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**Datasheet for the decision
of 7 November 2006**

Case Number: T 0411/02 - 3.3.04

Application Number: 92914009.3

Publication Number: 0606217

IPC: C12N 15/62

Language of the proceedings: EN

Title of invention:

CTL4A Receptor, fusion proteins containing it and uses thereof

Patentee:

Bristol-Myers Squibb Company

Opponent:

Genetics Institute

Headword:

CTL4A receptor/BRISTOL-MYERS SQUIBB

Relevant legal provisions:

-

Relevant legal provisions (EPC 1973):

EPC Art. 54, 83, 84, 114(2), 123(2), (3)

EPC R. 78(2), 83(4)

Keyword:

"Admissibility of the appeals (yes)"

"Admission into the proceedings of documents (yes)"

"Admission into the proceedings of requests (yes)"

"Main request - added matter (yes)"

"Auxiliary request 1 - extension of scope of protection (yes)"

"Auxiliary request 2b - added matter, extension of scope of protection (no), clarity, sufficiency, novelty, inventive step (yes)"

Decisions cited:

T 0292/85, T 0059/87, T 0049/89, T 0402/89, T 1002/92,
T 0325/95, T 1126/97, T 0579/01, T 0604/01

Catchword:

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Case Number: T 0411/02 - 3.3.04

DECISION
of the Technical Board of Appeal 3.3.04
of 7 November 2006

Appellant I:
(Patent Proprietor)

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Appellant II:
(Opponent)

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Decision under appeal:

Interlocutory decision of the Opposition
Division of the European Patent Office posted
20 February 2002 concerning maintenance of
European patent No. 0606217 in amended form.

Composition of the Board:

Chair: U. Kinkeldey
Members: B. Claes
D. S. Rogers

Summary of Facts and Submissions

I. European patent No. 0 606 217 was granted for European patent application 92914009.3 based on international application PCT/US92/05202, published as WO 93/00431, with the title "CTLA4A receptor, fusion proteins containing it and uses thereof".

II. The international application contained *inter alia* the following claims:

"3. CTLA4Ig fusion protein reactive with B7 antigen having a first amino acid sequence containing amino acid residues from about position 1 to about position 125 of the amino acid sequence corresponding to the extracellular domain of CTLA4 and a second amino acid sequence containing amino acid residues corresponding to the hinge, CH2 and CH3 regions of human immunoglobulin C γ 1."

"6. A method for regulating functional CTLA4 positive T cell interactions with B7 positive cells comprising contacting said B7 positive cells with a ligand for the B7 antigen to interfere with reaction of endogenous B7 antigen with CTLA4."

"7. The method of claim 6 wherein said ligand is a fusion protein that contains at least a portion of the extracellular domain of CTLA4."

"15. A method for regulating CTLA4-positive T cell interactions with other cells comprising inhibiting the interaction of CTLA4-positive cells with B7 positive

cells by contacting said T cells with a ligand for CTLA4."

"17. The method of claim 15 wherein said ligand is a monoclonal antibody reactive with CTLA4."

"24. A monoclonal antibody reactive with the CTLA4Ig fusion protein of claim 3."

III. The patent as granted contained *inter alia* the following claims for all designated Contracting States except ES and GR:

"3. A fusion protein reactive with B7 antigen having a first amino acid sequence from about position 1 to about position 125 of the amino acid sequence corresponding to the extracellular domain of CTLA4 according to claim 1 comprising amino acid residue Thr⁺¹¹¹ and a second amino acid sequence containing amino acid residues corresponding to the hinge, CH2 and CH3 regions of human immunoglobulin C γ 1."

"6. An in vitro method for regulating functional CTLA4 positive T cell interactions with B7 positive cells comprising contacting said B7 positive cells with a ligand for the B7 antigen to interfere with reaction of endogenous B7 antigen with CTLA4."

"7. The method of claim 6 wherein said ligand is a fusion protein that contains at least a portion of the extracellular domain of CTLA4."

"15. An in vitro method for regulating CTLA-positive T cell interactions with other cells comprising

inhibiting the interaction of CTLA4-positive T cells with B7 positive cells by contacting said T cells with a ligand for CTLA4."

"17. The method of claim 15 wherein said ligand is a monoclonal antibody reactive with CTLA4."

"18. The method of claim 17 wherein said ligand is a fragment of said monoclonal antibody."

"21. A monoclonal antibody specifically reactive with the fusion protein of claim 3."

"25. The use of a ligand as defined in claims 15 to 18 for preparing a pharmaceutical composition useful for regulating CTLA4 positive T cell interactions with other cells."

The claims for ES and GR corresponded to these claims.

- IV. The patent had been opposed to the extent of claims 6, 7, 10 to 13, 15 to 22, 24, 25 and 27 for all the designated Contracting States on the grounds of Article 100(a) EPC, combined with Articles 54 and 56 EPC, as well as Articles 100(b) and 100(c) EPC.
- V. On 21 February 2002 the opposition division posted a copy of its written decision to the patent proprietor under cover of a communication dated 21 February 2002. A copy of this decision was posted to the opponent on 20 February 2002 under cover of a communication with the same date.

VI. The receipt of delivery from the German Post Office ("Rückschein") concerning the communication to the proprietor and the records of the EPO show that these communications were dispatched by registered mail on 21 February 2002.

VII. Both the patent proprietor (appellant I) and the opponent (appellant II) have appealed the interlocutory decision of the opposition division to maintain the patent on the basis of an auxiliary request 2 comprising three sets of 27 claims for all designated Contracting States (except ES and GR), ES and GR, respectively, filed during oral proceedings before the opposition division (Article 102(3) EPC).

VIII. Appellant I filed its notice of appeal against the decision of the opposition division on 2 May 2002, paid the appeal fee on the same date and filed a written statement setting out the grounds of appeal on 3 July 2002.

IX. On 15 July 2002 the registry sent a communication to appellant I by order of the board informing them *inter alia* that:

"It appears from the file that the written statement of grounds of appeal against the decision of the Opposition Division of the European Patent Office of 20.02.2002 (*sic*) was filed out of time (date of receipt: 03.07.02). It is therefore to be expected that your appeal will be rejected as inadmissible pursuant to Article 108 EPC in conjunction with Rule 65(1) EPC."

- X. On 19 July 2002, appellant I submitted copies from their file of the communication from the opposition division dated 21 February 2002 under cover of which it had posted its written decision to appellant I.
- XI. On 11 September 2002 the board sent a further communication stating that following an internal investigation, in the:
- "(...) non-binding opinion of the Board (...) the decision of the opposition division was actually posted to the patent proprietor on 21 February 2002. Accordingly the statement of grounds of appeal must be considered as filed in due time pursuant to Article 108 and Rule 78(2) EPC".
- XII. Appellants I and II responded to the board's communication with letters dated 16 September 2002 and 22 April 2003, respectively.
- XIII. The parties were summoned to oral proceedings to take place on 6 and 7 November 2006.
- XIV. With letter dated 3 July 2006 appellant II submitted 13 further documents for consideration in the appeal proceedings.
- XV. With letter dated 21 September 2006, appellant I filed a main request and eight auxiliary requests, i.e. auxiliary requests 1, 2a, 2b, 3a, 3b, 3c, 3d and 4.

