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Datasheet for the decision of 9 June 2016

Case Number: T 0171/11 - 3.3.04

Application Number: 96942901.8

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Language of the proceedings: EN

Title of invention:
Blockade of T lymphocyte down-regulation associated with CTLA-4 signaling

Patent Proprietor:
The Regents of the University of California

Opponent:
Pfizer, Inc.

Headword:
Blockade of CTLA-4/UNIVERSITY OF CALIFORNIA

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - main request (no)

Decisions cited:
G 0005/83

Catchword:

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Case Number: T 0171/11 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 9 June 2016

Appellant: (Patent Proprietor)	The Regents of the University of California 1111 Franklin Street, 12th Floor Oakland, CA 94607 (US)
Representative:	Walton, Seán Malcolm Mewburn Ellis LLP City Tower 40 Basinghall Street London EC2V 5DE (GB)
Respondent: (Opponent)	Pfizer, Inc. 235 East 42nd Street New York, NY 10017-5755 (US)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 16 December 2010 revoking European patent No. 0865293 pursuant to Article 101(2) and (3)(b) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	A. Chakravarty
	M. Blasi

Summary of Facts and Submissions

I. The proprietor (appellant) lodged an appeal against the decision of the opposition division to revoke European patent No. 0 865 293.

II. The patent was opposed on the grounds of lack of novelty and inventive step (Article 100(a) EPC), failure to provide a disclosure of the invention sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(b) EPC) and because the subject-matter of the European patent extended beyond the content of the application as filed (Article 100(c) EPC).

III. The opposition division refused the main request (the claims as granted) because claims 3 to 7 were for subject-matter that extended beyond the content of the application as filed (Article 100(c) EPC). Auxiliary request 1 was refused because the subject-matter of claims 1, 3, 9 and 11 did not involve an inventive step (Article 100(a) EPC).

IV. With the statement of grounds of appeal, the appellant resubmitted the claims of former auxiliary request 1 considered by the opposition division as the main request.

V. The opponent (respondent) replied to the appellant's statement of grounds of appeal.

VI. The documents cited in this decision are:

D3: Leach et al., Science, 1996, 271, 1734-1736.

D5: Pardoll et al., Science, 1996, 271, 1691.

D15: Waterhouse et al., Science, 1995, 270, 985-988.

D16: Tivol et al., Immunity, 1995, 3, 541-547.

A13: Declaration of Dr Tak Wah Mak, dated 12 April 2011.

VII. Independent claims 1 and 9 of the main request are as follows:

"1. Use of an anti-CTLA-4 antibody or a fragment thereof in the manufacture of a medicament for treating melanoma.

9. An anti-CTLA-4 antibody or a fragment thereof for use in a method of treatment of melanoma".

VIII. Oral proceedings before the board were held on 9 June 2016.

The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the set of claims of the main request filed with the statement of grounds of appeal.

The respondent requested that the appeal be dismissed.

At the end of the proceedings, the Chairwoman announced the decision of the board.

IX. The appellant's arguments relevant to the decision can be summarised as follows:

Inventive step - Article 56 EPC

Claims 1 and 9

The effective date of the patent was the filing date, thus documents D3 and D5 were state of the art for the invention.

The claims related to the use of a blocking anti-CTLA-4 antibody or a blocking fragment thereof in the manufacture of a medicament for treating melanoma.

Document D3, an article published in the journal "*Science*", could be taken as representing the closest prior art for the subject-matter of claims 1 and 9 as it disclosed enhancement of immunity to a carcinoma cell line in mice.

Document D5, an editorial from the same issue of the journal "*Science*", provided a commentary on document D3 and was the only document in the state of the art that mentioned melanoma in connection with a CTLA-4 blockade.

However, neither document D3 or D5 gave the skilled person a reasonable expectation of successfully treating melanoma by CTLA-4 blockade for several reasons.

Firstly, the only evidence of successful treatment of tumours by treatment with an antibody blocking the binding of CLTA-4 with its ligand was for carcinoma and fibrosarcoma in document D3. The skilled person knew

that different cancer types responded differently to therapy and would not have expected that melanoma would respond in the same fashion as carcinoma.
Secondly, there were reports about various unsuccessful attempts to develop an anti-tumour vaccine for melanoma based on the tumour specific T-cell response to melanoma mentioned in document D5.

Thirdly, at the effective date of the patent, it was not generally established that blocking the binding of CTLA-4 to its receptor would always lead to an immune boost. In document A13, Dr Tak Wah Mak (one of the authors of document D15), stated "*...We concluded from our data that CTLA-4 played an important role in regulating lymphocyte homeostasis, and acted as a negative regulator of T cells [...]. We expressly noted, however, that our data did not preclude a role for CTLA-4 in thymic selection*" (see A13, section 4) and "*...Indeed, several researchers continued to espouse combined co-stimulatory and negative regulatory roles for the molecule, and proposed alternative explanations for our data based on CTLA-4 involvement in early thymic education [...]*" (see A13, section 5). This also made it clear that the exact function of CTLA-4 had not been entirely settled at that time.

