BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE | CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen
(D) [ ] No distribution

D E C I S I O N
of 5 November 2003

Case Number: T 1014/01 - 3.3.4

Application Number: 91100695.5

Publication Number: 0439095

IPC: A61K 47/48

Language of the proceedings: EN

Title of invention:
Recombinant immunoconjugates for therapy comprising interleukin 2

Patentee:
Bristol-Myers Squibb Company

Opponents:
Pharmacia & Upjohn S.p.A.
Edmund R Pitcher

Headword:
Recombinant immunoconjugates/BRISTOL-MYERS Squibb Co.

Relevant legal provisions:
EPC Art. 123(2)(3), 84, 87(4), 54(3), 56, 104(1)

Keyword:
"Main request - novelty (no)"
"Auxiliary request 1 - added subject-matter (yes)"
"Auxiliary request 2 - inventive step (no)"
"Auxiliary request 3 - inventive step (yes)"

Decisions cited:
T 0633/97, T 0815/90, T 0576/91

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1014/01 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 5 November 2003

Appellant I: (Proprietor of the patent)
Bristol-Myers Squibb Company
345 Park Avenue
New York, N.Y. 10154 (US)

Representative:
Schweiger, Georg, Dr
Patentanwälte
Reitstötter, Kinzebach und Partner
Postfach 86 06 49
D-81633 München (DE)

Appellant II: (Opponent 01)
Pharmacia & Upjohn S.p.A.
Via Robert Koch, 1.2
I-20152 Milan (IT)

Representative:
Woods, Geoffrey Corlett
J.A. KEMP & CO.
Gray's Inn
14 South Square
London WC1R 5JJ (GB)

Appellant III: (Opponent 02)
Edmund R Pitcher
High Street Tower
125 High Street
Boston
Massachusetts (US)

Representative:
Thomas, Philip John Duval
Eric Potter Clarkson
Park View House
58 The Ropewalk
Nottingham NG1 5DD (GB)

Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 13 July 2001 concerning maintenance of European patent No. 0439095 in amended form.

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: R. E. Gramaglia
S. C. Perryman

Summary of Facts and Submissions

I. European Patent No. 0 439 095 (application No. 91 100 695.5) claiming priority from US 468390 of 22 January 1990 was filed on 21 January 1991. The patent relates to recombinant immunoconjugates for therapy comprising interleukin 2 (IL 2) and was granted on the basis of 8 claims for the Contracting States AT, BE, CH, LI, DE, DK, FR, GB, GR, IT, LU, NL, SE and 8 claims for the Contracting State ES.

II. Notices of opposition were filed by opponents (01) and (02) all requesting the revocation of the European patent on the grounds of Article 100(a), (b) and (c) EPC. The opposition division maintained the patent on the basis of the claims of Auxiliary Request 3 then on file.

III. Appellant I (patentee), appellant II (opponent (01)) and appellant III (opponent (02)) filed appeals against the decision of the opposition division.

IV. Oral proceedings were held on 4 and 5 November 2003, on the second day of which appellant I filed a New Main Request and New Auxiliary Requests 1 to 3.

Claim 1 of the New Main Request read as follows:

"1. A recombinant antibody-based fusion protein comprising

(i) a portion of an immunoglobulin molecule capable of directing the fusion protein to a tumor cell or a tumor-associated antigen, and

(ii) an interleukin 2 molecule capable of promoting lymphocyte proliferation."

Claim 1 of New Auxiliary Request 1 read as follows:

"1. A recombinant antibody-based fusion protein comprising

(i) a portion of an immunoglobulin molecule capable of directing the fusion protein to a tumor cell or a tumor-associated antigen, and

(ii) an interleukin 2 molecule capable of promoting lymphocyte proliferation, wherein the interleukin 2 molecule is fused via its N-terminus."

Claims 1 to 3 of New Auxiliary Request 2 read as follows:

"1. A recombinant antibody-based fusion protein comprising

(i) a portion of an immunoglobulin molecule capable of directing the fusion protein to a tumor cell or a tumor-associated antigen,

(ii) an interleukin 2 molecule capable of promoting lymphocyte proliferation, and

(iii) a natural hinge region of an immunoglobulin molecule, or a modified version of the hinge region sequences of human IgG_1 wherein the two cysteine residues that normally mediate interchain

disulfide linkage are replaced by proline and serine so as to permit greater flexibility in the fused molecule.

2. The fusion protein of claim 1 in which the portion of the immunoglobulin molecule competitively inhibits the binding of monoclonal antibody L6.

3. The fusion protein of claim 1 or 2 wherein the portion of the immunoglobulin molecule is the variable region derived from monoclonal antibody L6."

Claim 1 of New Auxiliary Request 3 read as follows:

"1. A recombinant antibody-based fusion protein comprising

(i) a portion of an immunoglobulin molecule capable of directing the fusion protein to a tumor cell or a tumor-associated antigen,

(ii) an interleukin 2 molecule capable of promoting lymphocyte proliferation, and

(iii) a modified version of the hinge region sequences of human IgG_1 wherein the two cysteine residues that normally mediate interchain disulfide linkage are replaced by proline and serine so as to permit greater flexibility in the fused molecule."

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

(D2) EP-A-0 396 387;

(D2a) Priority document US 348237 for (D2);

(D5) EP-A-0 319 012;

(D8) WO-A-86/01533;

(D9) Schnee J.M. et al., Proc. Natl. Acad. Sci. USA, Vol. 84, pages 6904 to 6908 (October 1987);

(D11) Williams G.T. et al., Gene, Vol. 43, pages 319 to 324 (1986);

(D15) EP-A-0 256 714;

(D17) EP-A-0 350 230;

(D17a) Priority document US 216595 for (D17);

(D18) WO-A-88/09344;

(D19) Hellström I. et al., Proc. Natl. Acad. Sci. USA, Vol. 83, pages 7059 to 7063 (September 1986);

(D20) Senter P.D. et al., Proc. Natl. Acad. Sci. USA, Vol. 85, pages 4842 to 4846 (July 1988);

(D22) Reisfeld R.A. et al., J. Clin. Lab. Analysis, Vol. 10, pages 160 to 166 (1996);

(D23) EP-B-0 574 395;

(D23a) WO-A-92/08495 (coversheet);

(D23b) Communication of the Examining Division of 30 January 1997 in the application underlying patent (D23);

(D23c) Response to document (D23b);

(D24) Lode H.N. et al., J. Natl. Cancer Institute, Vol. 89, No. 21, pages 1586 to 1594 (5 November 1997);

(D30) WO-A-86/03838.

VI. The submissions by appellant I (patentee), insofar as they are relevant to the present decision, can be summarized as follows:

Apportionment of costs

- No apportionment of costs deviating from the rule laid down in Article 104(1) EPC was justified, as no "fresh" case had been made. Moreover the complexity of the case had only come to evidence during the oral proceedings.

New Main Request
Novelty

- Document (D2) could not form prior art under Article 54(3) EPC because it could not claim priority from its US priority document (D2a) because this was not the first application for the relevant invention. This was because a conjugate consisting of the anti-tumour 15A8 antibody and a biological response modifier (BRM) and falling

under the terms of claim 1 of document (D2) was already disclosed in priority document (D17a) filed by the same applicant before the filing date of priority document (D2a). Thus, document (D17a) rather than document (D2a) was the "first application" in respect of anti-tumour antibody-IL 2 fusion proteins, and only document (D17a) could have been a basis for a valid claim to priority, as required by Article 87(4) EPC.

- The recombinant anti-tumour antibody-IL 2 fusion protein of claim 1 was not directly and unambiguously derivable from the three lists of (i) antibodies (see document (D2), page 6, first full paragraph), (ii) BRMs (page 2, line 16 and page 4, lines 52 to 53) and (iii) coupling techniques (chemical coupling and recombinant fusion route).

- The skilled person would not have selected the non-cytotoxic IL 2 as a BRM, since cytotoxicity to cancer cells was a prerequisite of the conjugates disclosed by document (D2).

New Auxiliary Request 1
Article 123(2) EPC

- The feature in claim 1 (ii), according to which the N-terminus of IL 2 was fused to the C-terminus of the immunoglobulin could be derived from Example 7, Figures 6A and 6B in combination with the passage on page 9, lines 20 to 23 of the application as filed.

- Moreover, the presence of a 3' stop codon in the PCR-amplified IL 2 insert (see page 21, lines 23 to 25 and Figure 8 of the application as filed) could only mean that fusion to the immunoglobulin occurred via the N-terminus of IL 2.

New Auxiliary Request 2
Article 84 EPC

- As for the wording "hinge region" in claim 1 (iii) of this request, the hinge region of an immunoglobulin was illustrated in eg Figure 6A and 6B (see "h") of document (D8). Moreover, the skilled person was in a position to identify and locate the hinge region in Figure 2 of the patent in suit, relating to the hinge region of human IgG_1 flanked with polylinkers.

- The increase in flexibility could be tested by comparing the binding activity.

Article 123(2) EPC

- The embodiment according to claim 1 could be directly and unambiguously derived from the application as filed.

Article 83 EPC

- At the priority date of the patent in suit a great many monoclonal antibodies (moabs) directed to tumor-associated antigens were known and publicly available (eg, moab L6; antiganglioside GD2 moab 14.18; moab 225 directed against the human

epidermal growth factor receptor (EGFR)). For instance, the L6 hybridoma that produces moab L6 had been deposited with the American Type Culture Collection (ATCC) under accession No. HB8677 in connection with the filing of European patent application No. 207 963, published on January 14, 1987 as WO 86/03838 (see page 24, lines 18 to 20 of document (D30)). All these antibodies had been used after the priority date of the patent in suit to make recombinant Ab-IL 2 fusion proteins (see document (D22), page 161, 1-h column, last paragraph)

Inventive step

- Document (D17) related to conjugates of moab 15A8 with immunotoxins to be delivered into the tumor cells (the "magic bullet concept"). The claimed fusion proteins, however, provided a novel approach for tumor therapy which combined the direct targeting to tumor cells with an immunomodulatory action based on promotion of lymphocyte proliferation.