Claim 6 of the main request for all designated Contracting States except ES and GR read:

"6. A monoclonal antibody specifically reactive with the fusion protein of claim 3, which comprises an active binding region which is reactive with the extracellular domain of CTLA4 receptor."

Claim 10 of auxiliary request 1 for all designated Contracting States except ES and GR read:

"10. The use of a ligand for CTLA4 for preparing a pharmaceutical composition which ligand is useful for regulating CTLA4 positive T cell interactions with other cells, wherein said ligand is a monoclonal antibody reactive with CTLA4."

Claim 6 of auxiliary request 2a for all designated Contracting States except ES and GR was identical to claim 6 of the main request for the same States.

XVI. Oral proceedings took place on 6 and 7 November 2006 during which appellant I filed a new auxiliary request 2b. Claim 7 to 11 of auxiliary request 2b for all designated Contracting States except ES and GR read:

"7. The use of a ligand for the B7 antigen for preparing a pharmaceutical composition useful for regulating CTLA4 positive T cell interactions with B7 positive cells, which ligand is capable of interfering with reaction of endogenous B7 antigen with CTLA4, wherein said ligand is a fusion protein that contains at least a portion of the extracellular domain of CTLA4."

"8. The use of claim 7, wherein said ligand is a fusion protein of claim 3.

"9. The use of claim 7, wherein said ligand is a fusion protein as defined in claim 2 or encoded by the DNA of claim 4.

"10. The use of a ligand for CTLA4 for preparing a pharmaceutical composition useful for regulating CTLA4 positive T cell interactions with other cells, which ligand is capable of inhibiting the interaction of CTL4-positive T cells with B7 positive cells, wherein said ligand is a monoclonal antibody reactive with CTLA4."

"11. The use of claim 10, wherein said ligand is a fragment of said monoclonal antibody.

Claims 1 to 6 and 12 of auxiliary request 2b for the designated Contracting States AT *et al.* were identical to claims 1 to 5, 23 and 26 as granted. Claims 1 to 5, 6 and 12 of auxiliary request 2b for the designated Contracting States ES and GR were identical to claims 1 to 5, 23 and 26 as granted for that the States ES and GR, respectively. Claims 7 to 11 of auxiliary requests 2b for the Contracting States ES and GR were identical to the same claims of auxiliary request 2b for all designated Contracting States except ES and GR.

XVII. Appellant I (patentee) requested that its appeal be declared admissible, that the decision under appeal be set aside and the patent be maintained on the basis of (i) claims 1 to 14 of the main request, or claims 1 to 12 of auxiliary request 1, or claims 1 to 14 of auxiliary request 2a, all submitted on 21 September 2006; or (ii) claims 1 to 12 of new

auxiliary request 2b submitted on 6 November 2006 at the oral proceedings.

Appellant II (opponent) requested that the decision under appeal be set aside and that at least claims 6, 11, 12 and 14 of the main request submitted on 21 September 2006, and any subsequent claims based upon these claims be revoked.

XVIII. The following documents are relevant for this decision:

- (D1) WO 92/00092
- (D2) Linsley *et al.* (1991), *J. Exp. Med.*, Vol. 173, pages 721-730.
- (D3) Damle *et al.* (1991), *Eur. L. Immunol.*, Vol. 21, pages 1277-1282.
- (D4) Brunet *et al.* (1987), *Nature*, Vol. 328, pages 267-270.
- (D5) Linsley *et al.* (1990), *PNAS*, Vol. 87, pages 5031-5035.
- (D7) Brunet *et al.* (1988), *Immunological Reviews*, No. 103, pages 21-36.
- (D8) Dariavach *et al.* (1988), *Eur. J. Immunol.*, Vol. 18, pages 1901-1905.
- (D9) Linsley *et al.* (1991), *J. Exp. Med.*, Vol. 174, pages 561-569.

(D10) Lafage-Pochitaloff *et al.* (1990), *Immunogenetics*,
Vol. 31, pages 198-201.

(D20) Linsley *et al.* (1992), *J. Exp. Med.*,
Vol. 176, 1595-1604.

(D30) Linsley & Golstein (1996), *Current Biol.*,
Vol. 6(4), pages 398-400.

XIX. The arguments put forward by appellant I which are relevant for the present decision can be summarised as follows:

Admissibility of the appeal of appellant I

- The notification of the decision of the opposition division was dated 21 February 2002. On the basis of this date the grounds of appeal were thus filed in time.

Admission into the proceedings of documents filed by appellant II with letter of 3 July 2006

- With the exception of document D20, the 12 further documents filed by appellant II with his letter dated 3 July 2006 should not be admitted into the proceedings because they were filed late and were not relevant to any of the issues in the proceedings.

*Main request and auxiliary request 2a, claim 6 for all designated Contracting States except ES and GR,
Article 100(c) EPC*

- The term "specifically reactive" in claim 6 had been introduced during the examination proceedings in order to overcome a novelty objection raised by the examining division that monoclonal antibodies reactive with the fusion protein of claim 3 also comprised such antibodies which were commercially available in the state of the art that reacted with the Ig part of the fusion protein. The amendment had therefore been undertaken to exclude from the claimed subject-matter such monoclonal antibodies that were not reactive with the extracellular domain of CTLA4. Antibodies that were only reactive with the extracellular domain of CTLA4, i.e. those that had been intended to be retained after the amendment, found however a clear implicit basis in various passages and claims of the application as filed. Although there was no verbatim basis in the application as originally filed for the feature, the specific monoclonal antibodies of claim 6 were thus implicitly disclosed in the application as filed.

Auxiliary request 1, claim 10 for all designated Contracting States except ES and GR, Article 123(3) EPC

- The scope of protection conferred by claim 10 did not extend the protection conferred by either of claims 21 and 25 of the patent as granted. The claim therefore did not infringe the requirements of Article 123(3) EPC.

Auxiliary request 2b

Amendments, Articles 84, 123(2)(3) EPC

- The claims complied with all the formal requirements of the EPC.

Sufficiency of disclosure

- The relevant function of CTLA4 in the claims was that it binds to B7. For the enablement of the subject-matter of claims 7 and 10, the disclosure of the exact nature of the CTLA4-B7 interaction mechanism was not relevant. What was important under the provision of Article 83 EPC is that it works, which it did. The claims do not recite an up- or down regulation of the immune reaction.
- The methods recited in the patent at page 8, line 55 to page 9, line 14 are sufficient to enable monoclonal antibodies having the functions indicated in claims 7 and 10.

