IFN-γ variant. Although each of the illustrative Cys replacement/elimination compounds additionally included a Lys^{81} substitution, the latter was a separate and distinct class of modification (see page 47, lines 28-30). Therefore, the use of the term "and/or" made clear that any illustrated modification within each class, such as the des-[Cys^1-Tyr^2-Cys^3] modification within the cysteine replacement/deletion class could be carried out alone, thus yielding des-[Cys^1-Tyr^2-Cys^3]-IFN-γ.

- The separate nature of each class of modification was further confirmed by the statement on page 49, lines 33 to 35: "Replacement or deletions of cysteines at positions 1 and 3 involves only alteration of subunit IF-4." which gave the skilled person instruction to only alter subunit IF-4. Therefore, upon assembling a DNA encoding for an IFN-γ analog using the modified IF-4 referred to on page 50, lines 9-13:

  5'-ATC CAG-3'
  3'-TAC GTC-5'

  encoding Met^{-1}-Gln^4- in the amino acid specifying region, along with subunits IF-1, IF-2 and IF-3 of Table IV, the skilled person would have inevitably arrived at a DNA encoding Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-IFN-γ.

- The disclosure of document (A1) did not lend itself to be viewed as a traditional case involving a generic chemical formula containing multiple substituents R1, R2, R3, etc., because the presence of said substituents was not required.

- The fact that claim 1 also covered modifications and allelic variants of the amino acid sequence stated therein, had the consequence that if one modified what was disclaimed, the so modified variants would have fallen under claim 1 (ie, the disclaimer lost its distinguishing power). Therefore, document (A1) disclosed Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-IFN-γ variants which were not excluded by the disclaimer in claim 1 of the patent in suit.

Inventive step (Article 56 EPC)

- The proper question to be addressed was whether the skilled person was motivated to make a gamma interferon analog containing the Met^{-1}, des-[Cys^1-Tyr^2-Cys^3] modification without the [Lys^{81}] modification. The biological activity data reported in Table VI on page 52 of document (A1) provided a specific incentive for preparing an analog containing the Met^{-1}, des-[Cys^1-Tyr^2-Cys^3] modification alone. These data showed that the [Lys^{81}] modification alone reduced the biological activity by about 50%, while the further introduction of the des-[Cys^1-Tyr^2-Cys^3] modification improved its biological activity by 20%. The skilled person would thus have recognized that the des-[Cys^1-Tyr^2-Cys^3] modification alone would have achieved inter alia an activity-increasing effect.

- The skilled person would have understood from page 49, lines 3-6 that analogs exhibiting a deletion/replacement of cysteines at positions 1 and 3 would have been more stable and more easily isolated due to the lack of intermolecular disulphide bridges.

- The provision of C-terminal truncated variants covered by the claims of the patent in suit was obvious because these variants were already contemplated in document (A1), page 28, lines 25 to 32 and by reference [8] cited on page 5, line 42 of the patent in suit. These C-terminal truncated variants also did not solve any technical problem since C-terminal truncation reduced activity (page 6, line 3 and Table 1 of the patent in suit).

IV. The submissions by the respondent can be summarized as follows:

Novelty (Article 54 EPC)

- Document (A1) did not directly and unambiguously disclose the compound Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-IFN-γ variant as covered by claim 1 of the patent in suit, wherein X = Met, Y = Gln and n = 17, for the following reasons:

- The expression in claim 1 "exhibits biological activity equivalent to or greater than" was a distinguishing feature vis-à-vis the interferons-γ having a Cys^1-Tyr^2-Cys^3-structure disclosed by document (A1).

- Document (A1) did not direct the skilled person to make the specific embodiment Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-IFN-γ out of all the myriad embodiments covered by the generality of the original disclosure. This individualised embodiment was not specifically disclosed in Example 5 of this document. Therefore, the claimed embodiment was just one among the myriad of possible "examples".