Finally, the skilled person knew from the disclosure of documents D15 and D16 that loss of CTLA-4 functionality was associated with unwanted side-effects. Documents D15 and D16 disclosed that CTLA-4 knock-out mice died with symptoms of lymphoproliferative and autoimmune disease after 3 to 4 weeks. At best, document D15 showed that CTLA-4 can act as a negative regulator of T cell activation, but this was in the context of complete knock-out of CTLA-4 in early development. Moreover, such knock-out experiments did not provide

any information about whether it would be possible to treat melanoma using an anti-CTLA-4 antibody, as it was not a tumour model and was not relevant to the use of antibodies *in vivo* in an adult animal to treat the severe tumour, melanoma. While the evidence provided by the knock-out did not entirely rule out the possibility of using an antibody to inhibit the negative regulatory effect of CTLA-4, this information was of little use to the skilled person considering prospects for successful treatment of melanoma. Moreover, the knock-out mice became moribund at 3 to 4 weeks of age. Such an extreme effect would have led the skilled person to believe that anti-CTLA-4 treatment in a human might kill the patient, rather than treat a tumor. Thus, the potential risks associated with a CTLA-4 blockade meant that the skilled person would not have had a reasonable expectation that melanoma could be treated by therapy with an anti-CTLA-4 antibody.

X. The respondent's arguments relevant to the decision can be summarised as follows:

Inventive step - Article 56 EPC

Claims 1 and 9

In agreement with the appellant, the effective date of the patent for all claimed subject-matter was the filing date of the application.

Also in agreement with the appellant, document D3 represented the closest prior art and disclosed an anti-CTLA-4 antibody for use in the treatment of carcinoma and fibrosarcoma by means of CTLA-4 blockade. The difference between the claimed subject-matter and the closest prior art lay in the type of tumour to be

treated, i.e. melanoma instead of carcinoma or fibrosarcoma. Thus, the problem be to be solved by the skilled person was the putting into practice the anti-tumour treatments disclosed in document D3 for different types of tumour.
The teaching of document D3 was not limited to the particular tumour types used in the experiments, both the title and the abstract referring to tumours in general.

The skilled person would also have recognised that lifting of a blockade to T cell activation was not antigen or tumour specific. General statements such as the last sentence of the abstract of document D3 "*These results suggest that blockade of the inhibitory effects of CTLA-4 can allow for, and potentiate, effective immune responses against tumor cells*" would, correctly, have been taken at face value. This was further reflected for instance in document D5, which disclosed that "*The success of this approach* [the use of anti-CTLA-4 antibodies to release the brake on T-cell activation] *depends on the presence of a preexisting T cell response against the tumor antigens, which, under normal circumstances, fails to develop enough amplitude to win the battle against the tumor. This appears to be the case for at least one human tumor, melanoma, in which tumor-specific T cell responses can be readily identified in tumor- infiltrating lymphocytes*" (see right column, 1st paragraph) .

In the light of this disclosure, the skilled person would have considered that melanoma could be treated by therapy with anti-CTLA-4 antibodies acting to cause a CTLA-4 blockade (i.e. the blocking of the interaction between CTLA-4 and its receptor) because they knew that

this type of tumour generally elicited a T cell response.

Reasons for the Decision

Priority - Article 87 EPC

1. Both parties agree that the effective date of the patent for all claimed subject-matter is the filing date of the application. The board sees no reason to come to a different conclusion.

Inventive step - Article 56 EPC

Claims 1 and 9

2. The subject-matter of claims 1 and 9 is the medical use of an anti-CTLA-4 antibody or a fragment thereof for treating melanoma. Claim 1 is in the "*Swiss-type*" format instituted by decision G 5/83 (OJ EPO 1985, 64) and claim 9 is for a purpose-related product (Article 54(5) EPC).

3. The purpose of the invention claimed is the achievement of the therapeutic effect defined in the claims, i.e. treating melanoma.

Closest prior art

4. Document D3 is an article from the journal "*Science*" entitled "*Enhancement of Antitumor Immunity by CTLA-4 Blockade*". It discloses experiments in which *in vivo* administration of antibodies to CTLA-4 to mice resulted in the rejection of tumors, including pre-established ones. It was concluded that "*These results suggest that blockade of the inhibitory effects of CTLA-4 can allow*

for, and potentiate, effective immune responses against tumor cells" (see abstract). The tumour types treated in document D3 were carcinoma and fibrosarcoma. The results of the experiments led to the conclusion that "*CLTA-4 blockade enhances antitumor responses*" (see page 1736, left column, final paragraph).