Novelty and inventive step

- None of the cited prior art disclosed the subject-matter of claims 7 and 10 so that novelty for these claims could be assumed.
- Closest prior art for the subject-matter of claims 7 and 10 of the second auxiliary request was document (D4). The objective technical problem for these claims was the provision of a use for CTLA4 and for antibodies reactive with CTLA4.
- The function of CTLA4 was not known in the prior art. Without knowing the function of CTLA4, the skilled person had no motivation to solubilise

CTLA4, to incorporate the extracellular domain into a fusion protein, to raise antibodies against said fusion protein or to prepare pharmaceutical compositions which contain said fusion proteins and said anti CTLA4 antibodies.

- The subject-matter of claims 7 and 10 and the claims dependent thereon of auxiliary request 2b therefore involved an inventive step.

XX. The arguments put forward by appellant II which are relevant for the present decision can be summarised as follows:

Admission into the proceedings of documents filed by appellant II with letter of 3 July 2006

- The 13 documents filed with letter dated 3 July 2006 were not "late" filed. Furthermore, a duty of the EPO vis-à-vis the public was not to grant or maintain invalid patents. The EPO was therefore obliged to assess the citation's relevance by considering the facts. None of the documents would lead to any delay in the proceedings as they did not contain additional experiments. For these reasons the documents should be admitted in the proceedings and taken into account if relevant.

Late filed requests

- The requests filed by appellant I with his letter dated 21 September 2006 should not be allowed into the proceedings as these did not constitute a sequence of fall-back positions for the patentee

which would deal with a sequence of particular grounds of appeal which endangered the patent. The set of requests therefore bore the danger of actually constituting "a pleiades of requests" cascading into an undetermined number of possible alternatives.

- The late submission of the claims for the designated Contracting States ES and GR corresponding to the claims of auxiliary request 2b which originally, i.e. in its version as submitted with letter dated 3 July 2006, only contained claims for all designated Contracting States except these two states, should not be allowed.

Main request and auxiliary request 2a, claim 6 for all designated Contracting States except ES and GR, Article 100(c) EPC

- The amendment in claim 6 of the main request that the monoclonal antibody is "specifically" reactive with the CTLA4Ig fusion protein of claim 3 resulted in claimed subject-matter which extends beyond the content of the application as filed (Article 100(c) EPC). A skilled person would understand the term "specifically reactive" with a protein (here a fusion protein) as being reactive and *only* reactive with the protein (here fusion protein). Such monoclonal antibodies were not disclosed in the application as filed

Auxiliary request 1, claim 10 for all designated Contracting States except ES and GR, Article 123(3) EPC

- Claim 10 for all designated Contracting States except ES and GR of auxiliary request 1 amounts to an impermissible broadening of scope of the patent, in particular that of claims 21 and 25 and is therefore not allowable under Article 123(3) EPC.
- Claim 21 as granted could not afford any scope of protection whatsoever, because the claim was invalid for non-compliance with the requirements of Article 100(c) EPC.

Auxiliary request 2b

Amendments, Articles 84, 123(2)(3) EPC

- Claims 24 and 25 as granted referred to the use of a ligand as defined in claims 6 and 15 as granted, which are based on claims 6 and 15 as originally filed. Claims 6 and 15 defined the ligand not by being "capable of inhibiting the interaction of CTL4-positive T cells with B7 positive cells" but rather by the functionality of interfering or inhibiting the interaction in a method claim. The amendment therefore violates both the requirements of Article 84 and 123(3) EPC.

Sufficiency of disclosure

- The patent had been granted on the basis of incorrect science. In particular the patent did not provide the true function of CTLA4 and suggested the complete opposite, and wrong, function seeing that it was now known that CTLA4 is a negative regulator of T cell receptor signalling, counterbalancing the

stimulation of CD28. Although the patent stated that anti-CTLA4 antibodies may be used to inhibit T cell proliferation, such antibodies actually blocked the binding of CTLA4's ligands and therefore stimulated the immuneresponse. In order to enable a pharmaceutical composition as claimed the patent needed to disclose the correct function of CTLA4. For these reasons the patent as a whole was not enabled.

- The subject matter of claims referring to the monoclonal antibodies, i.e. claim 10, were not enabled. The patent did not provide a single anti-CTLA4 monoclonal antibody. Furthermore it suggested the use of the CTLA4Ig fusion protein as antigen in the disclosed anti-CTLA4 monoclonal antibody production method (patent, page 8, line 55 to page 9, line 14, in particular line 1 of page 9).
- Although the subject-matter of claim 10 was to the use of a ligand for CTLA4 for preparing a pharmaceutical composition useful for regulating CTLA4 positive T cell interactions with other cells, the patent only disclosed this functionality with B7⁺ CHO cells (patent, page 14, lines 7 to 12).
- The subject-matter of claim 10 was not sufficiently disclosed as the wording "inhibiting" in "capable of inhibiting the interaction of CTLA4-positive cells with B7 positive cells" also included the inhibition of the interaction of these cells, e.g. also covering the CD28/B7 interaction which was not influenced by the antibody.

Novelty and inventive step

- The closest prior art for the assessment of inventive step was the common general knowledge of the skilled person on T cell proliferation related diseases, i.e. the need to suppress T cell proliferation in the case of e.g. autoimmune diseases and graft vs. host reactions or the need to enhance T cell proliferation in the case of e.g. infectious diseases.

- The problem to be solved by the subject-matter of claims 7 and 10 was therefore the provision of a compound for regulating T cell proliferation. The patent solved this problem either by the provision of the CTLA4Ig fusion protein or of anti-CTLA4 antibodies.

- The CTLA4/B7 interaction was not the only molecular interaction between T cells and B cells. Accordingly, an anti-CTLA4 antibody would not be able to "inhibit" this interaction but would rather ensure the interaction of the cells by e.g. the means of the CD28/B7 interaction.

- Document (D10) disclosed the virtually identical chromosomal location of the genes encoding CD28 and CTLA4, that CD28 and CTLA4 are both members of the Ig superfamily belonging to a subgroup of membrane bound single V-domains and that both genes could have derived from a common ancestor through a process of duplication. The document stated further that the structural homology between CD28 and CTLA4 suggested that they could share some similarity at

the putative ligand-binding or transduction level. Document (D10) established a clear link between the CD28/B7 interaction and the CTLA4/B7 as it rendered it obvious to the skilled person that CTLA4 behaved similarly to CD28, i.e. the molecule which mediated T cell/B cell interaction by binding to the B7 antigen and which interaction could be regulated either by contacting said B cells with a monoclonal antibody specific for the B7 antigen or by contacting said T cells with a ligand for CD28.

- Seeing that the isolation of CTLA4 and the generation of antibodies thereto were a matter of routine in the technical field as could also be taken from the description of the patent, the skilled person would implement the subject-matter of claims 7 and 10 without requiring any undue experimentation.
- The subject-matter of claims 7 and 10 therefore lacked inventive step.