- Departing from the chemically linked cytotoxic conjugates disclosed by document (D17), all designed for "internalization" (see "entry" on page 5, line 25), the skilled person had no incentive to turn to recombinant fusion proteins because, *inter alia*, this would have deprived the conjugates of their capability of releasing their cytotoxic/cytolytic moiety within the cell upon intracellular "internalization", followed by enzymatic/pH cleavage, a feature critical for

killing cancer cells (see eg document (D20), page 4842, paragraph bridging l-h and r-h columns).

- Rather than document (D17), the closest prior art had to be represented by documents (D5) and/or (D15), which addressed the administration of the uncoupled anti-tumor antibody (Ab) and/or immunomodulatory IL 2 to treat tumors. The problem to be solved in view of these documents was to provide an improved IL 2-based tumor therapy. In fact, document (D22) (see page 164, first full paragraph) showed that the claimed fusion protein Ab-IL 2 was more effective in treating tumors than the uncoupled Ab and/or IL 2, in particular, in suppressing dissemination and growth of metastasis. Document (D24) further confirmed these experimental results.

- But the activity in vivo of the fusion protein Ab-IL 2 could not be predicted, as serious problems (eg short in vivo half-live of the molecule) could arise (see document (D22), page 162, r-h column, last paragraph). The skilled person had thus no expectation of success.

New Auxiliary Request 3
Inventive step

- It was not obvious to replace the two cysteine residues of the human IgG_1 hinge region by proline and serine so as to permit greater flexibility in the fused molecule.

- It was true that document (D18), on page 25, line 6 prescribed that "Cysteines should be avoided in the hinge", however, this suggestion was made in a different context. Moreover, document (D18) was silent about replacing cysteine with proline, the latter being notoriously a "helix-killer".

VII. The submissions by appellants II and III (opponents (01) and (02)), insofar as they are relevant to the present decision, can be summarized as follows:

Apportionment of costs

- There had been unfair conduct in the appeal procedure on the side of appellant I as regards the very late filing during the second day of the oral proceedings (5 November 2003) of the New Main Request and New Auxiliary Requests 1 to 3, which introduced a "fresh" case.

New Main Request
Novelty

- Claim 1 of this request lacked novelty (Article 54(3) EPC) over document (D2), dealing with conjugates of antibodies directed toward a tumour antigen and a BRM. One embodiment disclosed in this document was a gene fusion product recombinantly produced by fusion of a gene coding for the antigen recognition site of a moab with a gene coding for a BRM, which could be IL 2.

- As regards the citability under Article 54(3) EPC of document (D2), its US priority document (D2a) was the "first invention" in the sense of Article 87(4) EPC, as the earlier US application (D17a) from which pre-published document (D17) claimed priority did not disclose any recombinant fusion protein but merely chemical conjugates of the antibody with the BRM.

New Auxiliary Request 1
Article 123(2) EPC

- The feature according to claim 1 (ii) of this request that the IL 2 molecule had to be fused via its N-terminus to the C-terminus of the immunoglobulin was a generalisation lacking any basis in the application as filed.

New Auxiliary Request 2
Article 84 EPC

- In claim 1 (iii) the wording "hinge region" was not clear since there existed more than one hinge in an antibody, this term being used for designating any sequence between two globular domains thereof. Where this hinge had to be located (eg, between antibody and IL 2 or within the antibody itself) was also not clear.

- In claim 1 (iii) the wording "natural" lacked clarity. It was indeed impossible for a third party to determine whether an antibody not present in a database was a natural one or not. One had to know all the present and future natural hinge

regions, taking into account that the antibody sequence could also undergo spontaneous mutations.

- The wording "natural hinge region" also lacked support in the description, disclosing a hinge flanked by linkers.

- No test to measure the "greater flexibility" was available to the skilled person.

Article 123(2) EPC

- The subject-matter of claim 1 of this request represented an impermissible selection from a plethora of antibodies (listed on page 8, lines 1 to 4 of the application as filed), lymphokines/ cellular factors (ibidem, lines 5 to 31) and constructs (see page 7, lines 16 to 23 and 27 to 30 and page 9, lines 20 to 23).

Article 83 EPC

- Claim 1 covered any immunoglobulin molecule capable of directing the fusion protein to any tumour cell or any tumour associated antigen. The patent did not provide a sufficient disclosure across the whole breadth of claim 1, nor even in respect of the only exemplified antibody L6, specifically mentioned in claims 2 and 3 of this request.

- The relevant deposit for a cell line secreting L6 was not disclosed in the patent, which also failed to provide any technical information for the

skilled person to obtain the exemplified antibody L6.

- Although antibody L6 was described in literature references, such as documents (D19) and (D20), the latter were not sufficient to make a biological material available to the public in the sense required by Article 83 EPC (see decisions T 815/90 and T 576/91).

