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D E C I S I O N
of 15 June 2004

Case Number: T 0189/01 - 3.3.4

Application Number: 90110487.7

Publication Number: 0413908

IPC: C12P 21/02

Language of the proceedings: EN

Title of invention:
Soluble extracellular fragment of the human IFN-beta 2/IL-6 receptor, its preparation and pharmaceutical compositions containing it

Patentee:
YEDA RESEARCH AND DEVELOPMENT COMPANY LIMITED

Opponent:
Chugai Pharmaceutical Co., Ltd.

Headword:
IFN-beta 2/IL-6R/YEDA RESEARCH AND DEVELOPMENT CO., LTD.

Relevant legal provisions:
EPC Art. 114(2), 123(2), 83, 56
EPC R. 88

Keyword:
G 0009/91, G 0001/92, G 0001/03, T 0952/92, T 0728/98

Decisions cited:
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Case Number: T 0189/01 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 15 June 2004

Appellant I: (Proprietor of the patent)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 19 January 2001 concerning maintenance of European patent No. 0413908 in amended form.**

Composition of the Board:

Chairman: S. C. Perryman
Members: A. L. L. Marie
M. R. J. Wieser

Summary of Facts and Submissions

I. European patent No. 0 413 908, claiming priority from IL 90488 (1 June 1989) and IL 92444 (26 November 1989), was granted on the basis of 19 claims, claims 1 and 13 of which read:

"1. Soluble extracellular fragment of human natural interferon β2/interleukin-6 receptor having the following N-terminal amino acid sequence:

Leu-Ala-Pro-Arg-Arg-Cys-Pro-Ala-Gln-Glu-Val-Ala-Arg-Gly-Val-Leu-Thr-Ser-Leu-Pro-Gly-Asp-Ser-Val-Thr-Leu-Thr-Cys-Pro-Gly-

(herein designated IFN-β2/IL-6R), salts, functional derivatives and active fractions thereof having said N-terminal sequence and mixtures of any of the foregoing, being able to specifically bind IFN-β2/IL-6."

"13. An antibody against the IFN-β2/IL-6R soluble extracellular fragment of claim 1 which specifically recognizes said fragment."

II. An opposition was filed on the grounds of Article 100(a)(b) EPC for lack of novelty (Article 54 EPC) and inventive step (Article 56 EPC) and insufficiency of the disclosure (Article 83 EPC). The opposition division considered the subject-matter of a third auxiliary request containing 18 claims as novel in the meaning of Article 54(3) EPC over the disclosure of document (1)(*cf infra*, section IX), the conflicting subject-matter of which was disclaimed, and as

involving an inventive step over the closest prior art represented by document (2), seen in conjunction with documents (7) or (8) and maintained the patent pursuant to Article 102(3) EPC. Claims 1, 2, 9, 13, 14 and 18 of said third auxiliary request read:

"1. Soluble extracellular fragment of human natural interferon β2/interleukin-6 receptor having the following N-terminal amino acid sequence:

Leu-Ala-Pro-Arg-Arg-Cys-Pro-Ala-Gln-Glu-Val-Ala-Arg-Gly-Val-Leu-Thr-Ser-Leu-Pro-Gly-Asp-Ser-Val-Thr-Leu-Thr-Cys-Pro-Gly-

(herein designated IFN-β2/IL-6R), salts, functional derivatives and active fractions thereof having said N-terminal sequence and mixtures of any of the foregoing, being able to specifically bind IFN-β2/IL-6, provided that the extracellular fragment of IFN-β2/IL-6R is not a fragment consisting of amino acid 20 to 323 or 20 to 344 of IFN-β2/IL-6 receptor."

"2. The human IFN-β2/IL-6R soluble extracellular fragment according to claim 1 in substantially purified from."

"9. A DNA molecule having the nucleotide sequence coding for the IFN-β2/IL-6R soluble extracellular fragment of any one of claims 1 to 4 and 8, or for a protein substantially homologous therewith, provided that said nucleotide sequence does not encode an interferon-I-β2/IL-6R [sic] fragment

consisting of amino acids 1 to 323 or amino acids 1 to 344, respectively."

"13. A process for producing antibody against the IFN-β2/IL-6R soluble extracellular fragment comprising immunisation of an animal using the soluble extracellular fragment of claim 1."

"14. The process according to claim 13, wherein the process further comprises the preparation of hybridomas in compliance with the conventional hybridoma technique."