Reasons for the Decision

Admissibility of the appeals

1. The appeal of appellant II is admissible. As for the admissibility of the appeal of appellant I the board observes the following:
2. The investigations of the EPO and the evidence put forward by the proprietor establish that on 21 February 2002 the opposition division posted a

communication dated 21 February 2002 to the proprietor notifying the proprietor of its written decision. The opponent, Appellant II, has not contested this fact. Accordingly, the factual situation is that a notification was posted by registered letter to the proprietor on 21 February 2002.

3. Article 108 EPC provides that a written statement setting out the grounds of appeal be filed at the EPO within four months after the date of notification of the decision appealed from. Rule 78(2) EPC provides that in the case of a notification effected by registered letter, the notification is deemed to have been received ten days following the date of posting. Rule 83(4) EPC provides that where a period is expressed as a number of months, it expires in the relevant subsequent month on the day which has the same number as the day on which the relevant event occurred, the relevant event, in this case, being the notification of the decision.
4. The effect of Rule 78(2) EPC in the present case is that following the posting of the notification of the decision to the proprietor on 21 February 2002, the Proprietor is deemed to have received the notification on Sunday 3 March 2002. The combined effect of Article 108 EPC and Rule 83(4) EPC is that the four month time limit for the proprietor to file its written statement setting out the grounds of appeal expired on 3 July 2002.
5. By filing its written statement setting out the grounds of appeal on 3 July 2002, appellant I has thus complied with the relevant time limit set out in the EPC.

Admission into the proceedings of documents filed by appellant II with letter of 3 July 2006

6. In their submissions, both parties have relied on additional documents filed for the first time during the appeal proceedings. Appellant I has objected in particular to the submission of 12 of the 13 further documents by appellant II with letter of 3 July 2006, i.e. about 4 months before the oral proceedings (see section XIX).

7. In proceedings before the Boards of Appeal new facts and evidence which go beyond the facts and evidence presented in the notice of opposition should only be admitted into the proceedings if *prima facie* there are good reasons to suspect that such late-filed material would prejudice the maintenance of the European patent (see e.g. decision T 1002/92, OJ EPO 1995, 605).

According to the established case law of the Boards of Appeal new facts and evidence, e.g. documentary evidence filed shortly before or during the oral proceedings may not in principle be admitted into the opposition appeal proceedings, if they would lead to an undue delay in the proceedings. Accordingly, the Rules of Procedure of the Boards of Appeal (RPBA) provide that any amendment to a party's case after it has filed its grounds of appeal - or after its reply to the grounds of appeal - may be admitted and considered at the Board's discretion; amendments sought to be made after oral proceedings have been arranged shall not be admitted, if they raise issues which the Board or the other party cannot reasonably be expected to deal with

without adjournment of the oral proceedings
(Article 10(b), points 1 and 3 RPBA, OJ EPO 2003, 58).

8. The board is of the opinion that the content of the 12 documents submitted by appellant II with letter of 3 July 2006, i.e. about 4 months before the oral proceedings, and to the introduction of which appellant I had objected, was at a first glance helpful in deciding the case. Furthermore, the board considers that none of the late filed documentary evidence filed by the parties to the proceedings is such that it cannot be reasonably dealt with by the parties.
9. In view of the above considerations, the board, does not make use of its discretion pursuant to Article 114(2) EPC and admits these 12 documents into the proceedings.

Late filed requests

10. Appellant II has objected to the introduction of a main request and 8 auxiliary requests filed by appellant I with letter dated 21 September 2006, i.e. about 6 weeks before oral proceedings, for being late filed.
11. The Boards of Appeal have developed criteria for deciding on the admissibility of late-filed requests. Decision T 1126/97 of 13 December 2001, for example, summarises conditions under which late amendments are admissible:
 - (i) there should be some justification for the late filing;

(ii) the subject-matter of the new claims should not diverge considerably from the claims already filed, in particular they should not contain subject-matter which has not previously been claimed.

(iii) the new claims should be clearly allowable in the sense that they do not introduce new objections under the EPC and overcome all outstanding objections.

12. As to the **first condition**, the board accepts as a justification for the late filing of these requests that appellant I, in preparation for oral proceedings and as a reaction to appellant II's submissions of 3 July 2006, including the submission of 13 further documents, intended to focus the requests on certain claims relevant for its case. Accordingly, the requests corresponded to a large extent to, and are focussed on, certain claims as granted, contrary to requests filed previously which contained a number of claims newly formulated in comparison to the claims as granted. In addition, the new requests reduced the number of claims considerably, thereby deleting certain claims which no longer needed a decision of the board. The new requests therefore simplify the case considerably, as was agreed by appellant II.

13. The rationale behind the **second condition** is that it is difficult, and therefore contrary to the principle of fairness, for an opponent to deal properly with subject-matter which significantly differs from previously claimed subject-matter. In the board's view subject-matter may be regarded as "significantly different" or "diverging considerably" when it requires examination of for example, a new solution to a new

technical problem, or, in other words, when it creates a "new case". In the present case the requests reduced the number of claims considerably, thereby deleting certain claims which therefore no longer need a decision from the board. Appellant II has not argued that the new requests introduced subject-matter not previously claimed. The new requests can therefore not be considered to diverge considerably, in the above sense, from the previous requests on file.

14. As to the **third and last condition**, the notion of "clear allowability" does not mean that an amendment must be acceptable without any consideration. Rather it means that it should not introduce new objections under the EPC. The board considers that new objections under the EPC have not been introduced in this case.

15. The set of auxiliary requests filed with appellant I's letter dated 21 September 2006 is divided into four numbered groups which were intended to make clear which claims of the main request may be further amended and how. The board therefore agrees with appellant II that the requests do not merely constitute a simple and conventional sequence of fall-back positions for appellant I (patentee) which deal with a sequence of particular grounds of appeal which would endanger the patent. However, the board is satisfied that the four groups of auxiliary requests address respective objections put forward by appellant II endangering the patent. In particular, auxiliary request 1 dealt with the ground under Article 100(c) EPC which was relevant for claims 6 and 14 of the main request; the claims of auxiliary requests 2 and 2b address a possible problem of claims 8 and 11 of the main request under the

requirement of Article 123(2) EPC, whereas the claims of auxiliary requests 3a, 3b, 3c and 3d address the issues relevant under inventive step. Finally, auxiliary request 4 constituted the ultimate fall-back position of appellant I, solely comprising claims which had not been opposed. The board is therefore satisfied that the set of requests filed with letter of 21 September 2006, constitutes in fact a simplified presentation of possible reactions in defence of the patent addressing the respective objections against the patent in respect of various claims.

16. Appellant II has furthermore objected to the late submission of the claims for the designated Contracting States ES and GR corresponding to the claims of auxiliary request 2b which originally, i.e. in its version as submitted with letter dated 3 July 2006, only contained claims for all designated Contracting States except these two states. The fact that appellant I, contrary to the main request, has not completed the set of auxiliary requests with letter dated 21 September 2006 with sets of claims for ES and GR respectively, is considered by the board to be legitimate in the same context. The absence of claim sets for the auxiliary requests can not be interpreted as an abandonment of such, but rather as an indication that at a later stage in the procedure the claims for ES and GR would have to be adapted to any eventual set of claims for the all designated Contracting States except ES and GR which would be found patentable by the board.
17. For the above reasons the board has admitted the sets of claims for ES and GR, corresponding to new auxiliary

request 2b filed during oral proceedings, into the proceedings.