- Appellant I relied on an ATCC deposit of antibody L6 cited in earlier patent application (D30) filed in the name of Oncogen. However, the deposit cited in the earlier application could not cure the deficiency in the patent in suit, which certainly did not direct the skilled person to look to document (D30) for the deposit information.

- The skilled person could not reproduce the invention in the light of the exemplified plasmid pIL-2/L6 because it comprised DNA encoding only the heavy chain of antibody L6 (not the light chain). The heavy chain alone was, however, insufficient to mediate antigen binding activity.

Novelty

- The fusion protein disclosed by document (D2) implicitly comprised a "natural hinge region of an immunoglobulin molecule". Therefore the subject-matter of claim 1 of this request lacked novelty vis-à-vis document (D2).

Inventive step

- The closest prior art was represented by the chemically linked conjugate "15A8-IL 2" referred to on page 5, lines 13 to 19 of document (D17). The problem to be solved was to provide an alternative means for constructing it. However, the recombinant route for making antibody-IL 2 conjugates was obvious in the light of document (D9) (see page 6904, r-h column, first paragraph), which already showed the feasibility of this route (see also documents (D8) and (D11)).

New Auxiliary Request 3
Inventive step

- It was obvious to replace the cysteine residues in the hinge region of antibody-IL 2 fusion proteins (see document (D18), page 25, line 6: "Cysteines should be avoided in the hinge").

VIII. The appellant I (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of one of the sets of claims filed as New Main Request, New Auxiliary Request 1, New Auxiliary Request 2 or New Auxiliary Request 3, all filed at oral proceedings on 5 November 2003.

The appellant II (opponent 1) requested that the decision under appeal be set aside and that European patent No. 0 439 095 be revoked, that documents (D22) to (D24) should not be allowed into the proceedings, and that there be an apportionment of costs in his

favour in relation to costs incurred in respect of the oral proceedings before the board.

The appellant III (opponent 2) requested that the decision under appeal be set aside and that European patent No. 0 439 095 be revoked, and that there be an apportionment of costs in his favour in relation to costs incurred in respect of the oral proceedings before the board.

Reasons for the Decision

1. The appeals are admissible.

Admissibilty of documents (D22) to (D24) into the proceedings

2. Appellant II requests that documents (D22) to (D24) should not be allowed into the proceedings because of their irrelevance and too late filing.

3. The established Case Law of the Boards of Appeal of the European patent office (4th edition, 2001, pages 324 to 334) shows that one major criterion for the admission of late-filed documents into the proceedings is their relevance. Besides relevance, however, other criteria may also be taken into consideration, such as a possible abuse of procedure, the breach of the principle of good faith or the degree of procedural or technical complication.

4. The board considers that the admitting of late-filed documents (D22) to (D24) into the proceedings is an appropriate exercise of the board's discretion under

Article 114(2) EPC, since it neither hinders the appeal proceedings being conducted in an effective manner, nor increases the degree of procedural/technical complication (see eg decision T 633/97 of 19 July 2000). Moreover, these documents have been submitted in answer to the decision under appeal or to arguments of both appellants II and III and are to be seen in connection with arguments and evidence already on file, which they aim at rendering more convincing. This is the normal behaviour of a party adversely affected by the decision of the first instance.

5. The board also sees no convincing reasons to treat documents (D22) to (D24) differently from the other documents submitted by the parties in the course the appeal proceedings, the late filing of which, however, has not been questioned by appellant II.

New Main Request
Articles 84 and 123 EPC
Claim 1

6. No objections have been raised by appellants II and III under these Articles. The board agrees as well that claim 1, which is identical to claim 1 as granted, satisfies the requirements of Articles 84 and 123 EPC.

Novelty (Article 54(3) EPC)
Claim 1

7. Claim 1 of this request covers a recombinant anti-tumour antibody-IL 2 fusion protein. Appellants II and III maintain that claim 1 lacks novelty (Article 54(3) EPC) over document (D2).

Entitlement of document (D2) to priority

8. Appellant I argues that document (D2) does not form prior art under Article 54(3) EPC because it is not entitled to claim priority from its US priority document (D2a), as this is supposedly not the first application for the invention. Appellant I's reasoning is that a conjugate consisting of the tumour-binding 15A8 antibody and a biological response modifier, which conjugate falls under the terms of claim 1 of document (D2) is already disclosed in an earlier US application (D17a) of the same applicant, filed before the filing date of document (D2a), and which led to document (D17). Therefore the former document (D17a) rather than document (D2a) should be held as the "first application" in respect of antibody-IL 2 fusion proteins for a valid claim to priority, as required by Article 87(4) EPC.

9. However, in the board's view, document (D17a) fails to disclose any anti-tumour antibody-IL 2 fusion proteins. It is true that according to page 10, lines 12 to 15 of this document, the BRMs which may be coupled to the 15A8 antibody include lymphokines and cytokines such as IL 2, however, the coupling occurs chemically, via "bifunctional protein coupling agents" (see page 11, line 10). But a randomly cross-linked antibody-IL 2 conjugate is something different from a recombinant antibody-IL 2 fusion protein. In conclusion, document (D17a) cannot be considered as the "first application" in relation to recombinant anti-tumour antibody-IL 2 fusion proteins, and is no bar to document (D2) validly

claiming priority from document (D2a) under the provisions of Article 87(4) EPC.

10. This "first application" in respect of recombinant anti-tumour antibody-IL 2 fusion proteins is document (D2a). On page 9, lines 15 to 18 this document relates to an "immunoconjugate of an antibody with a biological response modifier... wherein said moiety is selected from ...IL-2". On page 6, lines 12 to 17 thereof it is stated that "alternatively, the immunoconjugate may be a fusion protein prepared by genetic engineering methods known to those in the art. Such a fusion protein would contain the antigen recognition site of an antibody molecule and the cytotoxic moiety of a biological response modifier". The antibody is one "directed toward a cell associated antigen specific for a tumor cell" (see page 6, lines 8 to 9). Insofar as document (D2) discloses recombinant anti-tumour antibody-IL 2 fusion proteins, it forms, therefore, prior art under Article 54(3) EPC because it is entitled to claim priority from its US priority document (D2a) for this information.

Disclosure by document (D2) of a recombinant anti-tumour antibody-IL 2 fusion protein

11. The object of document (D2) is to provide conjugates of antibodies with BRMs, in particular those wherein the antibody is directed toward a cell associated antigen specific for a tumour cell (see page 4, lines 43 to 44). On page 5, lines 3 to 5 reference is further made to "an immunoconjugate that is a gene-fusion product recombinantly produced by fusion of a gene coding for the antigen recognition site of a monoclonal antibody

with a gene coding for a biological response modifier". According to page 4, line 52 and page 5, line 47 of document (D2), this BRM can be IL 2.

12. Although document (D2) does not provide technical details as to how to prepare the recombinant anti-tumour antibody-IL 2 fusion protein, the parties do not dispute that, at the priority date of document (D2), the skilled person was in a position to arrive at this conjugate in the light of the common general knowledge, and the board agrees as well. This position is supported by document (D8), which for instance discloses in detail a very general process for the production of chimeric antibodies by transfection of immortalized mammalian (eg myeloma) cell lines with eg a vector comprising a promoter operably linked to a DNA insert, a first portion of which encodes the variable region of the light or heavy chain of an Ig molecule, which may be directed to cancer antigens (see page 7, last paragraph), whereas the second portion thereof encodes any protein. The myeloma cell may be co-transfected with a vector encoding the complementary heavy or light chain if the cell fails to produce this already. Further, the document also discloses a method for isolating the DNA encoding the light/heavy chain of moabs, which method can be extended to moabs directed to any tumor-associated antigen, a great many of which were known at the priority date of document (D2)(see eg document (D19)). DNA fragments coding for IL 2 were also known from eg document (D5). In view of this, it is the board's view that the technique disclosed by document (D8) provides convincing support that the teaching of document (D2) could be applied by the

skilled person to obtain an anti-tumour antibody-IL 2 fusion protein.

13. Appellant I further argues that the claimed recombinant anti-tumour antibody-IL 2 fusion protein is somehow concealed from the skilled person in the three lists of (i) antibodies (see document (D2), page 6, first full paragraph), (ii) BRMs (page 2, line 16 and page 4, lines 52 to 53) and (iii) coupling techniques (chemical coupling and recombinant route). While conceding that what is claimed can conceptually be derived from the three lists (i), (ii) and (iii) of possibilities mentioned above, the board considers that the decisive question in relation to the novelty issue is rather whether or not the skilled person would inevitably contemplate/arrive at a recombinant anti-tumour antibody-IL 2 fusion protein by reading/following the teaching of document (D2).

14. In order to answer this question, the board observes that the main teaching of document (D2) is to provide conjugates of anti-cancer antibodies with BRMs. In fact, the exemplified antibodies 15A8 and ZME-018 recognize human breast cancer cells (see page 9, lines 9 to 10) and human melanoma cells (see page 12, line 8), respectively. The coupling of these anti-cancer antibodies to the BRMs occurs via chemical coupling agents, the latter being either exemplified in the patent or listed on page 6, lines 1 to 6 thereof. As an **alternative** (see page 3, line 50: "Alternatively") to the chemical coupling of the anti-tumour antibodies to the BRMs, document (D2) teaches the recombinant fusion protein route. Moreover, the possibility that the BRM can be IL 2 is mentioned on page 4, line 52, page 5,

line 47 and in claim 4 of document (D2). The skilled person would consider that IL 2 is worth being used as a BRM (see point 15 infra). In view of the foregoing, the question of whether the skilled person would inevitably contemplate/arrive at a recombinant anti-tumour antibody-IL 2 fusion protein by reading/following the teaching of document (D2), has to be answered in the affirmative.

