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**D E C I S I O N**  
of 8 December 1999

**Case Number:** T 0658/98 - 3.3.4  
**Application Number:** 94113232.6  
**Publication Number:** 0645452  
**IPC:** C12N 15/24  
**Language of the proceedings:** EN

**Title of invention:**

Human interferon-beta 2A and interferon-beta 2B, vectors containing genes coding for said interferons, cell lines producing same and use of said interferons as pharmaceuticals

**Applicant:**

YEDA RESEARCH AND DEVELOPMENT CO. LTD.

**Opponent:**

-

**Headword:**

interferon-beta 2A/YEDA RESEARCH

**Relevant legal provisions:**

EPC Art. 123(2)

**Keyword:**

"Added subject-matter (yes)"

**Decisions cited:**

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**Catchword:**

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Case Number: T 0658/98 - 3.3.4

**D E C I S I O N**  
of the Technical Board of Appeal 3.3.4  
of 8 December 1999

**Appellant:** YEDA RESEARCH AND DEVELOPMENT CO.LTD.  
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**Decision under appeal:** Decision of the Examining Division of the  
European Patent Office posted 23 January 1998  
refusing European patent application  
No. 94 113 232.6 pursuant to Article 97(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 application No. 94 113 232.6, publication No. 0 645 452, with the title: "Human interferon-beta 2A and interferon beta 2B, vectors containing genes coding for said interferons, cell lines producing same and use of said interferons as pharmaceuticals" was filed as a divisional application of the earlier application No. 92 114 478.2 published under No. 0 536 520 which is itself a divisional application to the earlier application No. 86 114 049.9 published under No. 0 220 574. It was refused by the examining division pursuant to Article 97(1) EPC with decision dated 23 January 1998 on the grounds that the subject-matter of claim 1 on file extended beyond the content of the earlier application as filed and, thus, offended against Article 76(1) EPC.
- II. The appellants lodged an appeal against this decision, paid the appeal fee and submitted a statement of grounds for the appeal with a new main request and two auxiliary requests.
- III. A communication was sent by the board pursuant to Article 110(2) EPC, which outlined the provisional position of the board. This was answered by the appellants who filed a new main request.
- IV. Oral proceedings were summoned for 8 December 1999.
- V. At oral proceedings, the appellants filed a new main request and two auxiliary requests.

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

"1. A cDNA consisting essentially of a nucleotide sequence encoding the amino acid sequence of a mature biologically active interferon- $\beta_{2A}$  derivable from the amino acid sequence of Fig.1, said biologically active interferon- $\beta_{2A}$  being obtainable by in vitro translation of mRNA corresponding to the cDNA depicted in Fig.1 in reticulocyte lysate and contacting the in vitro translation product with dog pancreatic membranes."

Claim 1 of **auxiliary request 1** read as follows:

"1. A cDNA consisting essentially of a nucleotide sequence encoding the amino acid sequence of a **mature** biologically active interferon- $\beta_{2A}$  having a molecular weight of 21 Kd derivable from the amino acid sequence of Fig.1 by measuring hydropathicity along said sequence." (emphasis added)

Claim 1 of **auxiliary request 2** was identical to claim 1 of the first auxiliary request but for the fact that the word "mature" had been omitted.

VI. The appellants argued as follows:

*Main and first auxiliary requests:*

The application as originally filed, namely the application No. 86 114 049.9, explicitly provided disclosure for cDNA on page 9, lines 1 to 6 and Figure 1. Furthermore, it disclosed mature biologically active interferon- $\beta_{2A}$  as it provided on page 11, lines 6 to 36 at least two possible methods to obtain it. It was also clear from numerous passages in the description that means for expressing biologically active interferon- $\beta_{2A}$  were desired. The expression

"biologically active" meant the same as "mature biologically active" because in many cases of expressed pre-proteins, the pre-form was either completely inactive or less active than the mature, fully active protein.