"18. Use of the fragment according to claims 1 to 4 for preparing a medicament for stimulating and enhancing beneficial effects of IFN-β2/IL-6, such as its antiproliferative activity."

III. Notices of appeal against the decision of the opposition division were filed by both the patentee (appellant I) and the opponent (appellant II). Both appellants filed their statements of grounds of appeal and an exchange of arguments took place in writing between the parties.

IV. The Board sent a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal concerning issues related to the disclaimers and oral proceedings were scheduled on 15 June 2004.

V. With his letter of 17 May 2004, appellant I submitted a new main request and three auxiliary requests. He further indicated that four accompanying persons were

to attend the oral proceedings and requested that they be allowed to address the Board when appropriate.

VI. Appellant II (letter of 1 June 2004) requested that the submission of appellant I of 17 May 2004, which he only received on 26 May 2004, not be allowed into the proceeding as late-filed or, alternatively, that the scheduled oral proceedings be postponed.

VII. On the afternoon preceding the oral proceedings, appellant II submitted, as an attempt to answer the submission of appellant I of 17 May 2004, a document in the Japanese language with a translation of a part of it into English. This document was withdrawn during the oral proceedings.

VIII. During the oral proceedings, appellant I withdrew all the claim requests already on file and submitted a new main request with 21 claims, which differed from the claims maintained by the opposition division by the presence of claims 15 to 17 directed to antibodies, claims 16 and 17 being dependent on claim 15 which read:

"15. An antibody against IFN-β2/IL-6R soluble extracellular fragment which specifically recognizes said fragment, wherein said IFN-β2/IL-6R soluble extracellular fragment contains the following N-terminal amino acid sequence:

Leu-Ala-Pro-Arg-Arg-Cys-Pro-Ala-Gln-Glu-Val-Ala-Arg-Gly-Val-Leu-Thr-Ser-Leu-Pro-Gly-Asp-Ser-Val-Thr-Leu-Thr-Cys-Pro-Gly,

wherein said antibody is capable of inhibiting the hybridoma growth factor (HGF) activity of IFN-β2/IL-6."

IX. The following documents are cited in the present decision:

(1) EP-0 325 474

(2) K. Yamasaki et al., Science, 1988, Vol. 241, pages 825 to 828

(7) D.V. Weber et al., Journal of Chromatography, 1988, Vol. 431, pages 55 to 63

(8) D.H. Smith et al., Science, 1987, Vol. 238, pages 1704 to 1707

(12) I.M. Roitt et al., "Immunology", 2nd edition, 1989, Gower Medical Publishing, London, New York, page 25.8

(16) T. Taga et al., Cell, 1989, Vol. 58, pages 573 to 581

X. The arguments submitted by appellant I, as far as they apply to the subject-matter of the claims of the main request submitted during the oral proceedings or to the claims maintained by the opposition division, can be summarized as follows:

Correction under Rule 88 EPC: in claim 9 of the set of claims maintained by the opposition division "*or*" should be inserted before "*for a protein substantially*

homologous therewith" to obviate an obvious grammatical error.

Article 114(2) EPC: the claims of the main request were an attempt to meet the objections of appellant II. Claims 15 to 17, which were directed to antibodies to the soluble extracellular fragment of human IFN-β2/IL-6R, could not have taken appellant II by surprise, because such antibodies were already the subject-matter of claims 13 to 15 as granted.

Article 123(2) EPC: the disclaimer introduced into claim 9 in both claim requests to a nucleotide sequence coding for a soluble IFN-β2/IL-6R fragment consisting of amino acids 1 to 323 or amino acids 1 to 344 followed the principles defined in decision G 1/03 (8 April 2004) and precisely removed the conflicting subject-matter of document (1) while meeting the requirements of conciseness and clarity. The absence of the expression "*which specifically recognizes...*" as a feature of the antibody produced by the process of claim 13 as maintained by the opposition division did not extend beyond the content of the application as filed, which indicated on page 7 (lines 20 to 21) that the invention related to antibodies against the soluble extracellular fragment without any reference to their specificity.

Article 123(3) EPC: the absence of the expression "*which specifically recognizes...*" as a feature of the antibody produced by the process of claim 13 as maintained by the opposition division did not extend the scope of protection conferred by the granted patent, since it was the aim of any immunisation

technique to obtain antibodies which specifically recognized the antigen used for the immunisation and appellant II had not provided any evidence to the contrary. Claim 14 as maintained by the opposition division was dependent upon claim 13 and its scope was not rendered broader than that of the latter by the introduction of the expression "*in compliance with the conventional hybridoma technique*".

