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D E C I S I O N
of 14 February 2006

Case Number: T 0094/04 - 3.3.08

Application Number: 94930818.3

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Language of the proceedings: EN

Title of invention:
Cytokine antagonists

Patentee:
REGENERON PHARMACEUTICALS, INC.

Opponent:
Immunex Corporation

Headword:
Cytokine antagonists/REGENERON

Relevant legal provisions:
EPC Art. 54, 56, 83, 84, 123(2)(3)

Keyword:
"Admission of revised auxiliary request 2A into the proceedings as main request (yes)"
"Added matter (no)"
"Clarity (yes)"
"Novelty (yes)"
"Inventive step (yes)"
"Sufficiency of disclosure (yes)"

Decisions cited:
T 0019/90, T 0694/92, T 0840/93, T 0794/94

Catchword:
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Case Number: T 0094/04 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 14 February 2006

Appellant I: (Patent Proprietor)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 11 November 2003 concerning maintenance of European patent No. 0726954 in amended form.**

Composition of the Board:

Chairman: L. Galligani
Members: M. R. Vega Laso
S. Perryman

Summary of Facts and Submissions

I. The appeals lie from the interlocutory decision of the opposition division posted on 11 November 2003 concerning the European patent No. 0 726 954, based on application No. 94 930 818 (published as WO 95/11303) and having the title "Cytokine antagonists".

II. The patent was opposed by one party on the grounds of Article 100(a), (b) and (c) EPC, in particular lack of novelty (Article 54 EPC), lack of inventive step (Article 56 EPC), lack of sufficient disclosure (Article 83 EPC) and added matter (Article 123(2) EPC). The opposition division found that, whereas the main request (claims as granted) offended against Article 123(2) EPC, the first auxiliary request AR2B filed at the oral proceedings was allowable under the EPC. Pursuant to Article 102(3) EPC the patent was then maintained in amended form on the basis of the first auxiliary request then on file and a description amended accordingly.

III. The proprietor (appellant I) and the opponent (appellant II) each lodged an appeal against the decision of the opposition division. With the statement of grounds of appeal, appellant I filed six new auxiliary requests, whilst it maintained the granted claims as its main request. In its statement setting out its grounds of appeal, appellant II relied, *inter alia*, on a new document (D5) to support its line of argument on inventive step.

IV. Each of the parties was given the opportunity to comment on the grounds of appeal of the other party.

Together with its comments, appellant I submitted four additional auxiliary requests. Both appellants requested as a subsidiary request that oral proceedings be held under Article 116 EPC.

V. The parties were summoned to oral proceedings. In a communication pursuant to Article 11(1) of the Rules of Procedure of the Boards of Appeal attached to the summons, the board expressed its provisional opinion on some of the issues to be discussed at the oral proceedings, in particular on issues in connection with Article 123(2) EPC.

VI. Appellant II requested that the scheduled oral proceedings be postponed. In view of the reasons put forward in support of the request, the board decided to grant it.

VII. On 18 October 2005, appellant I filed a response to the board's communication including revised auxiliary requests 1 to 5 and 1A to 5A that replaced its previous auxiliary requests.

VIII. Oral proceedings were held on 14 February 2006. At the onset of the proceedings, appellant I withdrew its main request as well as the revised auxiliary requests 1, 1A and 2, and pursued the revised auxiliary request 2A (claims 1 to 11) filed on 18 October 2005 as its main request.

IX. Claim 1 of the revised auxiliary request 2A read as follows:

"1. A **soluble** cytokine antagonist protein capable of binding a cytokine to form a nonfunctional complex **wherein the cytokine activates a receptor by binding first an α-specificity determining component followed by binding to β1 and then β2 signal transducing components,** which antagonist **is heterodimeric and** comprises:

(a) the soluble α specificity determining component of the cytokine receptor; and

(b) an extracellular domain of a β_1-component of the cytokine receptor."

(Amendments introduced with respect to the granted claim 1 have been emphasized by the board)

Claims 2 to 5 corresponded to claims 2, 3, 5 and 6 as granted and related to various embodiments of the antagonist protein. Claims 6 and 7, which corresponded to claims 7 and 8 as granted, were directed to, respectively, a DNA sequence encoding the claimed antagonist protein and a pharmaceutical composition comprising the protein together with a pharmaceutically acceptable carrier. Claims 8 to 11 corresponded to claims 9 to 12 as granted and specified various uses for an antagonist protein according to claim 5.