5. Document D5, from the same journal issue as document D3, is a commentary on the latter, entitled "*Releasing the Brakes on Antitumor Immune Response*". It refers to the disclosure in document D3 of the successful immunotherapy in two murine cancer models using anti-CTLA-4 antibodies without overt toxicity. On the subject of the applicability of the therapy to other tumour types, it states that "*The success of this approach depends on the presence of a preexisting T cell response against the tumor antigens, which, under normal circumstances, fails to develop enough amplitude to win the battle against the tumor. This appears to be the case for at least one human tumor, melanoma, in which tumor-specific T cell responses can be readily identified in tumor-infiltrating lymphocytes*" (see right column, paragraph 1).

6. The board considers that document D3 may serve as closest prior art for the subject-matter of claims 1 and 9, since it is a scientific publication containing experimental data concerning the medical use of an anti-CTLA-4 antibody for treating tumours and forms the basis of the commentary provided in document D5. This is in agreement with the position taken by both parties and the opposition division.

The technical problem and its solution

7. The difference between the closest prior art, represented by document D3, and the claimed subject-matter lies in the type of tumour to be treated. Specifically, claims 1 and 9 are for the treatment of melanoma, whereas the treatment disclosed in document D3 was for carcinoma and fibrosarcoma.

8. In view of this difference, the objective technical problem is the provision of a pharmaceutical composition for the treatment of a further type of tumour.

Obviousness

9. The skilled person starting from document D3 and seeking to solve the problem formulated above would have been motivated to treat additional tumour types by CLTA-4 blockade using the blocking anti-CTLA-4 antibody successfully used in the treatment of carcinoma and fibrosarcoma because both document D3 and document D5 disclosed that this type of therapy was not antigen or tumour specific (see document D5, column 2, 2nd paragraph) but "*depends on the presence of a preexisting T cell response against the tumor antigens*" (*ibid*). Tumours that were known to elicit a T cell response would therefore have been considered good candidates for treatment by CTLA-4 blockade by an anti-CTLA-4 antibody already successfully used to treat carcinoma and fibrosarcoma. That melanoma was such a type of tumour was known from document D5 which further disclosed that "*this* [presence of a preexisting T cell response against the tumor antigens] *appears to be the case for [...] melanoma, in which tumor-specific T cell responses can be readily identified in tumor-*

infiltrating lymphocytes" (see right column, 1st paragraph).

10. Thus, the board is of the view that the skilled person would have had an incentive to apply CTLA-4 blockade therapy using blocking anti-CTLA-4 antibodies to treat melanoma and, in contrast to the respondent's view, that the skilled person had reasons to expect that such a treatment would be successful.

11. The board notes that document D5, reflecting on document D3, on the one hand states that "*...the window between development of an antitumor response and hyperimmunity or autoimmunity may be narrow*" (see right column, 2nd paragraph), it further states that "...*in contrast to genetic knockout, CTLA-4 blockade with antibodies allows a limited duration therapy to take maximal advantage of even a small therapeutic window*" (*ibid*). Furthermore, document D3 did not report any adverse effects on the mice treated.

12. The skilled person would therefore have been aware of the possibility of adverse effects such as hyperimmunity or autoimmunity, but would have considered that antibodies could be administered for a limited duration during a "*therapeutic window*".

13. In summary, the skilled person starting from document D3 and aware of document D5, would have been motivated at least to repeat the experimental treatments described in document D3 using a melanoma cell line instead of a carcinoma or fibrosarcoma cell line, such a repetition being an embodiment of the subject-matter of claims 1 and 9. In view of the above mentioned disclosure of documents D3 and D5, the skilled person

would have had a reasonable expectation that such treatment would be successful.

14. The board notes that document D15, entitled "*Lympho-proliferative Disorders with Early Lethality in Mice Deficient in Ctla-4*" did report that "*lymph nodes and spleens of CTLA-4-deficient mice [CTLA-4 knockout mice] accumulated T cell blasts with up-regulated activation markers. These blast cells also infiltrated liver, heart, lung, and pancreas tissue, and amounts of serum immunoglobulin were elevated. The mice invariably became moribund by 3 to 4 weeks of age*" (see abstract).

14.1 However, these experiments were not aimed at treating tumours but were done to determine the biological role of CTLA-4. They established that CTLA-4 "*acts as a negative regulator of T cells*" (see page 987, column 2). The results reported were, *inter alia,* the background to the work described in document D3 to investigate the "*possibility that blockade of inhibitory signals delivered by CTLA-4-B7 interactions might augment T cell responses to tumor cells and enhance antitumor immunity*" (see document D3, page 1734, column 2). Thus, there is nothing in the disclosure of document D15 that would have negatively affected the the skilled person's expectation that CTLA-4 blockade therapy using blocking anti-CTLA-4 antibodies to treat melanoma could reasonably be expected to be successful.

15. In view of the above considerations, the subject-matter of claims 1 and 9 is held to have been obvious to the skilled person having regard to the state of the art. The main request therefore does not meet the requirements of Article 56 EPC and is not allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated