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Datasheet for the decision of 7 December 2021

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Language of the proceedings: EN

Title of invention:
Compositions and methods for the treatment of infections and tumors

Patent Proprietors:
Emory University
Dana-Farber Cancer Institute, Inc.
President and Fellows of Harvard College

Opponent:
Pfizer Inc.

Headword:
Combined melanoma treatment/EMORY

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:

Catchword:

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Beschwerdekammern

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Case Number: T 2869/19 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 7 December 2021

Appellants: (Patent Proprietors)	Emory University 1599 Clifton Road, NE Fourth Floor Atlanta, GA 30322 (US) Dana-Farber Cancer Institute, Inc. 450 Brookline Avenue Boston, MA 02215 (US) President and Fellows of Harvard College 17 Quincy Street Cambridge, MA 02138 (US)
Representative:	Forresters IP LLP Skygarden Erika-Mann-Straße 11 80636 München (DE)
Respondent: (Opponent)	Pfizer Inc. 235 East 42nd Street New York, NY 10017 (US)
Representative:	Pfizer European Patent Department 23-25 avenue du Docteur Lannelongue 75668 Paris Cedex 14 (FR)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 13 August 2019 revoking European patent No. 2133365 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	B. Claes
Members:	O. Lechner
	R. Romandini

Summary of Facts and Submissions

I. The patentees (appellants) filed an appeal against the decision of the opposition division to revoke European patent No. 2 133 365. The patent is based on European patent application No. 09 166 886.3 ("application") and is entitled "*Compositions and methods for the treatment of infections and tumors*".

II. The opposition proceedings were based on the grounds for opposition under Article 100(a) (in conjunction with Articles 54 and 56 EPC), (b) and (c) EPC.

III. The opposition division revoked the patent, finding, *inter alia*, that the subject-matter of auxiliary request 1 (as filed during the oral proceedings) lacked an inventive step (Article 56 EPC).

Claim 1 of auxiliary request 1 reads:

"1. A combination of a therapeutically effective amount of activated T-cells that specifically recognize a tumor antigen of interest, and a therapeutically effective amount of a PD-1 antagonist for use in treating a tumor in a mammalian subject; comprising administering the combination to the subject thereby inducing an immune response to the tumor antigen of interest, wherein the PD-1 antagonist is an antibody that specifically binds PD-1, an antibody that specifically binds Programmed Death Ligand 1 (PD-L1); or wherein the PD-1 antagonist is an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-PD-1 RNAi, an anti-PD-L1 RNAi, an anti-PD-1 antisense RNA, an anti-PD-L1 antisense RNA, or combinations thereof; and wherein the tumor is a malignant melanoma."

IV. With their statement of grounds of appeal, the appellants submitted sets of claims of a main request and auxiliary request 1 (which is identical to the version of auxiliary request 1 that was addressed in the decision under appeal).

V. In its reply to the appeal, the opponent (respondent) submitted objections under Articles 54, 56, 76(1), 83 and 123(2) EPC.

VI. The board issued summons to oral proceedings and a communication pursuant to Article 15(1) RPBA in which the board *inter alia* expressed the preliminary opinion that the subject-matter claimed in auxiliary request 1 did not involve an inventive step.

VII. By letter dated 16 March 2021, in response to the board's communication, the appellants withdrew the main request and re-submitted auxiliary request 1 as the new (and sole) main request.

VIII. Oral proceedings took place in the form of a video conference, as requested by the appellants, in the absence of the respondent as had previously been announced. At the end of the oral proceedings, the Chair announced the board's decision.

IX. The following documents are referred to in this decision:

D4: Dong H. *et al.*, Nature Medicine (2002), Vol. 8(8): 793-800.

D6: Blank C. *et al.*, Cancer Immunol. Immunother. (2005),

Vol. 54: 307-314.

D8: Yee C. *et al.*, Proceedings of the National Academy of Sciences of the United States of America (2002), Vol. 99(25): 16168-16173.

D9: Cruiel T.J. *et al.*, Nature Medicine (2003), Vol. 9(5): 562-567.

X. The appellants' arguments on the inventive step of the subject-matter of claim 1 can be summarised as follows:

Closest prior art and difference over claimed invention

The claimed invention differed from the adoptive transfer therapy disclosed in document D8, which represented the closest prior art, in that it utilised a combination of programmed cell death protein 1 (PD-1) blockade and activated T-cells for treating malignant melanoma.