15. As for appellant I's contention that the skilled person would not turn to the non-cytotoxic IL 2 as a BRM, it is noted that the conjugates disclosed by document (D2) may also bear a non-cytotoxic BRM (see page 3, lines 55 to 56 of document (D2)), provided, however, this moiety exerts its cytotoxic activity indirectly, "by increased host defence mediated process" (see ibidem, page 5, lines 49 to 50). This is exactly the same biological effect relied on by the IL 2-bearing conjugates of the patent in suit (see page 5, last line to page 6, lines 1 to 2 thereof).

16. In conclusion, it is the board's view that document (D2) anticipates the recombinant anti-tumour antibody-IL 2 fusion protein of claim 1 of this request, which cannot be allowed.

New Auxiliary Request 1
Article 123(2) EPC
Claim 1

17. Claim 1 of this request is addressed to a recombinant antibody-IL 2 fusion protein wherein the interleukin 2 molecule is fused via its N-terminus. Such a conjugate does not appear explicitly in the application as filed.

Therefore, the relevant question to be decided is whether this antibody-IL 2 construct having an IL 2 attached via its N-terminus is implicitly but directly and unambiguously derivable therefrom.

18. As a basis for the claimed construct, appellant I relies on Example 7 (as illustrated by Figures 6A, 6B and 8), disclosing an antibody-IL 2 construct, wherein IL-2 is fused to a hinge region (linker) via its N-terminus. It is argued by appellant I that the skilled person would consider that this information that IL 2 is fused via its N-terminus is not restricted to the exemplified construct but has to be extended to any antibody-IL 2 conjugate since the passage on page 9, lines 20 to 23 of the application as filed ("a recombinant vector system may be created to accommodate sequences encoding the ligand in the correct reading frame with a natural or synthetic hinge region") relates to a construct including both a natural or synthetic hinge region.

19. It is not contested that in Example 7, the 5'→3' ternary construct C_1-linker-IL 2 gene indeed encodes the fusion protein L6/IL 2, wherein IL 2 is fused to a linker via its N-terminus (see Figure 6A and 6B of the application as filed, wherein the "novel gene" is IL 2; see also the "Stop" codon in the 3'-end of the mRNA encoding IL 2 in Figure 8). It is also not contested that page 9, lines 20 to 23 relates to a construct including both a natural or synthetic hinge ("linker") region.

20. From those and any other passages of the application as filed, though, it cannot be derived that the feature

according to which IL 2 must be fused to the antibody via its N-terminus is a **compulsory** requirement in respect of any antibody-IL 2 construct, regardless of whether it includes a synthetic linker, a natural linker, or no linker at all. In fact the application as filed in no way points the reader to subclasses of antibody-IL 2 conjugates exhibiting a natural linker or no linker at all, wherein IL 2 is fused to the antibody via its N-terminus, these constructs being now covered by claim 1 at issue.

21. Consequently, claim 1 is amended in such a way that it contains subject-matter which extends beyond the content of the application as filed, contrary to the requirement of Article 123(2) EPC. This request must thus also be refused.

New Auxiliary Request 2
Article 84 EPC
Claim 1

22. Appellants II and III maintain that in claim 1 (iii) the wording "hinge region" is not clear. However, it is commonly known that antibodies are Y-shaped molecules and that there is a hinge between the two arms of the Y and the Fc region. Figures 6A and 6B of document (D8) illustrate fusion proteins in which a hinge is incorporated (see "h"). Moreover, it can be taken from Figure 6B that said hinge comprises three cysteine residues that actually mediate interchain disulfide linkage. Another example of hinge is that of IgG_{2B} having four cysteines that normally mediate interchain disulfide linkage (see document (D8), Figure 3B). The

precise meaning of the term "hinge region" is thus well known to the skilled person.

23. The wording "natural" in claim 1 (iii) is further questioned by appellants II and III as lacking clarity, as it is impossible for a third party to determine whether an antibody (eg not present in a database) is a natural one or not.

In the board's judgement a "natural" hinge region is one as found in nature (eg, as isolated from a hybridoma), ie one which has not undergone any modification in the DNA and/or the amino acid sequence by the intervention of man. Examples of such (rather troublesome) intervention by man are illustrated in eg document (D8), last three lines of page 2 (*in vitro* mutagenesis) or in page 4, lines 8-ff of the patent specification (modification of the natural hinge region of human IgG_1). The skilled person is in a position to distinguish both situations, which never overlap.

24. As for the objection by appellants II and III that the wording "natural hinge region" also lacks support in the description, disclosing a hinge flanked by linkers, attention is drawn to the passage on page 9, line 23 of the application as filed, relating to a "natural…hinge region".

25. Finally, the "greater flexibility" can be measured by checking differences in the antibody binding activity, contrary to appellants II and III's view that no test to measure the flexibility exists.

Article 123(2) EPC

Claim 1

26. Contrary to the view of appellants II and III the subject-matter of claim 1 of this request does not represent an impermissible selection from a plethora of antibodies (listed on page 8, lines 1 to 4 of the application as filed), lymphokines/cellular factors (ibidem, lines 5 to 31) and constructs (see page 7, lines 16 to 23 and 27 to 30 and page 9, lines 20 to 23). This is because an antibody-IL 2 fusion protein including "a natural hinge region of an immunoglobulin molecule, or a modified version of the hinge region sequences of human IgG_1 wherein the two cysteine residues that normally mediate interchain disulfide linkage are replaced by proline and serine" is disclosed *expressis verbis* on page 9, lines 20 to 23 and 30 to 33 of the application as filed.