X. Appellant II requested that the requests filed on 18 October 2005, in particular the revised auxiliary request 2A not be admitted on the grounds of being late-filed. After discussion of this issue with the parties and subsequent deliberation, the board decided to admit into the proceedings the revised auxiliary

request 2A as main request. The parties were then allowed to put forward their arguments on the allowability of claims 1 to 11 and, after deliberation, the board expressed the provisional view that the patent could be maintained on the basis of the claims of the main request. Appellant I filed amended pages 3 to 11 of the description, and objections raised by appellant II to the introduced amendments were discussed. At the end of the oral proceedings, the board announced its decision.

XI. The following documents will be referred to in the present decision:

D1: S. Davis et al., Science, 18 June 1993, Vol. 260, pages 1805 to 1808;

D2: WO 93/10151, published on 27 May 1993;

D5: M. Hibi et al., Cell, 21 December 1990, Vol. 63, pages 1149 to 1157.

XII. The arguments put forward by appellant I can be summarized as follows:

Admission of revised auxiliary request 2A into the proceedings and Articles 123(2)(3) and 84 EPC

The amendments introduced into claim 1 were responsive to the observations made by the board in its communication and did not extend the claimed subject-matter beyond the content of the application as filed. The scope of protection conferred by the patent as

granted had not been extended and the requirements of clearness and conciseness were met.

Article 54 EPC

The CNTFRα/gp130 complex disclosed in D1 was not a cytokine antagonist since it would not prevent binding of CNTF to its receptor and initiation of signal transduction. The reason why the signal could not be transduced was that LIFRβ was not present and, therefore, a complete receptor complex could not be formed. Native gp130 comprised a membrane-spanning and an intracellular domain in addition to its soluble domain; thus, the CNTFRα/gp130 complex disclosed in D1 was associated with the cell membrane and was not a "soluble" protein as required in the claim. "Truncated" did not necessarily mean "soluble". Although D1 mentioned in passing truncated forms of the signal transducers, the components of the complex described in D1 were not truncated. Yet further, only the association of α and β components in the presence of the cytokine was described in D1, whereas the claims required that the α and β1 components were pre-associated and that the complex was capable of binding to the cytokine.

D2 related to a two-component cytokine receptor system and did not disclose cytokine antagonists comprising an α specificity determining component within the meaning of the claims, ie a receptor component which did not interact with intracellular signalling molecules.

Article 56 EPC

Document D2 disclosed a cytokine antagonist with two components derived from signal transducing proteins. There was, however, no suggestion in D2 to replace one of these two components by an α specificity determining component. Therefore, having regard to D2 alone, the claimed subject-matter was not obvious.

Nor was the claimed invention obvious in view of a combination of D2 with D1. D1 did not teach that the binding of the CNTF/CNTFRα complex to gp130 (the β1 component of the CNTF receptor) was a high affinity step. This finding, which was disclosed for the first time in Example 2 of the patent, made possible to design high affinity cytokine antagonists based on α/β component pairings.

Document D5 did not suggest the creation of a ligand trap in which components were pre-associated in the absence of a cytokine ligand. Nor did it suggest the use of extracellular domains of receptor components. Thus, a combination of documents D2 and D5 did not point the skilled person towards a cytokine antagonist as claimed.

Article 83 EPC

No evidence had been provided by appellant II demonstrating that claim 1 as a whole would be unworkable, or that embodiments falling within the scope of the claims did not work. The technical contribution of the patent to the art was the provision of the first soluble α/β cytokine antagonist. This

contribution was properly reflected by the scope of the claims.

XIII. The arguments submitted by appellant II, as far as they are relevant to this decision, were essentially as follows:

Admission of revised auxiliary request 2A into the proceedings

The revised auxiliary requests filed on 18 October 2005 were late-filed. They were not filed in response to any observations made by the board in its communication. The objections that they allegedly helped to overcome had been raised already in opposition proceedings.