Main request, claim 6 for all designated Contracting States except ES and GR, Article 100(c) EPC

18. The feature that the monoclonal antibody of claim 6 of the main request is "**specifically** reactive with the fusion protein of claim 3" has been introduced in claim 24 as originally filed by way of amendment during the examining proceedings and resulted in claim 21 as granted. Appellant II has argued that this amendment introduced added-matter which went beyond the disclosure of the application as filed.

19. It is accepted in the case law of the boards of appeal that a patent or a patent application may define technical terms and determine how a skilled person has to interpret a specific word when used in the description or in the claims. This is sometimes referred to as a patent being its own dictionary. This will not be necessary if the patent application or patent does not depart from the meaning a term normally has in the respective technical field and which a skilled person would attribute to it. If however it is intended to use a term which is known in the art to define a particular subject-matter to mean one thing to mean something different, the description must explicitly give this word a special, overriding definition.

20. Appellant II has submitted that in the context of monoclonal antibodies a skilled person would understand the term "specifically reactive" with a protein (here a

fusion protein) as being reactive and only reactive with the protein (here fusion protein). Such monoclonal antibodies were not disclosed in the application as filed so that the amendment infringed the requirements of Article 123(2) EPC, and consequently claim 6 infringed the requirements of Article 100(c) EPC.

21. The board notes that appellant I has not contested that the above interpretation of the term complies with the conventional understanding of the term in the relevant technical field. The board can also agree with this definition. Neither has appellant I argued that specific monoclonal antibodies which comply with the conventional definition are actually disclosed in the application as originally filed.

22. Appellant I has argued that the term had been introduced into the claims during the examination proceedings in order to overcome a novelty objection raised by the examining division that monoclonal antibodies reactive with the fusion protein of claim 3 also comprised such antibodies which were commercially available in the state of the art that reacted with the Ig part of the fusion protein. The amendment had therefore been undertaken to exclude from the claimed subject-matter such monoclonal antibodies that were not reactive with the extracellular domain of CTLA4. Antibodies that were only reactive with the extracellular domain of CTLA4, i.e. those that had been intended to be retained after the amendment, found however a clear implicit basis in various passages and claims of the application as filed. Although there was no expressis verbis basis in the application as originally filed for the feature, the specific

monoclonal antibodies of claim 6 were implicitly disclosed in the application as filed.

23. The term "specifically reactive" is not explicitly defined in the application as originally filed so that the present case is not within the framework of case law mentioned above, where a patent description may serve as its own dictionary. In application of the above principle therefore the term "specifically reactive" is to be interpreted as having the meaning the term normally has in the respective technical field and which a skilled person would attribute to it. In agreement with appellant I however the board notes that monoclonal antibodies which comply with the conventional definition of "specifically reactive" and which therefore could form a basis for the amendment are not disclosed in the application as originally filed. The board therefore judges that the amendment does not find a basis in the application as originally filed.

24. In view of the above, claim 6 of the main request, fails to meet the requirements of Article 100(c) EPC. Consequently, the main request is not allowable.

Auxiliary request 1, claim 10 for all designated Contracting States except ES and GR, Article 123(3) EPC

25. Article 123(3) EPC provides that during opposition proceedings the claims of the European patent may not be amended in such a way as to extend the protection conferred upon grant. So, an act which did not infringe the patent as granted cannot become an infringing act as a result of an amendment after grant (see T 59/87,

OJ EPO 1988, 347, reasons point 2; T 604/01 of 12 August 2004, reasons point 2.3, T 579/01 of 30 June 2004, reasons point 9). In accordance with the established case law of the Boards of Appeal (see T 49/89 of 10 July 1990, reasons point 3.2.2; T 402/89 of 12 August 1991, reasons point 2), the legal notion "protection conferred" in Article 123(3) EPC refers to the totality of protection established by the claims as granted and not necessarily to the scope of protection within the wording of each single claim as granted. Under Article 123(3) EPC, the patentee is generally allowed to redraft, amend or delete the features of some or all claims and is not bound to specific terms used in the claims as granted as long as the new wording of the claims does not extend the scope of protection conferred as a whole by the patent as granted. Thus, in order to assess any amendment under Article 123(3) EPC after grant, it is necessary to decide whether or not the totality of the claims before amendment in comparison with the totality of the claims after amendment extends the protection conferred (see T 579/01 of 30 June 2004, reasons point 9).

26. Claim 10 of auxiliary request 1 for all designated Contracting States except ES and GR is directed to the use of a ligand which is a monoclonal antibody reactive with CTLA4, which is useful for regulating CTLA4 positive T cell interactions with other cells, for preparing a pharmaceutical composition. Appellant I has argued that the scope of protection conferred by claim 10 does not extend the protection conferred by either of claims 21 and 25 of the patent as granted. The claim therefore did not infringe the requirements of Article 123(3) EPC.

27. Claim 25 as granted is directed to the use of a ligand as defined in claims 15 to 18 (as granted) for preparing a pharmaceutical composition which is useful for regulating CTLA4 positive T cell interactions with other cells. Claim 15 as granted in turn was directed to an *in vitro* method for regulating CTLA-positive T cell interactions with other cells comprising inhibiting the interaction of CTLA4-positive cells with B7 positive cells by contacting said T cells with a ligand for CTLA4 whereas claim 17 was directed to a method of claim 15 wherein said ligand is a monoclonal antibody reactive with CTLA4.
28. One of the substantive differences between claim 10 of auxiliary request 1 and claim 25 as granted is the definition of the ligand as being a monoclonal antibody reactive with CTLA4 which is useful for regulating CTLA4 positive T cell interactions with other cells (claim 10) as opposed to a ligand as defined in claim 15 and 17 as granted. Although the board agrees with appellant I that the structural definition of the ligand in accordance with claims 15 and 17 is that of a monoclonal antibody reactive with CTLA4, it notes however that the "usefulness" indicated in the claim is explicitly referring to the inhibition of the interaction of CTLA4-positive cells with **B7 positive cells** by contacting said T cells with the ligand. The monoclonal antibody reactive with CTLA4 which is therefore further characterised in claims 15 and 17 by the feature of its usefulness for regulating CTLA4 positive T cell interactions with **B7 positive cells**. This characterising feature is however narrower than a technical feature characterising a monoclonal antibody