Article 83 EPC: the argument of appellant II of the non-enabling character of the disclosure of the patent in suit lacked substantiation. The objection against the expression "*in substantially purified form*" as used in claim 2 of the new main request and of the claims maintained by the opposition division was in fact an Article 84 EPC objection and hence was not admissible in opposition proceedings, since this expression was already in claim 2 as granted.

Article 84 EPC: no evidence was provided by appellant II in support of his allegation that laboratories around the world used their own techniques to prepare hybridomas and there was no "*conventional hybridoma technique*" as mentioned in claim 14. On the contrary, document (12), a standard textbook on immunology published in 1989 and reflecting the common general knowledge at the priority date of the patent in suit, outlined the three-step conventional method of Milstein and Köhler.

Article 56 EPC: the purpose of the patent in suit was to find a binding partner for IL-6 and the disclosure of document (2) did not give any incentive that a soluble fragment could be such a partner. The skilled

person would not have combined the teaching of document (2) with that of documents (7) or (8) which concerned interleukine-2 (IL-2) and CD4, respectively, ie molecules structurally and functionally unrelated to IL-6.

As far as claim 18 of the new main request and as maintained by the opposition division was concerned, document (16) neither described nor suggested the preparation of a medicament, but was only concerned with scientific aspects of the signal transduction of IL-6. Furthermore, the stimulation of the beneficial effects of IFN-β2/IL-6 by the soluble extracellular fragment of IFN-β2/IL-6R was an unexpected effect.

XI. The arguments of appellant II, as far as they apply to the subject-matter of the new main request or to the claims maintained by the opposition division, can be summarized as follows:

Article 114(2) EPC: appellant II was taken by surprise by the subject-matter of claims 15 to 17 of the main request submitted during the oral proceedings, which were directed to antibodies raised against the soluble fragment of IFN-β2/IL-6R and by the corresponding claims of the main request and auxiliary requests I and II submitted with the letter of 17 May 2004, because the claims maintained by the opposition division or respectively filed by appellant I in his grounds of appeal and subsequent submissions up to 17 May 2004 were directed to only a process for producing such antibodies. Moreover, the sets of claims filed with the letter of 17 May 2004 had only been received on 26 May 2004, ie less than three weeks before the scheduled

oral proceedings. This late submission prevented appellant II from making counterexperiments or further investigations in the scientific literature or from developing an appropriate response with the assistance of technical experts.

Rule 88 EPC: no objection was raised against the correction requested in claim 9 as maintained by the opposition division.

Article 123(2) EPC: the disclaimer in claim 9 should be extended to a nucleotide sequence coding for amino acids 20 to 323 or amino acids 20 to 344 in order to remove the conflicting subject-matter of document (1).

The absence in process-claim 13 as maintained by the opposition division of the expression "*which specifically recognizes said fragment*" extended beyond the subject-matter of the application as filed, because it now covered also cross-reacting antibodies.

Article 123(3) EPC: through the absence of the feature "*which specifically recognizes said fragment*", the antibodies produced by the process of claim 13 as maintained by the opposition division were different from those defined in claim 13 as granted, since they embraced antibodies cross-reacting with other proteins. The introduction in claim 14 of the expression "*in compliance with the conventional hybridoma technique*" extended the scope of protection beyond that of the claims as granted.

Article 83 EPC: the unclear character of the expression "*in substantially purified form*" used claim 2

(reference was made to decision T 728/98 (EPO OJ 2001, 319)) made it impossible for the skilled person to determine whether an IL-6R protein that might be obtainable according to the teaching of the patent in suit was in said substantially purified form. Furthermore, should the subject-matter of the claims be considered as involving an inventive step over document (2), then the requirements of Article 83 EPC were not met, since the skilled person who was not in a position to produce a soluble extracellular fragment of IL-6R from document (2), would not have been in a better position to produce this fragment given the teaching of the patent in suit.

Article 84 EPC: there was no such "*conventional hybridoma technique*" as now referred to in claim 14, since laboratories around the world were using each their own differing techniques. There was no evidence that document (12), introduced by appellant I to underline the existence of such a conventional technique, was published before the priority date of the patent in suit.

Article 56 EPC: the closest prior art was document (2) which disclosed the cloning and expression of human IL-6R and identified in Figure 4b the various domains of the coding sequence. The technical problem to be solved was the provision of a soluble form of IL-6R capable of binding to IL-6. The common general knowledge described in the first priority document of the patent in suit under the heading "*Background of the invention*" taught the skilled person that an effective way to eliminate the negative effects of IL-6 was to prepare a soluble form of its receptor, so that the subject-matter of

claim 1 was deducible in an obvious manner from document (2) considered in conjunction with the common general knowledge.