27. The board is thus satisfied that the amendments made to claim 1 comply with the requirements of Articles 84 and 123(2) EPC.

Article 83 EPC

Claim 1

28. Appellants II and III argue that the patent in suit does not provide a sufficient disclosure across the whole breadth of claim 1, covering any immunoglobulin molecule capable of directing the fusion protein to any tumour cell or any tumour associated antigen. However, the board has already come to the conclusion that the skilled person was, before the priority date of document (D2) (5 May 1989), in a position to obtain any

anti-tumour antibody-IL 2 fusion protein in general (see point 12 supra) and this skilled person's ability persisted at the priority date of the patent in suit (22 January 1990). As to the question of whether the disclosure of the patent in suit also enables the skilled person to prepare a recombinant antibody-based fusion protein comprising a modified version of the hinge region sequences of human IgG_1 wherein the two cysteine residues that normally mediate interchain disulfide linkage are replaced by proline and serine (see claim 1 (iii) of this request), this has to be answered in the affirmative in view of Section 7.1.1 of the patent, giving in detail all the technical information for achieving this goal.

Claims 2 and 3

29. In a further line of argument, appellants II and III maintain that the patent is insufficient in respect of the exemplified antibody L6, specifically mentioned in claims 2 and 3 of this request, because the patent fails to provide any technical information (deposit) for the skilled person to obtain antibody L6.

In the board's view, however, for the purposes of sufficiency of disclosure, an applicant may refer to a micro-organism deposited by a third party and made available to the public before the application was filed. This is the case in the present situation, as hybridoma L6 that produces moab L6 had been deposited with the American Type Culture Collection (ATCC) under accession No. HB8677 in connection with the filing of European patent application No. 207 963, published on January 14, 1987 as WO 86/03838 (see document (D30),

page 24, lines 18 to 20). Therefore, since hybridoma L6 had become available to the public before the priority date of the patent in suit, it was for the applicant neither necessary to deposit the micro-organism anew, nor to refer in the patent to document (D30) for deposit information, as the meaning of the term "antibody L6" was deemed to be already known to the skilled person, eg from literature references such as documents (D19) and (D20) or from the ATCC catalog. In conclusion, no evidence is before the board that the skilled person could not have obtained access to the deposited and publicly available L6 hybridoma/ antibody.

30. The disclosure in the patent in suit of the exemplified plasmid pIL-2/L6, in the view of appellants II and III, is not sufficient because it comprises a DNA encoding only the heavy chain of antibody L6 (not the light chain). However, the patent in suit illustrates on page 5, lines 29 to 34 a technique for obtaining the antigen binding site comprising both the light and heavy chains. Another expedient for obtaining this bicatenary antigen binding site consists in co-transfecting cell lines with both the L6-IL 2 heavy chain fusion vector and a light chain vector (see paragraph 7.2.1).

31. In view of the above findings, the board concludes that no case has been made out that claims 1 to 3 of this request do not satisfy the requirements of Article 83 EPC.

Novelty

32. It is argued by appellants II and III that the subject-matter of claim 1 of this request lacks novelty vis-à-vis document (D2) since the fusion protein disclosed by document (D2) implicitly comprises a "natural hinge region of an immunoglobulin molecule".

However, this technical feature of present claim 1 (iii), namely the presence of a natural hinge region of an immunoglobulin molecule cannot be directly and unambiguously derived from the disclosure of document (D2), which merely relates to a recombinant anti-tumour antibody-IL 2 fusion protein in general (see point 11 supra), without any pointer to particular constructs. Insofar as claim 1 relates to the construct comprising "a modified version of the hinge region sequences of human IgG_1 wherein the two cysteine residues that normally mediate interchain disulfide linkage are replaced by proline and serine so as to permit greater flexibility in the fused molecule", no prior art document discloses such construct, either. Therefore, the board considers that the subject-matter of claim 1 is novel.

33. Appellants II and III do not raise any further objections under Articles 84, 123, 83 and 54 EPC to the remaining claims of New Auxiliary Request 2, not already dealt with under points 22 to 32 supra, and the board also sees none.

Inventive step

Claim 1

34. Appellant I argues that the problem to be solved by the claimed antibody-IL 2 conjugate lies with the provision of an improved IL 2-based tumor therapy compared to the therapy known from documents (D5) and (D15), which address the administration of the **uncoupled** anti-tumor antibody (Ab) and immunomodulatory IL 2 to treat cancer.