There was also abundant implied disclosure which related to the N-terminus of the mature, biologically active interferon- $\beta_{2A}$ . The specification taught how to obtain it. Once obtained, the protein could be subjected to amino acid analysis. Furthermore, it was also taught that hydropathy plots could be used to compare interferon- $\beta_{2A}$  to other interferons. The skilled person would find out in this way that the first amino acid in the protein was Ala<sup>28</sup>. Thus, the identification of this amino acid as being Ile<sup>57</sup> in Figure 7 of the instant and the parental application would be considered as an obvious mistake.

From the above, it could be concluded that the subject-matter of claim 1 did not extend beyond the contents of the application as originally filed.

*Second auxiliary request*

Claim 21 as filed of the earlier application No. 86 114 049.9 provided indirect support for the expression of biologically active interferon- $\beta_{2A}$  also in procaryots since it did not specify that the host cells had to be eukaryotic. As expression in procaryots could only be achieved from cDNAs which were smaller than the isolated cDNA encoding a 23.5 Kd protein, it was manifest that the application intended to cover cDNAs encoding biologically active interferon- $\beta_{2A}$  as claimed in claim 1.

VII. The appellants requested that the decision under appeal be set aside and that a patent be granted on the basis of the main, first auxiliary or second auxiliary request filed at the oral proceedings on 8 December 1999.

### Reasons for the Decision

1. The appeal is admissible.

*Claim 1, main and first auxiliary requests;*

2. The present application as filed discloses on page 9 lines 1 to 6 with reference to Figure 1 the nucleotide sequence of a cDNA named IFN- $\beta_{2A}$ AE 20 which comprises an open reading frame of 212 amino acids, predicting a protein of 23.5 Kd. This open reading frame is longer than necessary to encode mature interferon- $\beta_{2A}$  which is defined on page 11, lines 21 to 26 as having a molecular weight of 21 Kd. The same identical passages and Figure are found in both the earlier applications No. 92 114 478.2 and No. 86 114 049.9. No other cDNAs are mentioned in these applications exception made for the two cDNA subfragments used to construct IFN- $\beta_{2A}$ AE 20. Thus, no explicit disclosure is provided of a cDNA consisting essentially of a nucleotide sequence encoding the amino acid sequence of mature interferon- $\beta_{2A}$  as claimed in claim 1.

3. The appellants argue that the application as filed makes mature interferon- $\beta_{2A}$  available because it provides on page 11, lines 16 to 20 a way to obtain it and it also provides on page 11, lines 33 to 36 a way to determine its NH<sub>2</sub> terminus starting from Figure 1. This, in their view, amounts to disclosing the corresponding cDNA, albeit implicitly.

4. The board observes that the description indeed provides on page 11, lines 16 to 20 the information that mature interferon- $\beta_{2A}$  may be obtained by expressing the cloned IFN- $\beta_{2A}$ AE 20 cDNA in CHO cells. However, in the passage immediately below (lines 25 to 30), it is stated: "The N-terminus of the mature IFN- $\beta_{2A}$  21 Kd protein has not been determined and two potential glycosylation sites are present in the IFN- $\beta_{2A}$  sequence (Figure 1) making it difficult to calculate the size of the region removed by processing." Thus, it must be concluded that obtaining the mature protein and indicating its molecular weight is not sufficient *per se* to determine its N-terminus and, by implication, that it is not sufficient to determine the size of the corresponding cDNA.
5. With regard to the possibility of finding out the N-terminus of the mature protein by carrying out hydropathicity studies, it must be observed that such an experimentation would not have been considered necessary by the skilled person, since the first amino-acid of the protein is defined in Figure 7 of the parental and divisional applications as Ile<sup>57</sup>. Had the skilled person nonetheless carried out such studies and found out that, as now submitted by the appellants, the first amino acid was Ala<sup>28</sup>, he/she would necessarily have concluded that the application as filed was misleading with regard to the identity of said first amino acid and, by implication, with regard to the primary structure of the corresponding cDNA.
6. Thus, the application as filed fails to provide a clear and unambiguous characterisation of mature interferon- $\beta_{2A}$ . By way of consequence, it also fails to provide an implicit disclosure of the cDNA encoding the mature protein.