Alternatively, the combination of the teaching of document (2) with that of documents (7) or (8) on the purification of soluble forms of interleukin-2 receptor (IL-2R) by affinity chromatography on matrix-bound IL-2 or the blocking of the CD4-mediated HIV infectivity by a soluble form of CD4, led in an obvious manner to the subject-matter of claim 1.

Claim 18 as maintained by the opposition division could not enjoy the priority right of the first priority document, because it was directed to a stimulation of the beneficial effects of IFN-β2/IL-6, whereas the disclosure of the first priority document only focused on the neutralisation of the negative effects of IFN-β2/IL-6. Therefore, document (16), which disclosed on page 577 the enhancing effect of soluble IFN-β2/IL-6R fragment on the antiproliferative activity of IFN-β2/IL-6, was prior art in the meaning of Article 54(2) EPC. The subject-matter of claim 18 was hence directly derivable from document (16) considered in combination with document (1) indicating the promising character of the soluble IFN-β2/IL-6R fragment as therapeutic and diagnostic agent.

XII. Appellant I (patentee) requested as main request that the decision under appeal be set aside and that the patent be maintained on the basis of the claims of the main request submitted at oral proceedings on 15 June 2004 or as auxiliary request that the appeal of appellant II (opponent) be dismissed and further that

claim 9 as maintained by the opposition division be amended pursuant to Rule 88 EPC by the insertion in line 2 of "or" before "for a protein".

XIII. Appellant II (opponent) requested that the decision under appeal be set aside and that the European patent No. 0 413 908 be revoked.

Reasons for the Decision

New main request

Admissibility of the new main request

1. Claims 15 to 16 of the new main request submitted during the oral proceedings of 15 June 2004 are directed to an antibody against an IFN-β2/IL-6R soluble extracellular fragment, as were the corresponding claims of the main request and the auxiliary requests 1 and 2, submitted with the letter of 17 May 2004 and withdrawn during the oral proceedings.

2. Appellant II has argued that the late submission of claims directed to antibodies, whereas all the previous submissions from appellant I contained claims directed to a process for the preparation of such an antibody, took him by surprise and prevented him to prepare an adequate answer thereto.

3. A chronological analysis of the events from the time of the decision of the opposition division until the oral proceedings before the Board shows the following:

(a) the main request considered by the opposition division as not complying with the requirements of Article 54(3) EPC contained claims directed to an antibody,

(b) the third auxiliary request, on the basis of which the patent in suit was maintained, contained claims directed to a process for producing an antibody,

(c) in his notice of appeal (letter of 28 February 2001), appellant I requested that the decision under appeal be set aside and the patent maintained on the basis of the claims of the main request mentioned above in paragraph (a) directed to antibodies,

(d) however, with his statement of grounds of appeal (letter of 29 May 2001) appellant II filed a new set of 18 claims, in which the claims directed to an antibody were replaced by claims to a process for preparing an antibody (claims 13 and 14) and the argumentation submitted (pages 2, 3 and 10) was accordingly related to a process for preparing an antibody,

(e) an amended form of process claim 13 was filed with the letter of 21 August 2003,

(f) with the letter of 17 May 2004, appellant I filed a new main request and two auxiliary requests with claims directed to an antibody, whereas the third auxiliary request contained claims directed to a process for preparing an antibody,

(g) the main request filed during the oral proceedings before the Board also contained claims directed to an antibody.

This chronological survey shows that appellant I, during a period of time exceeding three years from the time of the decision of the opposition division, only focused on claims directed to a process for producing an antibody and only a few weeks before the oral proceedings switched to claims directed to an antibody. Accordingly, from the time of the oral proceedings before the opposition division, ie 27 October 1999, until 17 May 2004 the argumentation of appellant II related to claims directed to a process for producing an antibody.