Articles 123(2)(3) and 84 EPC

The reference to an "*α specificity determining component*" or a "*β signal transducing component*" in claim 1 made sense only with respect to a single specific receptor because different cytokine receptors shared a polypeptide chain that had one function in one of the receptors and a different function in another receptor. Since it was entirely unclear of which receptor the component addressed in (b) was a β1 component, the amendment introduced into part (b) of claim 1 to specify "β1 component" instead of "β component" contravened Article 84 EPC.

The claimed cytokine antagonists were defined by reference to a molecule that was not part of the claim, namely the receptor of the cytokine. These additional

features were unsuitable to distinguish the claimed subject-matter over the prior art.

Example 2 of the patent showed only that *full length*, membrane bound CNTFα, CNTFRα/gp130 and CNTFRα/gp130/LIFRβ bound CNTF with certain affinities. However, the claims were directed to *soluble* antagonists comprising only *soluble* fragments of the components. Such claims were not supported by the description.

Article 54 EPC

Document D2 disclosed and even exemplified fusion proteins comprising the specificity determining component of LIFRβ and the extracellular domain of the β1 component of that receptor, namely the gp130 sequence. A number of alternative constructs for producing the respective antagonist proteins were described in Examples 3 to 5, 7 and 8. D2 further disclosed that the antagonist protein could be present as the soluble form of the receptor and was capable of binding to the cytokine (LIF) to form a non-functional complex, ie a complex that was not capable of mediating signal transduction. As a consequence, the subject-matter of claim 1 was fully anticipated by D2. Furthermore, D2 disclosed that the antagonist proteins comprised the extracellular domain of gp130 (cf. claim 3 at issue) and that they could be prepared by fusing the genes coding for the polypeptides (claims 4 and 5 at issue). Pharmaceutical compositions as claimed in claim 7 at issue were also described. Thus, the subject-matter of claims 3 to 5 and 8 was also anticipated by D2.

Document D1 disclosed that CNTFRα and gp130 could be co-expressed in COS cells that did not express LIFRβ. The addition of the cytokine (CNTF) to the cells failed to induce signal transduction. Recombinant expression of the two receptor components CNTFRα and gp130 resulted in a cytokine antagonist protein which comprised the soluble α specificity determining component and the extracellular domain of a β component of the cytokine receptor, and was able to inhibit signal transduction. D1 explicitly suggested to use truncated forms of the receptor antagonists (page 1807, right column, first full paragraph) and disclosed that the components of the antagonist were crosslinked by ligand binding. The disclosure of document D1 provided essentially the same examples as the patent in suit and anticipated each and every aspect of the alleged invention.

Article 56 EPC

Document D2 was considered to be the closest prior art. The objective technical problem in view of D2 resided in identifying alternative cytokine antagonists. The purported solution was providing antagonists for cytokines that interact with three-component receptors.

This problem had evidently not been solved by the inventors. The patent in suit failed to disclose even one specific example of a receptor antagonist as defined in the claims, and all examples related to the analysis of receptor/cytokine interactions. The generic part of the description taught that receptor antagonists could be prepared according to methods for dimerizing proteins as disclosed in D2, and the patent

itself was based on the assumption that if one of ordinary skill in the art was provided with the suggestion to prepare a cytokine antagonist protein comprising the soluble α specificity determining component and an extracellular domain of a β component of a receptor, that person would be able to prepare any such antagonist. Since D2 already provided that suggestion, the teaching of the patent was obvious in view of D2 alone.

The subject-matter of all claims was obvious also in view of a combination of the disclosure of documents D2 and D1. Document D1, which related to the same cytokine receptor as the example of the patent in suit (CNTFR), taught that the combination of CNTFRα and gp130 (the α and β1 components of the CNTF receptor, respectively) formed an intermediary complex with a binding affinity for CNTF higher than the binding affinity of CNTFRα alone, and similar to the binding affinity of the three-component receptor (page 1806, left column, last sentence of the first full paragraph, and from note 16 on page 1808). Consequently D1 provided the same information as the examples of the patent. Since the suggestion to prepare CNTF antagonists was explicitly contained in D1 and corresponding antagonists were exemplified in D2, in view of a combination of these documents the claimed subject-matter lacked an inventive step.