7. In the absence in the application as filed, of any explicit or implicit disclosure of the cDNA consisting essentially of the nucleotide sequence encoding mature interferon- $\beta_{2A}$ , it must be concluded that claim 1 of both the main request and the first auxiliary request, which relates to said cDNA, offends against Article 123(2) EPC.
8. For these reasons, the main request and the first auxiliary request are rejected.

*Second auxiliary request*

9. Claim 1 of this request is directed to a cDNA encoding a biologically active interferon-beta<sub>2A</sub> of a molecular weight of 21Kd which need not be mature interferon-beta<sub>2A</sub>.
10. As stated in paragraph 2 above, the application as filed does not disclose any other cDNA than the cDNA which encodes the 23.5 Kd protein. Thus, there is no explicit support in the application as filed for the cDNA of claim 1.
11. A 21Kd biologically active interferon-beta<sub>2A</sub> is mentioned on page 11, lines 20 to 21 of the application as filed. In the passage which follows (lines 22 to 26), this interferon is compared in size with the processed **mature** form of interferon made from human fibroblasts, as well as with the 21 Kd **mature** interferon obtained in vitro by treating the primary translation product of interferon-beta<sub>2A</sub> RNA with dog pancreatic membranes. Reading this passage leaves no doubts that the molecular weight of 21Kd is a feature of the otherwise uncharacterised **mature** interferon-beta<sub>2A</sub>. As stated in paragraphs 2 to 6 above, there is no adequate disclosure even of the cDNA of mature



interferon-beta<sub>2A</sub> having a molecular weight of 21Kd, and this is the only interferon-beta<sub>2A</sub> having a molecular weight of 21 Kd mentioned at all. There is thus no basis for a claim to a cDNA of interferon-beta<sub>2A</sub> of molecular weight of 21Kd, whether mature or not.

12. The appellants argued that the invention as disclosed in the parental application No. 86 114 049.9 comprised cDNA encoding a 21Kd interferon-beta<sub>2A</sub> other than mature interferon-beta<sub>2A</sub> because claim 21 then on file read:

" A cell line transformed by a recombinant vector according to one of the claims 10 to 20",

said claims 10 to 20 being directed to various embodiments of a recombinant vector comprising a DNA sequence encoding interferon-beta<sub>2A</sub> of unspecified size. In their view, the skilled person would understand from claim 21 that expression in procaryots of active interferon-beta<sub>2A</sub> was part of the invention. This, in turn, implied that the use of a cDNA shorter than the one encoding the precursor 23.5Kd interferon was also disclosed as only expression from such a cDNA was likely to result in active interferon-beta<sub>2A</sub> being synthesized by procaryots.

13. The board understands this argument as being raised in relation to Article 76(1) EPC which states that the subject-matter of the European divisional application may not extend beyond the content of the earlier application as filed. This, in itself would have to be given close consideration as the instant application does not derive **directly** from application No. 86 114 049.4 but merely **indirectly** "through" the divisional application No. 92 114 478.2 (which never contained any claim equivalent to claim 21). However, the point need not be decided nor the validity of the

argument be assessed. This is because the subject-matter of the said claim 21 of the earliest parental application was left out of the present application on filing and so cannot be taken into account for the purpose of finding a fair basis under Article 123(2) EPC for present claim 1. As already stated above in paragraphs 10 and 11, the present application does not contain any explicit or implicit disclosure of the subject-matter of claim 1. Claim 1, therefore, offends against Article 123(2) EPC.

14. The second auxiliary request is thus rejected for failing to fulfill the requirements of Article 123(2) EPC.

**Order**

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

The appeal is dismissed

The Registrar:

The Chairman:

A. Townend

L. Galligani