4. A party is not obliged to appeal on all points decided adversely to it, but Article 108 EPC requiring that the appellant file a written statement setting out the grounds of appeal within four months after notification of the decision, makes clear that the appellant must within this time limit indicate the reasons on which he is indeed challenging the decision under appeal. The appeal procedure is a judicial procedure whose main purpose is to give the losing party the possibility of challenging the decision of the Opposition Division on its merits (cf. decision G 9/91 of the Enlarged Board of Appeal (OJ EPO 1993, 408) at point 18). That it is a judicial procedure means that the appellant must inform the other parties and the board at the proper time, namely within the time limit set for filing the grounds of appeal, of his case on appeal. If the appellant in his grounds of appeal asks for less than he asked for

in his broadest request refused by the opposition division, and only gives reasons justifying the grant of the patent on this reduced request, the appellant cannot at some later stage of the appeal ask for a broader request than he at least arguably justified in the statement of grounds. To allow an appellant to do so would amount to allowing him to evade the provisions of Article 108 EPC, and to mislead the other parties and possibly put them at a serious disadvantage in preparing their case. This is not a question of depriving an appellant of any rights, but of ensuring that he exercises them in a fair and proper way. Whereas it may be legitimate subsequently to add further reasoning, it is not legitimate for a patentee appellant to ask for more than he sought in the grounds of appeal.

In the present case it was a matter of hot dispute before the opposition division whether the antibodies claimed as such were novel, whereas the novelty of the method of making them would already exist if the means used for this purpose were new. The opposition division in its decision decided against the novelty of the claims to the antibodies as such, and considered as novel only the claims for making antibodies, as the means used were new. Appellant I did not challenge this aspect of the decision under appeal in his grounds of appeal, but was content to put forward a request including only the process claims for making the antibodies allowed by the Opposition Division, but not claims to the antibodies as such. For Appellant I to be allowed to go back on this, and ask for claims to the antibody as such, would condone an evasion of the

requirements of Article 108 EPC. The main request is thus inadmissible.

The arguments of Appellant II concerning his being deprived of an opportunity to file evidence because of this filing at a very late stage of the requests including claims to the antibodies as such, merely serve to underline the procedural problems that allowing an evasion of Article 108 EPC would cause.

Auxiliary request (claims as maintained by the opposition division)

Correction under Rule 88 EPC

5. Appellant II and the Board agree with the request of appellant I to insert into claim 9, pursuant to Rule 88 EPC, the word "*or*" before "*for a protein*", since its absence is an obvious grammatical error and the correction proposed evident.

Article 123(2) EPC

6. Appellant II objected that the disclaimer introduced in claim 9 does not properly remove the subject-matter disclosed in document (1), since it only mentions a nucleotide sequence coding for a fragment consisting of amino acids 1 to 323 or amino acids 1 to 344. However, the soluble fragment of document (1) being deprived of the signal sequence, claim 9 should also contain a disclaimer to a nucleotide sequence coding for a fragment consisting of amino acids 20 to 323 or amino acids 20 to 344.

7. First of all, claim 9 is directed to a nucleotide sequence coding for the soluble fragment of claim 1. Since claim 1 already disclaims a fragment, the amino acid sequence of which extends from amino acids 20 to 323 or from amino acids 20 to 344, a nucleotide sequence coding for such a fragment is excluded from the subject-matter of claim 9.

8. Moreover, a soluble IFN-β2/IL-6R fragment has only been obtained in document (1) upon expression of plasmids pSVL345 and pSVL324 (Example 10) which contain nucleotide sequences coding for proteins extending from amino acids 1 to 323 or amino acids 1 to 344. There is no disclosure in document (1) of the production of a soluble IFN-β2/IL-6R fragment using a nucleotide sequence containing codons 20 to 323 or codons 20 to 344.

9. The objection of appellant II has its origin in the fact that the cleavage point of the signal sequence in plasmids pVL324 and pSVL345 has been a matter of divergence between the appellants. In the Board's view, however, the *ratio decidendi* of decisions G 1/92 (EPO OJ 1993, 277) and T 952/92 (EPO OJ 1995, 755) applies to the present case, since prior art documents in the meaning of Article 54(3) EPC are also considered as comprised in the state of the art. According to these decisions, the chemical composition of a product is state of the art, when the product as such is available to the public and can be analysed. In the context of document (1), it was possible to the skilled person, using the analytical techniques of that time, to determine that the signal sequence of the IFN-β2/IL-6R extends from amino acid 1 to amino acid 19 and, hence,

that the expression of the nucleotide sequences contained in plasmids pSVL324 and pSVL345 does lead to a polypeptide having a sequence extending from amino acid 20 to amino acid 323 or 344. This is, for instance, corroborated by the teaching of document (2), which is concerned with the structure of IL-6R and the identification of its various domains (signal sequence, transmembrane and cytoplasmic domains and extracellular fragment) and, in particular, the identification of the signal sequence which is shown to extend from amino acid 1 to amino acid 19 (Figure 4). Therefore, the teaching of document (1), which needs to be disclaimed, is that nucleotide sequences coding for proteins consisting of amino acids 1 to 323 or amino acids 1 to 344 lead upon expression to a soluble IFN-β2/IL-6R fragment starting at amino acid 20.