The skilled person reading the passage on page 1807, right hand column, first full paragraph of D1 in context and in the light of his/her knowledge would immediately think of using a *soluble* signal transducing element. This passage clearly required that the

truncated forms of the signal transducers blocked ligand induced activation. To this effect, at least the extracellular ligand binding domain had to be present, and at least enough of the intracellular signalling domain had to be eliminated for signal transduction to be inactivated. By using the term "truncated" in the cited passage, the authors of D1 intended to include the concept of soluble signal transducing fragments. Moreover, soluble variants of gp130 and LIFRβ were disclosed in document D2.

Patentee's argument that the dissociation constants provided in the patent made it possible to design high affinity cytokine antagonists based on α/β component pairings was flawed. This argument ignored the disclosure of D1, wherein it was explicitly stated that a stable complex of cytokine, CNTFRα and gp130 was formed. From the paragraph bridging middle and right column on page 1806, the stepwise nature of cytokine binding and receptor assembly was apparent. Knowing this, the skilled person would expect that a soluble cytokine antagonist analogous to those taught in D2 could be made for three-component systems simply by using soluble forms of the cytokine-binding receptor intermediates illustrated in Figure 4 of D1.

Document D5 reported an analysis of the affinity of different polypeptide chains of the IL-6 receptor for its ligand, and provided the same results as the examples of the patent in suit for a different receptor. Thus, before the priority date of the patent it was known that in the CNTF family the β1 component increases the affinity of the α component for its ligand. The

claimed subject-matter was thus rendered obvious by a combination of the disclosure of D2 and D5.

Article 83 EPC

The patent did not disclose, identify or exemplify a single specific antagonist protein adding anything to the art, and its disclosure did not extend beyond the disclosure of D1. The present case was fully comparable to the situation addressed in decisions T 694/92 (OJ EPO 1997, 408) and T 794/94 of 17 September 1998.

XIV. Appellant I (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the revised auxiliary request 2A submitted on 18 October 2005 and amended pages 3 to 11 of the description.

Appellant II (opponent) requested that the decision under appeal be set aside and the patent be revoked.

Reasons for the Decision

Admission of revised auxiliary request 2A into the proceedings

1. Appellant II opposed the introduction of the revised auxiliary request 2A into the proceedings on the grounds of being late-filed.

2. The request in question was filed within the time limit set by the board in its communication under Article 11(1) of the Rules of Procedure attached to the summons. According to the practice of the boards of

appeal of the EPO, requests submitted during the appeal procedure are admitted and considered by the board only if such requests represent *bona fide* attempts to overcome objections raised in the proceedings (cf. T 840/93, OJ EPO 1996, 335; points 3.1 and 3.2.1 of the Reasons). With the amendments introduced into claim 1 of the revised auxiliary request 2A, appellant I intended to overcome objections under Article 123(2) EPC raised by appellant II that had been specifically addressed by the board in its communication (see point 13 of the board's communication). Thus, even if introduced at a late stage of the proceedings, the amendments to claim 1 should not have taken appellant II by surprise. Although it is true that the objections that these amendments intended to overcome had been raised already in opposition proceedings or at an early stage of the appeal proceedings, their significance might nevertheless have become clear to appellant I only when the board pointed to them in its communication as issues to be discussed at oral proceedings.

3. The board considered the amendments introduced into claim 1 of the revised auxiliary request 2A and found the amendments to be appropriate and necessary to take account of the objections raised by appellant II under Article 100(c) EPC. Furthermore, the claims of the revised auxiliary request 2A did not give rise to new objections under Article 123(2) EPC and were, *prima facie*, allowable. Their admission was not likely to cause any substantial procedural complication. For these reasons, the board, availing itself of its discretionary power, decided to admit the revised auxiliary request 2A into the proceedings. After

withdrawal of the main request and the revised auxiliary requests 1, 1A and 2, the revised auxiliary request 2A became appellant I's main request.