- reactive with CTLA4 which is useful for regulating CTLA4 positive T cell interactions with **other cells**, as the latter does not necessarily require the antibody to regulate the interaction with B7 positive cells only.
29. In view of the above considerations, the ligand of claim 15 and 17 as granted is more narrowly defined than the ligand of claim 10. Accordingly, the protection conferred by claim 10 is broader than that provided by claim 25 as granted.
30. Claim 21 as granted concerns a monoclonal antibody specifically reactive with the fusion protein of claim 3, being a fusion protein reactive with B7 antigen having a first amino acid sequence from about position 1 to about position 125 of the amino acid sequence corresponding to the extracellular domain of CTLA4 according to claim 1 comprising amino acid residue Thr+111 and a second amino acid sequence containing amino acid residues corresponding to the hinge, CH2 and CH3 regions of human immunoglobulin C γ 1. The board notes in this context that the monoclonal antibody of claim 21 is, contrary to the monoclonal antibody of claim 10 which is defined to be "reactive" with CTLA4, "specifically reactive" with certain structurally defined parts of CTLA4. The definition of the antibody as subject-matter of claim 21 as granted is therefore narrower than the definition of the monoclonal antibody in claim 10. Accordingly, the protection conferred by claim 10 is also broader than that provided by claim 21 as granted.
31. The board therefore concludes that the scope of protection conferred by claim 10 is extended as

compared to that conferred by the patent as granted and does therefore not meet the requirements of Article 123(3) EPC.

32. In view of the above conclusion, the board sees no necessity to decide on the objection of appellant II, that claim 21 as granted could not actually afford any scope of protection whatsoever, because the claim was invalid for non-compliance with the requirements of Article 100(c) EPC. The board nevertheless draws attention to decision T 325/95 of 18 November 1997, point 2.2) deciding on an analogous issue.

Auxiliary request 2a, claim 6 for all designated Contracting States except ES and GR, Article 100(c) EPC

33. Claim 6 of auxiliary request 2a is identical to claim 6 of the main request. For the same reasons that apply to the main request (see point 18 to 24 *supra*), this request fails to comply with the requirements of Article 100(c) EPC.

Auxiliary request 2b

Amendments, Articles 84, 123(2)(3) EPC

34. Since the requirements of Article 84 EPC are not a ground of opposition and the ground of opposition under Article 100(c) EPC has not been invoked against claims 24 and 25 of the patent as granted by appellant II, the examination of the requirements of Articles 84 and 123(2) EPC of claims 7 and 10 of auxiliary request 2b is restricted to amendments made over the patent in its granted form.

35. Claim 7 of this request for all designated Contracting States except ES and GR is an amended version of claim 24 as granted, whereby the ligand is defined as being "for the B7 antigen", being a fusion protein that contains at least a portion of the extracellular domain of CTLA4 and **being capable** of interfering with the reaction of endogenous B7 antigen with CTLA4. Claim 24 as granted contained a direct reference to the ligand as defined in claims 6 and 7 as granted. The ligand as defined in present claim 7 is defined in the same technical terms as the ligand defined in claims 6 and 7 as granted which in turn find a basis in claims 6 and 7 as originally filed. Accordingly, the board concludes that the amendments over claim 24 as granted, contained in claim 7, do not constitute added-matter.
36. Claim 10 of the request for all designated Contracting States except ES and GR is an amended version of claim 25 as granted, whereby the ligand is further defined as being for CTLA4, being a monoclonal antibody reactive with CTLA4 and **being capable** of inhibiting the interaction of CTLA4 positive T cells with B7 positive cells. Claim 25 as granted contained a direct reference to the ligand as defined in claims 15 and 17 as granted. The ligand as defined in claim 10 is defined in the same technical terms as the ligand defined in claims 15 and 17 as granted which in turn finds a basis in claims 15 and 19 as originally filed. Accordingly, the board concludes that the amendments over claim 25 as granted contained in claim 10 do not constitute added-matter.

37. Claims 8 and 9 which are dependent on claim 7 and claim 11 which is dependent on claim 10 correspond to claim 24 as granted with reference to claims 8 and 9 as granted and claim 25 as granted with reference to claim 18 as granted which in turn have claims 8, 9 and 18 as counterpart in the application as originally filed. These claims therefore comply with the requirements of Article 123(2) EPC.
38. In view of the above considerations the amendments in claims 7 to 11 comply with the requirements of Article 123(2) EPC.
39. Appellant II has argued that the ligands as defined in claims 6 and 15 as granted are not merely "capable" of interfering or inhibiting the interaction of the compounds or the cells, but "are" actually interfering or inhibiting such interactions, respectively. The amendments in claims 7 and 10 were therefore unclear within the meaning of Article 84 and infringed the requirements of Article 123(3) EPC.
40. The board considers however that the qualification of a product by means of a feature defined in terms of "capable of" is clear within the meaning of Article 84 EPC if the function defined is clear and testable. The board considers that in the present case both conditions are fulfilled by the amendments, as has not been contested by appellant II, so that no case under Article 84 can be made out.
41. Concerning the objections relevant under Article 123(3) EPC, the board notes that the ligands "defined" in claims 6 and 15 are the ligands as now defined in

claims 7 and 10 and that the wording of method claims 6 and 15 does not restrict the definition of these compounds as only being disclosed for the ligands "in action". Claims 7 and 10 therefore comply with the requirements of Article 123(3) EPC.

42. In view of the above considerations, the board judges that the amendments are clear within the meaning of Article 84 EPC and that the protection conferred by claim 7 to 11 does not extend the protection conferred by the patent as granted and therefore meets the requirements of Article 123(3) EPC.

43. The above reasoning applies *mutatis mutandis* also to the identical claims and the corresponding claims drafted as method claims for ES and GR

Sufficiency of disclosure

44. Article 83 EPC requires that the description of an invention be such that a skilled person can carry out the invention according to the technical teaching provided in the specification, and the established case law of the boards of appeal further provides that the skilled person shall be able to do so without undue burden. The subject-matter of claims 7 and 10, to which objections of insufficiency of disclosure were raised by appellant II, relate to the preparation of a pharmaceutical composition using either a ligand for the B7 antigen (claim 7) or for CTLA4 (claim 10). The effect in both cases is to "regulate cellular interactions and immune responses" (page 6, lines 35 and 36 of the published application) which makes available a method for treating immune system diseases

mediated by T cell interactions with B7 positive cells by administering a ligand in a pharmaceutical composition as claimed in either of claims 7 and 10, which represent in a way "complementary" applications to achieve the same goal.

45. The objections raised by appellant II in the above context are not in the first place the "classical/conventional" one that as such the use of a ligand for preparing a pharmaceutical composition as claimed in claims 7 and 10 could not be carried out or that the ligands claimed for this purpose, i.e. a fusion protein in claim 7 and a monoclonal antibody as in claim 10, as such could not be produced according to the guidance given in the specification of the patent in suit (see, however, points 50 and 51 below).

Rather, appellant II has emphasised in its submissions that both claims have a certain, precise wording, namely "which ligand is capable of interfering with reaction of endogenous B7 antigen with CTLA4" in claim 7 and "which ligand is capable of inhibiting the interaction of CTLA4-positive cells with B7 positive cells" in claim 10 and that these wordings have to be taken as technical features because the claims are for pharmaceutical compositions serving a medical purpose. However, it was evident from post-published document (D30) that the molecular mechanism reflected by this wording, which indeed was described throughout the whole specification, was scientifically wrong.