10. In this context, the Board does not share the view of appellant I that there is an ambiguity in document (1) concerning the cleavage point of the signal sequence and a contradiction on this point between Figure 19 and the description (page 5, lines 36 to 43; page 14, lines 29 to 45). Indeed, there is no doubt that the signal sequence in Figure 19 ends up after amino acid 19. On the other hand, the presence of two hydrophobic regions in IFN-β2/IL-6R is disclosed on page 5, lines 36 to 43, the first one of which being defined as a "*signal peptide **region***" and said to extend up to amino acid 22. The simultaneous presence in this expression of the terms "*peptide*" and "*region*" implies a difference in the meaning of these terms. The term "*region*" has a broader and less defined meaning than "*peptide*", so that this expression is to be understood as meaning "*a region which comprises the signal peptide,*

but which is not by itself the signal peptide and is in fact more extended than the signal peptide itself". There is thus no contradiction between the description (page 5, lines 36 to 43 and page 14, lines 29 to 45) and Figure 19 of document (1), the former defining the region in which the signal peptide is and the latter giving its precise limit.

11. There is, therefore, nothing in document (1) that requires, or would justify, a disclaimer to nucleotide sequences extending from codons 20 to 323 or from codons 20 to 344 to be introduced into claim 9 and this claim meets the requirements of Article 123(2) EPC.

12. The Board further does not share the opinion of appellant II that the absence of the expression "*which specifically recognizes said fragment*" in claim 13 results in an extension of the subject-matter beyond the content of the application as filed. This expression is mentioned in claim 16 and on page 2 (line 24) of the application as filed, whereas the term "*specific*" in this context is used on page 6 (line 23). However, the description (page 1, line 8; page 3, lines 9 and 10 and from page 14, line 1 to page 15, line 14) also refers to "*antibodies against FN-b2/IL-6R*" without reference to any kind of specificity. Therefore, in the Board's view, there is a basis in the application as filed for claim 13 of the auxiliary request, so that the requirements of Article 123(2) EPC are fulfilled.

Article 123(3) EPC

13. Appellant II has objected that the deletion of the expression "*which specifically recognizes said fragment*" extended the scope of protection given by claim 13 to a process for antibodies which may also cross-react with polypeptides other than the IFN-β2/IL-6R fragment.

14. The notion of specificity, which is an expression of the high affinity of a given antibody for the antigen against which it has been raised, is inherent to the nature of the antibodies and, hence, already contained in the denomination "antibody", so that reference to the specificity can be, but does not need to be explicitly made. This is exemplified in the patent in suit, in which an explicit reference is only made in antibody claim 13 as granted, whereas the description (page 2, lines 54 to 54; page 3, lines 54 to 55; page 5, lines 6 to 14; page 10, line 21) simply mentions that the process involves raising antibodies against the soluble extracellular IFN-β2/IL-6R fragment. The notion of specificity does not exclude that an antibody may cross-react with other polypeptides than that against which it has been raised. This is because the cross-reaction is in fact not a feature of an antibody, but much more a feature of the antigenic epitope, against which the antibody has been raised, which can be present on several different molecules. Therefore, in the Board's view the absence of the expression "*which specifically recognizes...*" does not result in an extension of the scope of protection.

15. The expression "*in compliance with the conventional hybridoma technique*" used in claim 14 is, in the Board's view, derivable from claim 15 as granted which defines the antibody as being monoclonal. In the patent in suit (page 6, lines 21 and 22) the monoclonal antibodies are said to be prepared according to the method of Milstein and Köhler, for which two references are given. This method is defined in the patent in suit as said *conventional hybridoma technique*. The Board accepts from its own knowledge that this was accepted by the priority date as a conventional technique, even if individual laboratories, as argued by appellant II, used their own variation of this technique. Furthermore, the Board cannot see how the introduction into a claim of a restrictive feature could extend the scope of protection given by the claims as granted.

16. In view of the foregoing, the Board considers that the requirements of Article 123(3) EPC are met.

Article 83 EPC

17. Appellant II argued that the term "*in substantially purified form*" as used in claim 2 lacked clarity, so that the skilled person was not in a position to determine whether or not an IL-6R protein that might be obtainable according to the teaching of the patent in suit was indeed substantially pure.