Article 123(2) and (3) and Article 84 EPC

4. Appellant II alleged lack of support in the application as filed for the amendment introduced into claim 1 to define the type of cytokine at which the claimed antagonist proteins are targeted, as a cytokine that "*activates a receptor by binding first an α-specificity determining component followed by binding to β1 and then β2 signal transducing components*". This allegation is unsubstantiated. In the board's view, the amendment in question is clearly and unambiguously derivable from the passage bridging pages 7 and 8 of the application as filed. While it is true that this passage discloses further details on the mechanism by which the binding of the cytokine to the receptor triggers signal transduction (nonfunctional intermediate resulting from the binding of the cytokine/α component complex to the β1 component, and β receptor dimerization followed by signal transduction), the amendment introduced into claim 1 is restricted to the essential functional features which are necessary and, at the same time, sufficient for a clear and concise definition of the targeted cytokines and, consequently, of the claimed antagonist proteins. The board is convinced that the further details disclosed in the passage cited above do not add any essential information to this definition, and that their omission results neither in a broadening of the scope of cytokines targeted by the claimed antagonist proteins, nor in an extension of the subject-matter of the amended claim beyond the content

of the application as filed. Hence, the requirement of Article 123(2) EPC is considered to be met.

5. No objections have been raised by appellant II under Article 123(3) EPC and the board does not see any reason to do so of its own motion.

6. With respect to the objections raised under Article 84 EPC, the board judges that in view of the amendment introduced to characterize the cytokine targeted by the claimed antagonist proteins (see point 4 above), the functional features "*α specificity determining component*" and "*β1 signal transducing component*" in claim 1 have a clear meaning for a person skilled in the art. The fact that a particular β polypeptide may have different functions in different cytokine receptors (for instance, the gp130 polypeptide functions as a β1 component in the CNTF receptor and as β1 or β2 component in the IL-6 receptor) is immaterial in the present case. In view of the language "*an extracellular domain of a β_1-component of* ***the*** *cytokine receptor*" in claim 1, a person skilled in the art reading the claim with a mind willing to understand would realize immediately that the β1 component of the claimed antagonist proteins corresponds to the β1 component of the specific receptor to which the antagonized cytokine binds, irrespective of the function this polypeptide may have in a different receptor for a different cytokine.

7. The board cannot share appellant II's view that the claimed soluble antagonist proteins comprising soluble fragments of the α and β1 receptor components are not supported by the description of the patent. It is

conceded that only antagonist proteins comprising the full-length α and β1 components are described in the examples of the patent. Nevertheless, throughout the description the antagonist proteins of the invention are defined as heterodimers comprising the soluble α component and an extracellular domain of a β1 component of the cytokine receptor. As the extracellular domain of a β1 component lacks both the hydrophobic domain that attaches this component to the cell membrane and the cytoplasmic domain, it is readily apparent to a person skilled in the art that this component and, consequently, also the claimed sRα:β1 heterodimer must be soluble. This is confirmed by the description of the patent, specifically the passage on page 7, lines 24 to 25 (which corresponds to page 15, lines 8 to 9 of the application as filed) in which reference is made to the "*αβ1 heterodimeric* ***soluble*** *receptors described above*" (emphasis added).

8. For the reasons given above, the board concludes that claim 1 complies with the requirements of Article 123(2) and (3) and Article 84 EPC. No objections under these articles were raised in respect of the remaining claims.

Article 54 EPC - Novelty

9. The novelty of the subject-matter of claim 1 with regard to the disclosure of documents D1 and D2 has been questioned by appellant II. According to the established case law of the boards of appeal of the EPO, for an invention to lack novelty its subject-matter must be clearly and directly derivable from the prior art, ie all its features must have been disclosed, either explicitly or implicitly, in the prior art.

Document D1

10. Document D1 is a scientific publication showing that signal initiation induced by the cytokine CNTF depends on the heterodimerization of LIFRβ and gp130, the β1 and β2 signal transducing components of the CNTF receptor. D1 discloses that when CNTF was added to cells lacking LIFRβ, a complex between CNTF, CNTFα (the α specificity determining component of the CNTF receptor) and gp130 was formed, but tyrosine phosphorylation and signal initiation were not observed (see abstract).

11. It is readily apparent from the disclosure of D1 that the CNTF/CNTFα/gp130 complex disclosed therein did not - and because of the bound CNTF even could not - function as an antagonist for the cytokine, and that the lack of signal initiation reported in this document was not due to an antagonistic effect associated with the CNTF/CNTFα/gp130 complex, but rather to the fact that the third component of the receptor (LIFRβ), which according to the authors of D1 is critical for signal initiation, was not available. A soluble CNTFα/gp130 complex as such (ie detached from the cell membrane and without the cytokine bound to it) is not disclosed in document D1, let alone the concept of using such a complex as an antagonist of the CNTF cytokine. Thus, the disclosure of document D1 is not prejudicial for the novelty of the subject-matter of claim 1.