Technical effect and objective technical problem

The patent taught that the chronic viral infection lymphocytic choriomeningitis virus (LCMV) model, which was used in Example 16, paralleled that of T cell cyto-immune therapy for malignant melanoma, due to the similar immunological barriers that limited the applicability of these therapies. T cell exhaustion was one of the immunological barriers common to both mechanisms. Given the similarity of malignant melanoma and viral antigens, Example 16 provided the skilled person with a clear and accepted equivalence between the LCMV model and malignant melanoma. The LCMV model and malignant melanoma displayed similar immune

responses to the same treatments that worked on their common underlying immunosuppressive mechanism.

Since the LCMV model and malignant melanoma shared an underlying immunosuppressive mechanism, it was evident that the quantitative data produced using the established LCMV model in Example 16 could be extrapolated to malignant melanoma.

Documents D4 and D8 taught that a PD-1 antagonist, or activated T-cells, independently provided an effective treatment of malignant melanoma. Figures 14A, 14B and 15 of the patent demonstrated that adoptive T-cell immunotherapy was more effective in mice infected with LCMV when combined with an anti-PD-L1 therapy. Example 16 showed that the addition of the PD-1 blockade could be utilised to enhance an effective adoptive T-cell immunotherapy.

The objective technical problem to be solved was "*the need for an improved treatment for malignant melanoma*". In case the board was not persuaded that the data in the patent could be extrapolated to malignant melanoma, the objective technical problem to be solved was "*the need for an alternative treatment for malignant melanoma.*"

Obviousness

Starting from the disclosure in document D8 and considering the teaching in document D6, the skilled person had no reasonable expectation that the claimed invention provided an alternative treatment, let alone an improved treatment, for malignant melanoma.

Providing a combined therapy with no reasonable expectation of improvement over the single treatment therapy, as disclosed, for example, in document D8, presented many apparent disadvantages to the skilled person. A combination therapy was more expensive, more complicated and more time-consuming than a single treatment therapy. Moreover, it was not known whether adoptive T-cell transfer and treatment with a PD-1 antagonist would have independent effects or even whether they would negatively influence each other when used in combination.

The speculative language used in document D6 presented the skilled person with the idea that it would be interesting to try the combination of activated T-cells and a PD-1 antagonist. However, document D6 did not demonstrate that the combination of activated T-cells and a PD-1 antagonist provided an improved treatment.

Document D6 did not teach that the combination of adoptive T-cell therapy and PD-L1 antagonists had already been successfully used in the art for the treatment of cancers. None of the documents referenced in document D6 disclosed the combination of adoptive T-cell therapy and PD-L1 antagonists. The passage on page 311 in the section under the heading "*Implications of PD-L1 for tumor immunotherapy*" discussed the results of single treatment therapy approaches, because document D4 (reference 17 in document D6), for example, disclosed the therapy with a PD-1 blockade alone.

The disclosure in document D6 that PD-L1 was expressed in a broad range of cancers, including melanoma, only taught the skilled person that the PD-1 pathway was present in melanoma. It did not provide a teaching that a PD-1 inhibitor combined with adoptive T-cell therapy

could result in a superior treatment of malignant melanoma.

XI. The respondent's arguments on the inventive step of the subject-matter of claim 1 can be summarised as follows:

Closest prior art and difference over claimed invention

The claimed invention differed from the disclosure in document D8, which represented the closest prior art, by the additional treatment of malignant melanoma with a PD-1 antagonist.

Technical effect and objective technical problem

The patent lacked data supporting the use of such a combination therapy of adoptive T-cell transfer and PD-L1 antagonist for the treatment of melanoma. The chronic infection with lymphocytic choriomeningitis virus (LCMV) used in Example 16 was not a model for melanoma. The patent neither alleged this nor said that results of such a chronic virus infection model could be predictive of success in the treatment of melanoma. The second sentence in paragraph [0319] of the patent taught the skilled person, at best, that the model used in Example 16 could have some relevance to T-cell cyto-immune therapy for tumours.

The objective problem to be solved was to provide an alternative treatment for malignant melanoma.

Obviousness

The use of anti-PD-L1 antibodies to improve adoptive T-cell therapy directed to a tumour expressing PD-L1 had been extensively disclosed in scientific

literature. It was known that human melanoma expressed PD-L1, in particular in the presence of interferon gamma (IFNγ), which was produced by T-cells.

Document D6 disclosed (page 309, right-hand column, last sentence before the chapter entitled "*Immunological functions of PD-L1*") that PD-L1 was expressed *inter alia* on the surface of human melanoma and melanoma tumour cell lines. Similar to endothelial cells, murine and human tumour cells up-regulated PD-L1 upon IFNγ stimulation. These observations had led to the hypothesis that tumours might escape from the host immune system by negative attenuation of tumour-specific T-cell responses via PD-L1/PD-1 interactions.