18. The Board does not share the view of appellant II on this point, because the patent in suit gives on page 3, lines 40 to 50 a definition of the level of purity meant by this expression. It is the level of purity of a receptor which has been prepared following the

process described in steps (a) to (d) leading to a product moving as a single peak in reversed-phase HPLC. Therefore, the skilled person is provided by the patent in suit with a reference which enables him to determine whether a soluble extracellular IFN-β2/IL-6R fragment has been obtained "*in a substantially purified form*" and, accordingly, the requirements of Article 83 EPC are fulfilled.

Article 84 EPC

19. In view of the objection of appellant II that the expression "*conventional hybridoma technique*", as mentioned in claim 14, was unclear because there was no such technique, the argumentation given by the Board in view of the objection raised under Article 123(3) EPC in relation to this expression also applies here (*cf supra* point 15). Therefore, the Board considers that the requirements of Article 84 EPC are met.

Article 56 EPC

20. Claim 1 is directed to a soluble fragment of IFN-β2/IL6R which is able to specifically bind to IFN-β2/Il-6. Document (2), which has been considered by both parties as the closest prior art, discloses the cloning and expression of human IFN-β2/IL-6R. In Figure 4 of document (2), the nucleotide and amino acid sequences of IL-6R are shown and in Figure 4 and on page 827 (middle column, second paragraph) the various domains of the molecule are identified.

21. The opposition division treated document (2) as the closest prior art and defined the technical problem to

be solved in relation thereto as being the provision of a soluble fragment of IL-6R capable of binding IL-6. The Board considers that both the choice of document (2) as closest prior art, and the formulation of the problem in respect thereto depend too much on hindsight of the claimed invention to be acceptable.

22. The patent in suit states (page 2, lines 36 to 38) that the effect that has been discovered for the subject matter claimed is the property of enhancing the (known) beneficial biological activity of IFN-β2/IL-6. The Board thus considers that a proper formulation of the problem would be to find something that enhances the known beneficial biological effects of IFN-β2/IL-6. The information in the patent allows this problem to be regarded as solved. Documents such as (2), (7) and (8) thus require to be looked at as material that the skilled person might consult when trying to enhance the known biological effects of IFN-β2/IL-6, and the question in the context of the assessment of inventive step is whether the skilled person would have arrived at the solution proposed in claim 1 in an obvious manner by a consideration of these documents alone or in combination with other prior art documents or the common general knowledge.

23. In document (2) the various domains of IL-6R are described, but the skilled person is not provided with any incentive to modify the structure of IL-6R by cutting or re-arranging the various domains, nor is he told what effect might be achieved on IFN-β2/Il-6 by adding the fragment claimed. Therefore, considered alone, document (2) does not lead the skilled person to the solution defined in claim 1.

24. Appellant II has argued that the first priority document of the patent in suit under the heading "*Background of the invention*" points at the undesirable effects of IL-6 which could be antagonized in an efficient way by providing a soluble form of its receptor. Appellant II has concluded therefrom that the combination of the teaching of document (2) with the common general knowledge of the skilled person, as defined in said first priority document, leads in an obvious manner to the subject-matter of claim 1. However, said priority document was not available to the skilled person and appellant II has provided no evidence that the allegations contained in this part of the first priority document do in fact reflect knowledge in the art. Therefore, there is no evidence, in the Board's view, that the combination of the teaching of document (2) with the common general knowledge of the skilled person would lead in an obvious manner to the subject-matter of claim 1.

25. Appellant II has also argued that the combination of the teaching of document (2) with that of documents (7) or (8) on the purification of soluble forms of IL-2R by affinity chromatography on matrix-bound IL-2 or the blocking of CD4-mediated HIV infectivity by soluble CD4 leads to the solution defined in claim 1. First of all, there is in document (2) no incentive for such a combination. Furthermore, both documents (7) and (8) concern molecules structurally and functionally different from IL-6R, namely IL-2R and CD4, so that there is no evidence that the skilled person involved in the field of IFN-β2/IL-6R would have been aware of them. Nevertheless, if it is assumed, for the sake of