Document D2

12. Document D2 discloses and exemplifies soluble LIFRβ/gp130 heterodimers which bind LIF and oncostatin M and are suitable as antagonists for these cytokines. As indicated by the opposition division in the decision under appeal (see point 3.2.2), both LIFRβ and gp130 function as β signal transducing components and are capable of dimerization and signal initiation in the absence of a separate α specificity determining component. Thus, neither LIF nor oncostatin M can be considered to be a cytokine that "*activates a receptor by binding first an α-specificity determining component followed by binding to β1 and then β2 signal transducing components*", as required in claim 1. Furthermore, contrary to appellant II's view neither LIFRβ nor gp130 represent an "*α specificity determining component of the cytokine receptor*" within the meaning given in the patent in suit, ie a component which binds to the cytokine and determines the specificity of the binding to the receptor, but does not have an immediate signal transducing role (cf. Figure 1 of the patent).

13. It follows from the above that the subject-matter of claim 1 is not anticipated by the disclosure of either D1 or D2. Consequently, with regard to these prior art documents the subject-matter of claim 1 as well as of the further claims depending on or referring to claim 1 is considered to be novel.

Article 56 EPC - Inventive step

14. It is undisputed that document D2 represents the closest prior art on file. As indicated above (see point 12), D2 teaches soluble antagonist proteins capable of binding the cytokines LIF and oncostatin M to form nonfunctional complexes. LIF and oncostatin M activate their respective receptor by binding a first signal transducing component (LIFRβ for LIF and gp130 for oncostatin M), and then a second transducing component (gp130 and LIFRβ, respectively). The antagonist proteins disclosed in D2 are heterodimers consisting of two β signal transducing components, LIFRβ and gp130. Methods for preparing soluble LIFRβ and gp130 polypeptides including those lacking all or part of the transmembrane region or the cytoplasmatic domain of the polypeptide (see Examples 7 and 8) by a number of conventional techniques, eg chemical synthesis or recombinant expression, are also disclosed in document D2.

15. Starting from D2, the objective technical problem to be solved can be defined as the provision of antagonist proteins for further cytokines.

16. The board is convinced that this problem is solved by an antagonist protein having the features specified in claim 1. According to the patent (see last sentence of paragraph [0026]), the claimed sRα:β1 heterodimer provides an effective trap for its ligand, as it is capable of binding the respective cytokine with high affinity without creating a functional intermediate. This teaching is supported by Example 2 of the patent which shows that CNTF binds with equally high affinity

to a complex containing only CNTFRα and gp130 (the α and β1 components of the CNTF receptor), as it does to a complex which additionally contains LIFRβ (see last sentence of paragraph [0054]). While the CNTFRα/gp130 complex described in Example 2 is attached to the cell membrane rather than in soluble form as required by claim 1, the board judges it technically plausible that a soluble complex comprising a soluble CNTFα and an extracellular domain of the gp130 component may also be capable of binding CNTF to form a nonfunctional complex, as it is the extracellular domain of gp130 which is involved in the binding to the cytokine. Furthermore, in view of the fact that the affinity of CTNF for the CNTFRα/gp130 complex is as high as that for its receptor (cf. Figure 3 of the patent), it appears likely that the CNTFRα/gp130 complex will function as an antagonist of CNTF by blocking the cytokine and thus impeding the activation of the receptor. There is no apparent reason to doubt that antagonist proteins targeted at other cytokines sharing with CNTF the mechanism for receptor activation (eg IL-6, which activates its receptor by binding first to IL-6Rα, followed by binding a first and, subsequently, a second gp130 molecule as β1 and β2 components, respectively) may be prepared in the same manner. Thus, in the absence of evidence to the contrary, appellant II's objection that the posed problem has not been solved by the claimed subject-matter cannot be accepted.

17. Hence, the question to be decided in the context of assessing inventive step is whether having regard to the disclosure of document D2, either alone or in combination with further prior art documents on file, the solution provided in claim 1 was obvious to the

skilled person. As noted above, document D2 concerns soluble cytokines which elicit signal transduction by binding first to a β1 receptor component and then to a β2 receptor component, thereby effecting dimerization of the two receptor components. The cytokine antagonists disclosed in this document consist of the soluble extracellular part of each of the two β components, ie a sRβ1:β2 heterodimer. In contrast, the present invention concerns cytokines which activate through a three-component receptor (α, β1 and β2 receptor components) and the claimed cytokine antagonists comprise the soluble α component and a soluble extracellular part of the β1 component, ie they are sRα:β1 heterodimers.