35. However, in the board's judgement, tumor therapy by means of a **coupled** anti-tumor antibody-IL 2 conjugate such as the chemically linked conjugate "15A8-IL 2" described in document (D17) must be viewed as closer prior art than tumor therapy involving a mixture of the anti-tumor antibody with IL 2 (documents (D5) and (D15)). This is because conjugate "15A8-IL 2", like the claimed conjugate, exerts its tumor killing effect by targeting IL 2 to malignant cells, where a "host defence mediated process" takes place (compare page 5, lines 13 to 19 of document (D17) with page 3, lines 1 to 3 of the patent in suit; see also point 15 supra). Yet no such targeting of IL 2 to malignant cells is described in documents (D5) and (D15), which thus represent a more remote starting point.

36. Insofar as claim 1 at issue relates to the antibody-IL 2 fusion protein comprising a "natural hinge region of an immunoglobulin molecule", the problem to be solved in view of the chemically linked conjugate "15A8-IL 2" described in document (D17) is thus to provide an alternative means for constructing it. However, in the board's opinion, the recombinant route for making antibody-IL 2 conjugates having a "natural

hinge region of an immunoglobulin molecule" is obvious in the light of document (D9) (see page 6904, r-h column, first paragraph: "the feasibility of using recombinant techniques to attach peptides to the hinge region of the immunoglobulin heavy chain")), which already shows the feasibility of this route and documents (D8) (see page 14, line 13 from the bottom: "hinge") and (D11) (see Figure 1: "h") confirm this view.

Thus, claim 1 comprises an alternative embodiment which is obvious for a skilled person. Consequently New Auxiliary Request 2, which comprises said claim, cannot be allowed.

New Auxiliary Request 3
Articles 84, 123, 83 and 54 EPC
Claims 1 to 6

37. The claims of this request differ from those of New Auxiliary Request 2 in that the recombinant fusion protein of claim 1 of this request is limited to one comprising "a modified version of the hinge region sequences of human IgG_1 wherein the two cysteine residues that normally mediate interchain disulfide linkage are replaced by proline and serine so as to permit greater flexibility in the fused molecule" (see feature (iii)). The conclusions arrived at by the board under points 22 to 33 supra that the claims of New Auxiliary Request 2 satisfy the requirements of the above Articles also apply to those of New Auxiliary Request 3.

Article 56 EPC
Claims 1 to 6

38. The only issue left is the inventive step. Appellants II and III maintain that it would be obvious for the skilled person entering the recombinant route for making antibody-IL 2 conjugates, to replace the cysteine residues in the hinge region (see document (D18), page 25, line 6: "Cysteines should be avoided in the hinge").

39. It is true that document (D18) states: "The spacer sequence may mimic the sequence of a hinge region of an immunoglobulin" (see page 25, lines 7 to 9); "Cysteines should be avoided" (see page 25, line 6) and "The preferred linkers and spacers are cystein free" (see page 7, lines 8 to 9). However, the skilled person coming across document (D18) is taught that this measure is taken for avoiding the presence of reactive side groups in the amino acid sequence of the linker (see page 7, lines 10 to 11), not for increasing the flexibility. Moreover, this document contains no pointer to replace cysteine with proline. On the contrary the skilled person has good reasons for avoiding proline since this "imino acid" (-NH- instead of H_2N-), by subtracting a hydrogen bridge, behaves notoriously as a "helix-killer". But document (D18) prescribes a helix structure (see page 27, line 7 from the bottom: "helically coiled").

40. Therefore, the board must conclude that providing the antibody-IL 2 conjugate recited in claim 1 of this request involves an inventive step. This conclusion has to be extended to claims 2 and 3, relating to specific

embodiments of the conjugate of claim 1 and to claims 4 and 5, addressed to medical uses involving the fusion protein according to claims 1 to 3. Claim 6, covering a DNA molecule encoding the fusion protein of claims 1 to 3 is also inventive.

41. Finally, the above conclusions have to be extended to claims 1 to 6 for the Contracting State ES since they are drafted as corresponding method claims.

Apportionment of costs

42. The request for apportionment of costs has to be decided on the basis of Article 104(1) EPC according to which any party to the proceedings should meet the costs it has incurred unless the instance seized decides differently for reasons of equity. In the present case, the board cannot identify any undue, unfair or abusive conduct in the appeal procedure on the side of appellant I. Concerning the filing during the second day of the oral proceedings (5 November 2003) of the New Main Request and New Auxiliary Requests 1 to 3, it has to be noted that it was done in an attempt to overcome the board's objections: it is the right of the patent proprietor to defend its patent with any argument/claim requests considered useful even if they prove not to succeed in the end. Neither can the conclusion be drawn that the filing of these claim requests introduced a "fresh" case, as they merely represented restricted versions of the claim requests previously on file. In addition, the complexity and the need for restriction have only come to evidence during the oral proceedings. For all these reasons, a different apportionment of costs deviating from the

basic rule laid down in Article 104(1) EPC would not be equitable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

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

   Claims: Claims of New Auxiliary Request 3 submitted at oral proceedings on 5 November 2003

   Description: Pages 2, 3, 4, 5, 6 and 8 as submitted at oral proceedings on 5 November 2003, Page 7 as granted

   Figures: As granted

3. The requests by appellants II and III for apportionment of costs are refused.

The Registrar: The Chairwoman:

P. Cremona U. M. Kinkeldey