The patent in suit did not therefore provide the true function of CTLA4 but rather suggested an opposite, and therefore wrong, function. Whereas for example claim 10

requires that the antibodies may be used to inhibit T cell proliferation, it was now known from document (D30) that CTLA4 is a negative regulator of T cell receptor signalling, counterbalancing the stimulation of CD28. Therefore, ligands (fusion proteins, claim 7) or antibodies (claim 10) which block the binding of the ligand of CTLA4 actually promote the immune response, i.e. an effect just opposite to that desired and therefore, potentially dangerous for the medical application as claimed. The whole teaching in the patent in suit was therefore mistaken and incomplete concerning the true function of the ligand bound by CTLA4. This had the consequence that the wording of claims 7 and 10 lead to a violation of the requirement of Article 83 EPC.

46. Appellant I has argued that it was at least clear that CTLA4 is only expressed when a T cell/B cell interaction has taken place, which is an important technical fact. While document (D30) might disclose some insight about the regulation of this interaction, the exact mechanism of the interaction has, to date, not been conclusively elucidated. But this was not decisive for the question whether the skilled person was or was not in a position to reproduce the subject-matter of either claim 7 or 10. What, however, counts in this context is the undisputed fact that patients currently are being treated in a safe and effective manner with ligands which, as claimed in both claims in dispute, are "regulating" and "interfering" and thus interactive with CTLA4.

47. The board notes that it is an established principle of patent law that it is the technical teaching in a

patent specification as such, and not a presumed (and possibly wrongly) scientific explanation why a certain effect is achieved if this teaching is carried out, which has to fulfil the requirements of Article 83 EPC. Claims 7 and 10 require that the ligand, i.e. a fusion protein or an antibody, respectively, "is capable" of "interfering with reaction of endogenous B7 antigen with CTLA4" (claim 7) or "inhibiting the interaction of CTLA4-positive T cells with B7 positive cells" (claim 10). Although the wording of claim 10, as emphasised by appellant II, requires that the interaction of CTLA4 positive T cells with B7 positive cells is inhibited, which turned out to be "wrong science" as far as the molecular mechanism is concerned, the board does not see a violation of the requirement of sufficiency of disclosure because, if and when the antibody inhibits the interaction of CTLA4 and B7, it also necessarily inhibits the interaction of the cells whereon these molecules are present so that the desired effect in a patient when treated with the pharmaceutical compositions as claimed in the two respective claims is achieved. Already for this reason the board is not convinced by this line of argument against sufficiency of disclosure.

The board considers that appellant II's interpretation of document (D30) to support its argument above is not entirely convincing. The board draws attention to the passage starting on page 398 right hand column, last paragraph under the headline: "Studies of CTLA-4 function using monoclonal antibodies" continuing on page 399, left hand column, first three lines of this document which starts with the sentence "*Addition of anti-CTLA-4 monoclonal antibodies to in vitro model*

systems of T-cell activation generally leads to increased T-cell proliferation, but the mechanism by which this occurs has been controversial (...). However, the stimulatory effects of anti-CTLA-4 monoclonal antibodies have also been attributed to blocking of CTLA-4-B7 interactions, which have an inherently negative effect on T-cell activation (5) - by blocking an interaction that has inhibitory effects, T-cell activation is increased (...). Thus two seemingly exclusive models predicted either positive or negative effects of CTLA-4 engagement during T-cell activation." Further down, above the headline "Knockout mice" it is then concluded: "**Regardless of the mechanism, this study clearly establishes the potential benefits of anti-CTLA-4 monoclonal antibodies for stimulating anti-tumor immunity. It will be important to extend these studies to other tumor systems.**" (emphasis by board).

48. Appellant I has repeatedly emphasised, and appellant II was not in a position to prove the contrary, that the monoclonal antibodies according to the patent in suit are used to treat immune-diseases with success.
49. The board thus does not accept appellant II's objections that the patent in suit was granted on the basis of incorrect science and thus "as a whole is non-enabled", that the "true function of CTLA-4 had not been ascertained" in the patent, so that it "is *prima facie* invalid", that claims "reciting anti-CTLA-4 monoclonal antibodies (...) are even further *prima facie* invalid since the function of those antibodies had been completely mischaracterised in" the patent and that the patent "instructs the skilled person to use the alleged invention in a manner that is completely at

odds and different than that possible." (see appellant II's letter dated 3 July 2006, point 4).

50. In the framework of sufficiency of disclosure, appellant II has further argued that in the specification of the patent in suit the production of the fusion proteins was disclosed only via CHO cells and, therefore, for the skilled person it amounted to undue burden to reproduce these proteins in other host-systems and consequently the claimed subject matter was not reliably and without undue burden workable over the whole breadth of the claims. The board is not convinced. Rather it sees the present technical fact matrix as being very similar to that on which the early decision T 292/85 (OJ EPO 1989, 275) was based. Here, and in T 292/85 the production of a fusion protein is at issue whereby only one way of producing the fusion protein is disclosed. The present board agrees with the conclusion drawn in decision T 292/85 that Article 83 EPC does not require that the patentee provides the public with the technical teaching of many possible ways to produce a certain product as long as there are no doubts that at least one reliable and reproducible way is described leading the skilled person to success. In the present case it is the CHO cell system which undisputedly works to produce the fusion proteins. Appellant II has not argued against this nor is there any evidence to the contrary on file.

51. Finally, appellant II has based an Article 83 EPC argument on the fact that in the patent specification merely the isolation of antibodies raised against the CTLA4-Ig fusion protein is disclosed. Such antibodies,

however, were not necessarily the same as the ones that are subject of claim 10.

However, the patent plainly enables the production of the anti-CTLA4 antibody of the invention (as confirmed in post-published document (D9)). Furthermore, the fusion protein of the invention had been tested sufficiently to demonstrate that it binds to B7 as confirmed in document (D20).

In view of the above considerations the board considers that appellant II has not made out a case of insufficient disclosure.

Novelty

52. None of the documents cited during the present appeal proceedings discloses either a fusion protein that contains at least a portion of the extracellular domain of CTLA4 which is used for the preparation of a pharmaceutical composition useful for regulating CTLA4 positive T cell interactions with other cells, or a monoclonal antibody reactive with CTLA4. The board therefore concludes that the subject matter of independent claims 7 and 10 and dependent claims 8, 9 and 11 is novel.

Inventive step

53. The cited prior art can be divided into two groups of documents. A first group of documents relate to interaction between the T cell antigen CD28 and B cell activation antigen B7, i.e. documents (D1), (D2), (D3) and (D5). A second group of documents relate to CTLA4

cDNA and genes, i.e. documents (D4), (D7) and (D8). Documents (D4) and (D7) concern partial cDNA sequences of murine CTLA4, whereas document (D8) discloses a human genomic sequence encoding CTLA4. These documents do not disclose the preparation of the CTLA4 protein but the former two suggest studies on expression distribution and the production of antibodies for investigating the function of the protein (see document (D4), page 269, right-hand column, lines 2 to 5; document (D7), page 31, lines 1 to 9).