- Even taking the elimination of cysteines at positions 1 and 3 as representing a particular class of modification of its own right, it would embrace more embodiments (> 400) than simply deleting Cys^1-Tyr^2-Cys^3. For instance one could remove the two cysteines by leaving Tyr^2 in place or replaced with another amino acid.

- The statement on page 49, lines 33 to 35:

  "Replacement or deletions of cysteines at positions 1 and 3 involves only alteration of subunit IF-4."

  was not an instruction to alter only IF-4. It did not direct the skilled person to synthesize the DNA encoding Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-IFN-γ because it opened the way to more embodiments (> 400) than simply deleting Cys^1-Tyr^2-Cys^3.

Inventive step (Article 56 EPC)

- The motivation of removing [Cys^1-Tyr^2-Cys^3] in order to achieve higher activity and stability was absent from documents (A1) and (A2). The only suggestion given in document (A1) was that elimination or replacement of the cysteines (nothing was said about Tyr^2) could facilitate the isolation of these variants since no intermolecular disulphide bridges would have formed.

- Table VI of document (A1) would not have motivated the skilled person to make a gamma interferon analog containing the Met^{-1}, des-[Cys^1-Tyr^2-Cys^3] modification without the [Lys^{81}] modification because the data there indicated a trend toward lowering the activity.

- The data of Table VI of document (A1) were in contradiction with those of Table 3 of document (A2), which showed that there was a 30% drop in activity by further introduction of the des-[Cys^1-Tyr^2-Cys^3] modification to [Lys^{81}] variant, instead of the improvement by 20% (Table VI of document (A1)).

- It could not be predicted that C-truncation would have resulted in retention of biological activity.

V. The appellant (opponent) requested that the decision under appeal be set aside and that the patent be revoked.

The respondent (patentee) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Article 123(2) EPC

2. At the oral proceedings, the appellant sought to object that the claims extended beyond the content of the application as filed. The board, however, refused to allow this issue into the proceedings pursuant to Article 114 (2) EPC, as it had not been submitted in due time, the respondent had not had the opportunity to assess it or to provide its own counterarguments, and its relevance was not immediately apparent.

Novelty

3. The board agrees that the specific embodiment Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-IFN-γ is not mentioned expressis verbis in document (A1). The question to be answered, however, is whether or not this compound is nevertheless directly and unambiguously derivable from said document.

4. Turning to the passages of document (A1) relied upon by the appellant for questioning the novelty, the board views them as comparable to generic chemical formulae containing multiple substituents R1, R2, R3, etc., contrary to the appellant's contention. This is because the wording:

"Other classes of IFNγ analogs consists of polypeptides wherein the [Trp^{39}] residue is replaced by [Phe^{39}], and/or wherein one or more of the methionine residues at amino acid positions 48, 80, 120 and 137 are replaced by, e.g., leucine, and/or wherein cysteines at amino acid positions 1 and 3 are replaced by, e.g., serine or are completely eliminated." (paragraph bridging pages 48 and 49 of document (A1)),

interpreted in the light of the paragraph on page 49, line 33 to page 50, line 13, relating to three examples of replacement/deletion of the cysteines at positions 1 and 3, is susceptible of being expressed in an equivalent but more concise manner under the form of a generic chemical formula, for example:

Met^{-1}-R1-R2-R3-U1-R39-U2-R48-U3-R80-R81-U4-R120-U5-R137-U6

wherein R1 to R137 are the amino acid substituents at the positions indicated in the cited passages or the "native" residue (cf. the "and/or"), wherein R1 and/or R3 or R1 to R3 may additionally represent a covalent

bond (ie, residues R1 and/or R3 or R1 to R3 are absent) and wherein U1, U2, U3, U4, U5 and U6 designate, for the sake of simplicity, the unaltered stretches of IFN-γ. Both the "phrased" version, ie, the cited passages of document (A1) and the above more concise "formula" version, having identical content as regards the technical information which can be derived therefrom, **conceptually** cover several hundreds of possible IFN-γ variants and are interchangeable for the purpose of the present decision.