In the paragraph bridging pages 311 and 312, document D6 considered that the blockade of PD-L1 on tumour cells might increase the numbers of surviving cells during T-cell transfer, improve the induction of type I immune responses and improve stimulation of T-cells after infiltration, thus allowing for improved lysis of target cells *in vivo*.

Document D6 concluded that "*interfering with the interaction of PD-L1, either on antigen-presenting dendritic cells or the tumor cells themselves, with its receptor PD-1 on T cells, either adoptively transferred or induced by vaccination, might potentiate anti-tumor T-cell effector function in vivo. Translating these ideas to therapy approaches for human cancer patients should be a high priority in future studies*".

Thus, document D6 incited the skilled person to treat tumours that express PD-L1, e.g. melanoma, with a combination of adoptive T-cell therapy and anti-PD-L1 antibodies.

When considering the combination of the teaching in document D8 and that in document D6, the claimed invention would thus have been obvious to the skilled person.

XII. The appellants requested that the decision under appeal be set aside and the patent be maintained in amended form based on the set of claims of the main request (filed with their letter of 16 March 2021 as auxiliary request 1).

The respondent (opponent) requested in writing that the appeal be dismissed.

Reasons for the Decision

Main request - claim 1 - inventive step (Article 56 EPC)

Closest prior art and difference over claimed invention

1. Document D8 (see abstract) discloses adoptive T-cell therapy in the treatment of patients with metastatic melanoma in combination with low-dose interleukin 2 (IL-2). The latter is used to improve the *in vivo* persistence of transferred CD8+ T-cells (see page 16 170, left-hand column, 2nd full paragraph). The treatment resulted in minor, mixed, or stable responses in 8 out of 10 patients, for an average response duration of 11 months, and for as long as 21 months, and provided potential evidence of significant anti-tumour effects and meaningful clinical responses (see abstract, page 16172, right-hand column, last three paragraphs).

2. That the disclosure in document D8 represents the closest prior art has not been disputed.

3. The claimed subject-matter (see section III.) differs from the disclosure in document D8 in that it combines the adoptive T-cell therapy disclosed in document D8 with a PD-L1 antagonist treatment.

Technical effect and objective technical problem

4. The patent provides no experimental data for the treatment of malignant melanoma with a combination therapy of adoptive T-cell transfer and PD-L1 antagonist treatment. Indeed, Example 15 of the patent discloses that the combination therapy of adoptive T-cell transfer and PD-L1 antagonist treatment synergistically improves the immune control of chronic viral infection and Example 16 discloses the role of the PD-1 pathway in a model of cyto-immune therapy for chronic viral infection.

The LCMV chronic viral infection model is described as "[paralleling] *that of T cell cyto-immune therapy for tumours in regard to the immunological barriers that limit the applicability of these therapies, such as corrupted or suppressed T cell/anti-tumour responses*" (see second sentence in paragraph [0319]). Splenocytes from LCMV-immune mice were adoptively transferred into LCMV carrier mice (a model for chronic viral infection), which additionally received anti-PD-L1 antibody treatment.

Figure 14 shows that animals treated with anti-PD-L1 therapy during the first 15 days following adoptive transfer developed significantly larger numbers of

LCMV-specific CD8+ T-cells. Figure 15 shows that a blockade of the PD-1/PD-L1 pathway following adoptive T-cell immunotherapy enhanced cytokine production in antigen-specific CD8+ T-cells.

5. The appellants argued that based on the parallels of the model described in paragraph [0319], the skilled person would have extrapolated the synergistic effects observed in chronic viral infection to the treatment of malignant melanoma. The technical problem starting from the disclosure in document D8 was therefore to solve a "*need for an improved treatment for malignant melanoma*".

6. The board notes, however, that although the skilled person might have been aware that similar "*immunological barriers*" such as "*corrupted or suppressed T-cell anti-tumor responses*" which "*limit the applicability of* [cyto-immune therapy]" can be observed in chronic viral infection and tumours in general, the applied model is not a model for human melanoma. A possible similarity to tumour models in general does not necessarily imply that results disclosed in the context of chronic viral infection can be readily extrapolated to the treatment of malignant melanoma, i.e. a specific cancer type.

7. The board has not seen any argument going beyond the reference to the rather general statement in the second sentence in paragraph [0319] of the patent (see point 4. above) as to why a synergistic or improved therapeutic effect observed in the context of vaccination in combination with anti-PD-1 antibody administration in the treatment of chronic viral infection should also apply to the treatment of tumours or more specifically to malignant melanoma.

Accordingly, the objective technical problem has to be formulated as the provision of an alternative therapy for malignant melanoma.

Obviousness

8. Starting from the adoptive T-cell therapy disclosed in document D8, a skilled person looking for an alternative melanoma therapy would be aware of the relevant trends in the technical field of adoptive T-cell therapy and of, for example, the teaching of document D6.