18. There is no suggestion in document D2 that would prompt the skilled person to try to extrapolate the teaching of this document to cytokines having a three-component receptor. But even if one assumes that the skilled person, who may be defined as a biochemist knowledgeable in the field of clinically relevant cytokines and working in a pharmaceutical environment, would nevertheless try and see whether or not the type of cytokine antagonists described in D2 may also work for cytokines having a three-component receptor, he/she might, at most, consider modifying the antagonists of D2 by adding an α component, thus obtaining a soluble heterotrimer (sRα:β1:β2). No hint whatsoever is given in document D2 that would prompt the person skilled in the art to depart from the teaching of this document by additionally omitting the β2 component, thereby obtaining a sRα:β1 heterodimer as claimed. Thus, in view of the disclosure of document D2 alone the subject-matter of claim 1 cannot be considered obvious.

19. Appellant II alleged that the disclosure in document D1 of an intermediary CNTFRα/gp130 complex with a binding affinity for CNTF similar to the binding affinity of the three-component receptor provided the required hint towards antagonist proteins as claimed. In support of its allegation appellant II pointed to the following passage on page 1806, left column, last sentence of the first full paragraph:

> "*Thus, CNTF, CNTFα, and gp130 apparently form an intermediate that must engage LIFRβ in order to complete assembly of the receptor complex; this last step apparently initiates signalling (18).*"

20. The board fails to see in the cited passage or in the note (16) on page 1808, to which appellant II has also pointed in this context, any indication that might suggest to the skilled person the possibility of using a soluble CNTFRα/gp130 complex as competitor for CNTF to block the binding of this cytokine to its receptor and the consequent signal transduction. Contrary to appellant II's view, the cited passage does not contain any information whatsoever indicating that the affinity for the binding of CNTF to the CNTFRα/gp130 complex is similar to that for the binding to the three-component receptor. Nor is such information derivable from the fact that stable CNTF/CNTFRα and CNTF/CNTFRα/gp130 complexes were observed (cf. page 1806, paragraph bridging the middle and right columns). From this observation it can only be concluded - as the authors of D1 did - that the complex formation in response to CNTF occurs by an ordered process in which CNTF first binds to CNTFRα, then recruits a single molecule of gp130, and finally engages LIFRβ as well.

21. In the board's view, the disclosure of D2 combined with the disclosure in D1 of a stepwise mechanism of binding of CNTF to its receptor does not give to the skilled person the critical hint towards the invention. In view of the disclosure of these documents, the skilled person would possibly consider coupling the two β components of a cytokine antagonist as described in D2 with the corresponding soluble CNTFRα, thus obtaining a heterotrimer sRα:β1:β2. However, no hint is given in either D1 or D2 in the direction of omitting the β2 component to obtain a sRα:β1 heterodimer which may function as cytokine antagonist. Consequently, the subject-matter of claim 1 cannot be considered obvious having regard to the disclosure of documents D1 and D2 combined.

22. Appellant II contended further that the claimed subject-matter was obvious in view of a combination of documents D2 and D5. Document D5 aims at the characterisation of gp130 as an IL-6 signal transducer. Even if it is acknowledged that - as appellant II contended - the results shown in D5 suggest that gp130 may be involved in the formation of high affinity IL-6 binding sites, the board notes that this document also suggests that the association of gp130 with a complex of IL-6 and soluble IL-6Rα (designated IL-6 receptor in D5) leads to **transduction of the growth signal** (see last sentence of the Abstract). Having regard to this disclosure, the skilled person seeking to provide a IL-6 antagonist protein, ie a protein that binds to IL-6 with high affinity and thereby **impedes signal transduction**, would not regard a sIL-6Rα:gp130 complex as a suitable candidate. Consequently, the subject-

matter of claim 1 cannot be considered to be obvious in view of a combination of the disclosure of documents D2 and D5.