5. It is jurisprudence of the Boards of Appeal that a class of chemical compounds, defined only by a general structural formula having one or more variable group(s) does not specifically disclose each and any of the individual compounds which would result from the **mental** combination of all possible variants within such group(s). Rather, the novelty of an individual chemical compound can only be denied if there is a direct and unambiguous disclosure in the prior art of this very same compound in the form of a technical teaching (see T 181/82, OJ EPO 1984, 401, No. 8 of the reasons, and T 296/87, OJ EPO 1990, 195, Nos. 6 and 7 of the reasons).

6. Turning to the present case, it is therefore not sufficient for denying novelty of the claims at issue covering Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-IFN-γ, that the latter compound belongs conceptually to the group of possible variants embraced by the cited passages of document (A1) and its equivalent, more concise formula set out above, unless there is a direct and unambiguous pointer in the prior art document to this individual member. When applying this principle to document (A1), it turns out that Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-IFN-γ is neither exemplified, nor specifically mentioned, nor the inevitable result of carrying out the instructions

disclosed. Under these circumstances, in accordance with the rationale emerging from decision T 181/82 (loc. cit.) and T 296/87 (loc. cit.), it must be concluded that there is no direct and unambiguous disclosure in the prior art of this compound in the form of a technical teaching. Consequently, the subject-matter of claim 1 and dependent claims 2-26 meets the requirements of Article 54 EPC. This conclusion also applies to claims 1-21 for the Contracting State AT.

7. The appellant argues that Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-IFN-γ is the inevitable result of carrying out the instructions given on page 49, lines 33-34 of document (A1) to "only alter subunit IF-4" and to assemble a DNA encoding for an IFN-γ analog using the IF-4 along with subunits IF-1, IF-2 and IF-3 of Table IV, which DNA yields upon expression this protein. In the board's judgement, however, this passage cannot be considered as an instruction to alter **only** subunit IF-4 since it does not per se exclude the possibility of modifying one or more of subunits IF-1, IF-2 and IF-3 of Table IV. There is also no teaching in document (A1) that combining modified subunit IF-4 with unmodified subunits IF-1, IF-2 and IF-3 of Table IV is a privileged direction to be followed, among the remaining hundreds of possible mental combinations, when making IFN-γ variants. Under these circumstances, the conclusion cannot be drawn that Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-IFN-γ is the inevitable result of carrying out the instructions given in document (A1).

8. The appellant maintains that document (A1) discloses Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-IFN-γ variants which are not excluded by the disclaimer in claim 1 of the patent in suit. However, in the board's view, claim 1 also requires that any variant should "exhibit biological

activity equivalent to or greater than that of gamma interferon of the amino acid sequence 1-143 depicted in Fig. 1 hereof". Since the experimental results referred to in Table VI on page 52 of document (A1) show that the alterations proposed in document (A1) are all deleterious to the biological activity, the above expression in claim 1 is a distinguishing feature vis-à-vis any interferons-γ variant disclosed by document (A1).

Inventive step (Article 56 EPC)

9. The closest prior art is represented by document (A1) relating to various Cys^1-Tyr^2-Cys^3-IFN-γ variants. This document comprises on page 49, lines 1 to 6, a suggestion to replace or eliminate Cys^1 and/or Cys^3 for avoiding intermolecular bonds, and hence for facilitating isolation of the variants. This cysteine replacement/deletion class is illustrated by three examples on page 49, line 33 to page 50, line 13, one of which is Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-Lys^{81}-IFN-γ. The problem to be solved by the patent in suit is to provide IFN-γ variants that are more active and more stable than the prior art ones (see eg the patent in suit on page 5, lines 33-35 and page 12, lines 40-43). In view of the experimental results of Table 2 and Fig. 3 showing respectively the superior antiproliferative activity and stability of des-[Cys^1-Tyr^2-Cys^3]-IFN-γ compared with those of Cys^1-Tyr^2-Cys^3-IFN-γ, the board is satisfied that the above problem is solved by the claimed subject-matter.