54. For assessing whether or not a claimed invention meets the requirements of Article 56 EPC, the boards of appeal apply the "problem and solution" approach, which requires as a first step the identification of the closest prior art. In accordance with the established case law of the boards of appeal, the closest prior art is a teaching in a document conceived for the same purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications to arrive at the claimed invention.
55. In view of the above principles, the board considers, rather than the common general knowledge of the skilled person on T cell proliferation as argued by appellant II, that either of documents (D4) or (D8) represents the closest prior art for the assessment of inventive step of the subject-matter of claims 7 and 10.
56. During the oral proceedings appellant II mainly argued that the subject-matter of claim 10 was obvious to the skilled person, and restricted its attack against claim

7 to the contention that the arguments against claim 10 also applied to the subject-matter of claim 7. The board will therefore first examine whether the subject-matter of claim 10 is obvious or not.

57. The problem to be solved by the invention in claim 10 is considered to be the provision of a compound which can regulate CTLA4-positive T cell interactions with other cells and which can be used in a pharmaceutical composition. The invention in claim 10 solves this problem by the provision of a monoclonal antibody reactive with CTLA4 which is capable of inhibiting the interaction of CTLA4-positive T cells with B7 positive cells.
58. Appellant II has argued that the CTLA4/B7 interaction is not the only molecular interaction between T cell and B cells. Accordingly, an anti-CTLA4 antibody would not be able to "inhibit" this interaction but would rather ensure the interaction of the cells by e.g. the means of the CD28/B7 interaction. The board notes however that claim 10 recites the capability of the ligand "of inhibiting the interaction of CTLA4-positive T cells with B7 positive cells" so that it is clear that "regulation of the interaction" as recited in the claim concerns that interaction mediated by the CTLA4/B7 binding pair. Accordingly, the board cannot accept appellant II's argument and sees no reason to doubt that this solution solves the above problem (see also points 44 to 47 above, answering the corresponding objections raised under the heading of sufficiency of disclosure).

59. Neither document (D4) nor document (D8) itself refers to T cell/B cell interactions. All document (D4) mentions is the possibility of an interactive role for CTLA4 (page 269, right-hand column, lines 2 to 5, "maybe interactive role") without indicating the partners of the CTLA4 expressing T cells in this interaction, be it cellular or molecular. Similarly, on page 1905, in lines 7 to 9 of the "Concluding remarks", document (D8) states that "*CTLA4 may take part in molecular interactions possibly leading to the transduction of an inducing signal through the lymphocyte membrane*". The board therefore concludes that the closest state of the art alone does not render the subject-matter of claim 10 obvious.
60. It therefore needs to be established whether or not the remainder of the cited prior art suggests to the skilled person that monoclonal antibodies reactive with CTLA4 can be capable of inhibiting the interaction of CTLA4-positive T cells with B7 positive cells and therefore provide a solution for the problem to be solved, i.e. the provision of a compound which can regulate CTLA4-positive T cell interactions with other cells and which can be used in a pharmaceutical composition. None of the cited prior art documents disclose, and this has not been disputed by appellant II, the interaction of CTLA4 with B7 and its involvement in T cell/B cell interaction.
61. Appellant II has noted that document (D10) discloses the virtually identical chromosomal location of the genes encoding CD28 and CTLA4, that CD28 and CTLA4 are both members of the Ig superfamily belonging to a subgroup of membrane bound single V-domains (see

abstract lines 6 to 9) and that both genes could have derived from a common ancestor through a process of duplication (page 199, right-hand column, lines 7 to 9). Document (10) further states that their structural homology suggested that they could also share some similarity at the putative ligand-binding or transduction level (page 199, right-hand column, lines 15 to 17). Appellant II has therefore argued that document (D10) rendered it obvious to the skilled person that CTLA4 behaved similarly to CD28, i.e. the molecule which mediated T cell/B cell interaction by binding to the B7 antigen and which interaction could be regulated either by contacting said B cells with a monoclonal antibody specific for the B7 antigen or by contacting said T cells with a ligand for CD28 (see e.g. document (D2)). Document (D10) therefore established a clear link between the CD28/B7 interaction and the CTLA4/B7 interaction.

62. The board notes however that document (D10) as such merely concerns genomic experimentation and is silent on the function of CTLA4 (but merely suggests that "*functional studies will help us to compare the roles of these two molecules*" (page 199, right-hand column, lines 14 to 15) and is devoid of any hint to the possible production of antibodies thereto to formulate a pharmaceutical composition. Combination of the teaching in document (D4) with that of document (D10) does not therefore lead the skilled person to the subject-matter of claim 10 in an obvious manner.
63. The problem to be solved by the invention in claim 7, similar to that for claim 10, is considered to be the provision of a compound which can regulate CTLA4-

positive T cell interactions with B7 positive cells and which can be used in a pharmaceutical composition. The invention in claim 7 solves this problem by the provision of a fusion protein that contains at least a portion of the extracellular domain of CTLA4 which is capable of interfering with the reaction of endogenous B7 antigen with CTLA4. The board is satisfied in view of the examples of the patent in suit that the claimed subject-matter provides a solution for this problem. Appellant II has not contested this view.

64. None of the cited documents contained in the prior art for the subject-matter of claim 7 suggest the involvement of CTLA4 in the interaction of T cells and B cells by means of binding to the B7 antigen. The board therefore concludes that the prior art does not render obvious the subject-matter of claim 7.

65. In view of the above considerations, the subject-matter of claims 7 and 10, and the claims dependent thereon, involve an inventive step (Article 56 EPC).

Adaptation of the description to the claims of auxiliary request 2b

66. At the end of the oral proceedings, appellant II no longer had objections to the final version of the description containing amended pages 3, 3a, 4 and 9 of the description of the patent in suit. The board considers this description indeed in line with the claims of the auxiliary request 2b.

Order

For these reasons it is decided that:

1. The appeal of appellant I is admissible.
2. The decision under appeal is set aside.
3. The case is remitted to the department of first instance with the order to maintain the patent on the basis of:
 - claims 1-12 of the New Auxiliary request 2b (AT, BE, ...) submitted on 6 November 2006 at the oral proceedings, for all designated states except GR and ES,
 - claims 1-12 of Auxiliary Request 2b (GR), submitted on 7 November 2006 at the oral proceedings, for GR,
 - claims 1-12 of Auxiliary Request 2b (ES), submitted on 7 November 2006 at the oral proceedings, for ES,
 - amended pages 3, 3a, 4 and 9 of the description of EP 0 606 217 B1 dated 7 November 2006,
 - pages 2, 5-8, 10-25 of the patent EP 0 606 217 B1,
 - figures 1-10 of the patent EP 0 606 217 B1.

The Registrar:

The Chair:

P. Cremona

U. M. Kinkeldey