argumentation, that the skilled person was indeed aware of documents (7) and (8), and, even if document (8) mentions on page 1704 (right column, middle of the first paragraph), in the context of CD4, that "*...One successful strategy for the treatment of receptor mediated abnormalities has been the design of antagonists that block binding of the natural ligand...*", appellant II has not provided any evidence that this strategy could be of general applicability and, in particular, that it could be used with IFN-β2/IL-6R. Moreover, this sentence has to be seen in the context of document (8), which is directed to the CD4-mediated blocking of HIV-1 infectivity by a soluble, secreted form of the CD4 antigen. Applied to the patent in suit, this means that the teaching of document (8) could only be of value for a skilled person interested in blocking the negative effects of IL-6. This purpose, however, is exactly the opposite of the aim followed in the patent in suit, since the soluble extracellular IFN-β2/IL-6R fragment is used to enhance the beneficial effects (antiproliferative activity) of IL-6 (page 2, lines 36 to 38; page 3, lines 3 to 5; page 12, lines 27 to 28). Therefore, the skilled person can derive nothing of assistance from the teaching of document (8) which would rather point him away from the solution defined in the claims.

26. Appellant II has further argued that the subject-matter of claim 18, which is not entitled to the first priority, is rendered obvious by the combined teaching of documents (1) and (16). Indeed, the subject-matter of claim 18, which is directed to the use of the soluble IL-6R fragment for preparing a medicament for enhancing the beneficial effects of IL-6R, cannot enjoy

the priority right from the first application which is directed to the neutralisation of the negative effects of IL-6. Accordingly, the relevant date for the assessment of the prior art for the subject-matter of claim 18 is the second priority date, ie 26 November 1989, and both documents (1) and (16) are prior art documents in the meaning of Article 54(2) EPC. Document (16), which is concerned with the interaction between IL-6, IL-6R and a possible signal transducer, gp130, states on page 577 (right column, last paragraph before heading "*Discussion*") that soluble IL-6R augments the sensitivity of (mouse myeloid leukemia) M1 cells to IL-6 to their growth inhibition. The subject-matter of claim 18 is then rendered obvious, according to appellant II, by the combination with the teaching of document (1) stating on page 2, lines 24 and 25 that "*the BSF2 receptor released from cell surface* (ie the soluble IL-6R fragment) *is promising as diagnostic, prophylactic and therapeutic agent*".

27. In the Board's view, the indication in a scientific publication of the existence of a biological effect described for a given molecule is not *prima facie* sufficient to motivate the skilled person to use said molecule in the preparation of a medicament designed for human medicine. The level of confidence conveyed by the disclosure and its enabling character have also to be considered. In the case of document (16), which only concerns scientific aspects of the signal transduction of IL-6, the authors are cautious in their formulation and, hence, dissuasive, as shown, for instance, on page 578 (left column) "*...Thus the results indicate that association of IL-6R and gp130* ***could*** *occur in a physiological concentration of IL-6 and* ***might*** *not be an*

artefact *caused by an extreme dose of IL-6.*" or on page 578 (right column) "*...The possibility* ***may*** *not be* ***excluded completely*** *that soluble IL-6R* ***may*** *form a multimerized complex...*" or on page 579 (left column) "*...Very little is known about IL-6 signal transduction...*" and "*...The possibility has yet to be demonstrated.*"

28. Furthermore, in document (16) there is no evidence that the phenomenon observed *in vitro* with murine cells (M1 cells) in Figure 6B may at all be reproduced *in vivo* in humans under conditions in agreement with human physiology. In document (16) it is indeed indicated on page 578 (right column) that "*...the effect of soluble IL-6R on the growth inhibition of M1 cells was more apparent at higher dose...*" and that M1 cells are more sensitive to IL-6 than M12 cells, so that a dose dependency of the effect observed and variations in said dependency among cells of various origins have to be expected.

29. The disclosure of document (16), in the Board's opinion, is not such as to motivate the skilled person, known to be cautious and to have a conservative attitude, to envisage a therapeutic application of the disclosed teaching. In the Board's opinion, the skilled person would rather conclude from the disclosure of document (16) that there is still a large amount of research work to be done before a use, if any, in human medicine could be envisaged. If the skilled person nevertheless embarked on a research program with an unforeseeable outcome, this would be in the hope of making some invention, and not because a favourable outcome was obvious.

30. In view of the foregoing, The Board considers that the subject-matter of claims 1 and 18 meets the requirements of Article 56 EPC, as does the subject-matter of claims 2 to 17, depending on claim 1 or relating essentially to the same subject-matter.

Order

For these reasons it is decided that:

1. The request of appellant I (patentee) pursuant to Rule 88 EPC to amend claim 9 of the patent as maintained by the opposition division by the insertion of "or" before "for a protein" is allowed.

2. The respective appeals of appellant I (patentee) and appellant II (opponent) are dismissed.

The Registrar: The Chairman:

P. Cremona S. Perryman