Document D6 - a scientific review article on negative T-cell regulation via PD-1, the blockade of PD-L1/PD-1 interactions and the implications for adoptive T-cell therapies (see abstract) - discloses, with reference to, *inter alia,* document D4, that PD-L1 is expressed on the surface of certain human cancers such as melanoma and human melanoma cell lines. Similar to endothelial cells, murine and human tumour cells up-regulate PD-L1 upon IFNγ stimulation. These observations are stated to have led to the hypothesis that tumours might escape from the host immune system by negative attenuation of tumour-specific T-cell responses via PD-L1/PD-1 interactions (page 309, right-hand column, last sentence before the chapter entitled "*Immunological functions of PD-L1*").

Under the heading "*Implications of PD-L1 for tumor immunotherapy*" (see paragraph bridging pages 311 and 312), document D6 further discloses that a major challenge for adoptive T-cell therapies was to ensure the long-term survival of the transferred T-cells. However, the data on the long-term survival of

transferred T-cells in patients were controversial. Document D6 further states that "*in mouse tumor experiments the blockade of PD-L1 resulted in an increased expansion of tumor-specific T cells and relatively decreased numbers of apoptotic T cells early after transfer [14, 17]. Therefore, the blockade of PD-L1 during T-cell transfer might increase the numbers of surviving cells*" (note: references 14 and 17 are documents D4 and D9 in the appeal proceedings, respectively).

9. The board therefore concludes that, starting from the teaching in document D8 and based on the teaching in document D6, the claimed subject-matter was obvious to the skilled person.

10. The appellants further argued that document D6 was speculative and did not show that the combination of adoptive T-cell therapy and PD-L1 antagonists had already been successfully used in the art for the treatment of cancers.

11. However, document D4 (see page 795, right-hand column, and Figure 5) discloses the use of a mouse adoptive transfer model involving tumour antigen-specific T-cells. In order to establish progressively growing tumours, (B- and T-cell deficient) recombination activating gene-1 negative (RAG-$1^{-/-}$) mice were inoculated either with a) B7-H1 (= PD-L1) expressing tumour cells or b) with the same tumour cells which did not express B7-H1. *In vitro* activated, tumour antigen-specific T-cells from normal (BALB/c) mice were injected into the tumour-bearing mice. While the number of tumour antigen-specific T-cells greatly increased in animals with the B7-H1-negative tumours, this could not be observed in those with B7-H1-positive tumours.

In addition, tumour antigen-specific T-cells ("1B2" cells) underwent significant apoptosis after transfer into animals with the B7-H1 positive tumour. The rapid increase in T-cell apoptosis is reported to be suggestive of *in vivo* deletion of activated T-cells by tumour-associated B7-H1. The number of B7-H1-positive tumour cells increased in the animals. Infusion of a neutralising anti-B7-H1 antibody (i.e. anti-PD-L1 antibody) inhibited the growth of B7-H1-positive tumour cells *in vivo* (see Figure 5c).

12. Thus, contrary to the appellants' allegation, document D4 does disclose a combination of adoptive T-cell therapy and a PD-1 pathway blockade for treating cancer and the board sees no reason to doubt the validity of the relevant corresponding statements made in document D6.

13. Moreover, the board cannot agree with the appellants that the results of the adoptive T-cell therapy reported in document D8 would provide an optimal treatment with no need for improvement. As evidenced by the data therein, not all patients showed a response and not all responses were stable, leaving room for the therapy to be further optimised.

14. Furthermore, the board cannot concur with the appellants that a skilled person would have refrained from developing alternative therapies since a combination therapy of adoptive T-cell transfer and PD-L1 antagonist treatment would be more expensive, more complicated and more time-consuming than a single therapy.

15. In view of the difficulties and insufficient response rate associated with the treatment of malignant melanoma, a skilled person would have been motivated to provide alternative therapies. In addition, the therapy disclosed in document D8 also provides adoptive T-cell therapy in combination with low-dose interleukin-2 (IL-2) treatment (see point 1. above).

16. Based on the explanations provided in document D6 concerning the inhibitory activity of the PD-L1 pathway on the function of adoptively transferred T-cells, a skilled person would clearly have been motivated to exclude such a negative impact on the transferred T-cells and would have combined adoptive T-cell therapy with the inhibition of the PD-L1 pathway in the therapy of PD-L1 positive cancers such as malignant melanoma.

17. Thus, the skilled person, when starting from the disclosure in document D8 and embarking on solving the technical problem, would have arrived in an obvious manner at the combination therapy of adoptive T-cell transfer and PD-L1 antagonist treatment for melanoma as claimed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

I. Aperribay B. Claes

Decision electronically authenticated