23. Summarising the above: having regard to document D2, either alone or in combination with D1 or D5, the provision of cytokine antagonist proteins as defined in claim 1 is considered to involve an inventive step. The same is true for the specific embodiments of the antagonist proteins claimed in claims 2 to 5, and for the subject-matter of claims 6, 7 and 8 to 11, which are directed to a DNA sequence, a pharmaceutical composition and various uses of the claimed antagonists, respectively.

Article 83 EPC - Sufficiency of disclosure

24. Even though the patent does not provide a technically detailed example for the claimed antagonist proteins, the board is convinced that at the priority date the skilled person had at his/her disposal, either in the specification or on the basis of the common general knowledge in the field of protein engineering, adequate information that allowed him/her to prepare cytokine antagonist proteins as claimed, without undue burden of experimentation and without needing inventive skill. At the priority date of the patent, the genes encoding α and $\beta 1$ components of the pertinent cytokine receptors had been cloned and their sequence determined (cf. in this respect paragraph [0027] of the patent in suit), and methods for producing soluble fusion proteins were known in the art (cf. paragraphs [0030] to [0034] of the patent). Appellant II has not contested these facts, nor has it put forward any specific arguments,

substantiated by verifiable facts (cf. T 19/90, OJ EPO 1990, 476, point 3.3. of the Reasons) which may justify its objection of lack of sufficient disclosure.

25. The board does not share appellant II's view that the situation in the present case is fully comparable to the situation addressed in decisions T 694/92 (OJ EPO 1997, 408) and T 794/94 of 17 September 1998. In decision T 694/92, the then competent board held that the actual technical contribution to the state of the art by the disclosure of the patent consisted of providing experimental support for a general prior art teaching that anticipated the teaching of the patent in explicit, though predictive terms, and that the experimental evidence and technical details in the description of the patent were not sufficient for the skilled person to reliably achieve without undue burden the desired technical effect in the broad area of the claim (cf. points 11 and 19 of the Reasons). Consequently, the claim request was refused under the provisions of Articles 83 and 84 EPC.

26. In contrast, in the present case the patent contributes to the art a theoretical concept for the preparation of antagonist proteins targeted at a defined group of cytokines, and indicates the technical means necessary to put this concept into practice. The concept underlying the invention is not anticipated at either the theoretical or the practical level by any of the prior art documents on file and, in the absence of any evidence to the contrary, the technical means indicated in the patent are considered to be sufficient for the skilled person to be able to carry out the invention without an undue burden of experimentation. Thus, the

facts in decision T 694/92 (*supra*) are by no means comparable to the facts in the present case.

27. Nor are the facts in decision T 794/94 (*supra*) comparable, in which decision the then competent board was unable to formulate any problem in relation to the claim under scrutiny, for which it could be said that it had been solved by the information provided for the first time in the patent in question. The board there was unable to define the actual contribution to the state of the art made by the disclosure of the patent (see point 3.4.4 of the Reasons). The board therefore considered that the claim at issue had to fail either for contravening Article 83 EPC, or for lack of inventive step (Article 56 EPC). In the absence of clear evidence that the information provided by the patent or by the prior art was insufficient to allow the skilled person to carry out the invention, the claimed subject-matter was held to be devoid of an inventive step.

28. In the present case, neither the board nor - as it is apparent from its submissions - appellant II had any difficulty in formulating the technical problem to be solved. Furthermore, the board was able to define the actual contribution to the state of the art made by the disclosure of the patent (cf. point 26 above) without difficulty, even though such a contribution has been contested by appellant II.

29. It follows from the above that the legal principles concerning insufficiency on which decisions in cases T 694/92 and T 794/94 were based do not lead the board

to a finding of insufficiency on the rather different facts of the present case.

Amendments to the description

30. The amendments introduced to bring the description into conformity with the amended claims do not contravene either Article 123(2) and (3) or Article 84 EPC. The board failed to see any reason that justified amending paragraph [0023] by introducing the exact language of the amended claim 1, as requested by appellant II. Literal support for this claim is found already in paragraph [0008] of the amended description.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the following documents:

   (a) Claims 1 to 11 filed as revised auxiliary request 2A on 18 October 2005;

   (b) Amended description pages 3 to 11 filed during the oral proceedings;

   (c) Figures as granted.

The Registrar: The Chairman:

A. Wolinski L. Galligani