10. Departing from the disclosure of document (A1), the proper question to be addressed is whether the skilled person is motivated to make an IFN-γ analog containing the Met^{-1}, des-[Cys^1-Tyr^2-Cys^3] modification without the [Lys^{81}] modification or in general to go into the

direction of removing Cys^1-Tyr^2-Cys^3 **alone**, optionally in the presence of a C-terminal truncation, in order to solve the problem of providing IFN-γ variants that are more active and more stable than the prior art ones.

11. The board observes that document (A1) opens the way to a great number (several hundreds) of possible variants. There is no pointer for the skilled person to go into the direction of removing Cys^1-Tyr^2-Cys^3 alone in order to obtain IFN-γ variants that are more active and more stable than the prior art ones. Rather, the experimental results referred to in Table VI on page 52 of document (A1) show that the alterations, including removing Cys^1-Tyr^2-Cys^3 proposed in this Table are deleterious to the biological activity: if anything, this fact does not appear to be encouraging for somebody looking for more active compounds.

12. It is true that the document comprises on page 49, lines 1 to 6 a suggestion to replace or eliminate Cys^1 and/or Cys^3 for avoiding intermolecular bonds, and hence for facilitating isolation of the variants. However, nothing is said about the destination of Tyr^2 or about the necessity of effecting this change alone. Therefore, a suggestion cannot be derived from this passage to eliminate Cys^1-Tyr^2-Cys^3 alone, optionally in the presence of a C-terminal truncation, in order to obtain IFN-γ variants that are more active and more stable than the prior art ones.

13. The appellant argues that C-terminal truncation is either already contemplated in the prior art or reduces activity and, hence, these C-terminal truncated variants do not involve an inventive step.

14. In the board's judgement, however, even assuming that the C-terminal truncation is an obvious measure already contemplated in the prior art, the des-[Cys^1-Tyr^2-Cys^3] feature shared by all the claimed compounds, as seen above, is not.

15. As for the reduction of biological activity achieved by C-terminal truncation, it has to be noted that the distinguishing feature vis-à-vis the prior art is the des-[Cys^1-Tyr^2-Cys^3] feature exhibited by **all** the claimed compounds rather than the C-terminal truncation, which is an optional feature. It is this distinguishing feature which has to be responsible for the improved effect invoked in the patent in suit, following decision T 197/86 (OJ EPO 1989, 371). Therefore, the proper question to be answered in the context of the inventive step of C-terminal truncated variants is whether or not the des-Cys^1-Tyr^2-Cys^3 feature achieves an improved effect **also** for these C-terminal truncated variants. Reduction of the biological activity of Met^{-1}, des-[Cys^1-Tyr^2-Cys^3]-IFN-γ (see Table 1 of the patent in suit) upon C-terminal truncation, as invoked by the appellant, fails to provide an answer to this question and is therefore irrelevant. Rather, in order to deny the presence of an inventive step, the board must have been persuaded that the des-[Cys^1-Tyr^2-Cys^3] feature fails to achieve an improved effect in the case of C-terminal truncated variants, ie that a des-[Cys^1-Tyr^2-Cys^3], C-truncated IFN-γ variant is less active than the corresponding Cys^1-Tyr^2-Cys^3, C-truncated IFN-γ variant having the same C-terminal. However, since there is no evidence before the board that such is the case, the patentee should be given the benefit of doubt that the des-[Cys^1-Tyr^2-Cys^3] feature achieves an improved effect irrespective of C-terminal truncation. Hence, the

presence of an inventive step has to be acknowledged also for the claimed C-terminal truncated IFN-γ variants.

16. Therefore, it must be concluded that the claimed Cys^1-Tyr^2-Cys^3 deleted IFN-γ variants do not follow in an obvious fashion from the prior art. Consequently, the subject-matter of claim 1 and dependent claims 2-26 meets the requirements of Article 56 EPC. This conclusion also applies to claims 1-21 for the Contracting State AT.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

U. Bultmann U. M. Kinkeldey