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**Datasheet for the decision
of 15 January 2019**

Case Number: T 1702/16 - 3.3.04

Application Number: 05815888.2

Publication Number: 1827604

IPC: A61P35/00, A61K31/12, A61K39/44

Language of the proceedings: EN

Title of invention:
Methods and compositions for adoptive immunotherapy

Applicant:
Peter MacCallum Cancer Institute

Headword:
Adoptive immunotherapy/PETER MACCALLUM CANCER INSTITUTE

Relevant legal provisions:
EPC Art. 54, 56, 84, 111(1)

Keyword:
Main request - claim 1 - clarity, novelty, inventive step
(yes)
Remittal to the department of first instance - (yes)

Decisions cited:

Catchword:

-



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Case Number: T 1702/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 15 January 2019

Appellant: Peter MacCallum Cancer Institute
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Decision under appeal: **Decision of the Examining Division of the
European Patent Office posted on
17 December 2015 refusing European patent
application No. 05815888.2 pursuant to
Article 97(2) EPC**

Composition of the Board:

Chairwoman G. Alt
Members: B. Claes
M. Blasi

Summary of Facts and Submissions

- I. The appeal lies from the decision of the examining division to refuse the European patent application No. 05 815 888.2 having the title "*Methods and compositions for adoptive immune therapy*".
- II. The following documents are cited in this decision:
- D1: Teng *et al.* (2004), Human Gene Therapy, Vol. 15, pages 699 to 708.
- D3: Altenschmidt *et al.* (1997), J. Immunology, Vol. 159, No. 11, pages 5509 to 5515.
- D10: Declaration by Phillip K. Darcy and Michael H. Kershaw dated 26 April 2016
- III. The examining division based its decision solely on the finding that the subject-matter of claim 1 of the main request and all three auxiliary requests did not involve an inventive step (Article 56 EPC). The decision further contained an *obiter dictum* relating to the clarity requirement in Article 84 EPC and concerning claim 1 of all requests.
- IV. With its statement of grounds of appeal, the applicant (hereinafter "appellant") re-submitted the sets of claims of the main request and the three auxiliary requests, filed claims of an additional auxiliary request, filed two new documents including document D10, and argued in favour of inventive step in relation to the claimed subject-matter.

V. In a communication pursuant to Article 15(1) RPBA which was annexed to the summons to oral proceedings, the board expressed its preliminary opinion on issues of the appeal.

VI. With a letter dated 17 December 2018 in response to the board's communication, the appellant submitted a set of claims of a new main request and four new auxiliary requests.

Claim 1 of the new main request read:

"1. A composition for use in a method of treatment or prevention of cancer in a subject, the method comprising systemic injection of the composition, the composition comprising cells, wherein the cells consist of (a) a population of CD4+ T cells, the population comprising CD4+ T cells engineered to express a molecule capable of binding to an antigen on a target cell of the cancer; and (b) a population of CD8+ T cells, the population comprising CD8+ T cells engineered to express the molecule capable of binding to the antigen on the target cell of the cancer; wherein the ratio of engineered CD4+ T cells to engineered CD8+ T cells in the composition is greater than 1:3 and less than 3:1."

VII. Oral proceedings took place as requested by the appellant. At the end the chair announced the decision of the board.

VIII. The arguments of the appellant, in as far as they are relevant for the present decision, can be summarised as follows:

Main request - claim 1

Clarity (Article 84 EPC)

The claim was clear to a skilled person.

Novelty (Article 54 EPC)

The subject-matter of the claim was novel over the disclosures in document D1 and D3 as these documents did not disclose adoptive immunotherapy with compositions as defined in the claim.

Inventive step (Article 56 EPC)

The closest prior art for the assessment of inventive step of the claimed subject-matter was represented by the disclosure in document D1.

Document D1 was an earlier publication by the inventors also relating to adoptive immunotherapy. It disclosed the same chimeric single-chain receptors as in the application and their use to modify T cells to target cancer cells and subcutaneous ErbB2-expressing tumours in mice. Systemic administration of the composition of engineered T cells by intravenous injection resulted in the suppression of distant subcutaneous tumours (see page 700, left-hand column, final paragraph, and section starting on page 704, left-hand column). The intravenous administration did not, however, result in any tumors being eradicated or any improvements in the

long-term survival of treated mice (page 706, right-hand column, lines 12 to 13 and Figure 5).

The claim required that the composition comprised both engineered CD4+ T cells and CD8+ T cells, and that these were present at a ratio of between 1:3 and 3:1.

From the relevant data disclosed on page 701 (right-hand column, lines 40 to 50) and the paragraph bridging the columns on page 702, it could be calculated that the ratio of engineered CD4+ T cells (i.e. 17.5 to 28% of the composition or 70% of 25 to 40%) to engineered CD8+ T cells (i.e. 3.75 to 5% of the composition or 25% of 15 to 20%) was less than required by the claim.

The difference between the disclosure in document D1 and the claimed invention was therefore the nature of the cellular compound making up the composition used for the adoptive immunotherapy.

Document D1 reported the suppression of distant subcutaneous tumours after systemic delivery of engineered T cells, but no tumours were treated, and no mice were cured of cancer and/or exhibited prolonged survival over control mice.

However, systemic injection of a composition in accordance with the claimed subject-matter, i.e. a composition of which the cellular compound has engineered CD4+ and CD8+ T cells within a ratio of 1:3 and 3:1, enhanced the tumour-free survival of mice (see, *inter alia*, Figure 3 of the application).

A technical effect of the difference was therefore increased tumour-free survival in mice treated with the composition in accordance with the claim.

Thus, the objective technical problem was the provision of an improved composition for adoptive immunotherapy.

The solution as claimed was not obvious to the skilled person. The prior art cited by the examining division did not appreciate the contribution of engineered CD4+ T cells to adoptive immunotherapy compositions, let alone that improved results could be achieved by ensuring that the T cells in the composition were present in the ratio defined in the claim.

Furthermore, the technical effect disclosed in the application was not predictable from the prior art. None of the cited documents suggested that the proportions of engineered CD4+ and CD8+ T cells contributed to the effectiveness of the composition, or that the claimed ratio would result in enhanced tumour-free survival.

Accordingly, when confronted with the problem to provide an improved, or even an alternative, composition for adoptive immunotherapy, the skilled person would not have been motivated to investigate the ratio of engineered CD4+ and engineered CD8+ T cells in their composition. Nor would they have appreciated that advantages could be achieved if the ratio of these cells was kept to between 1:3 and 3:1.

The claimed solution was therefore not obvious.

IX. At the end of the oral proceedings the appellant requested that the decision under appeal be set aside and that the case be remitted to the examining division for further prosecution.

Reasons for the Decision

1. The appeal is admissible.

Main request - claim 1

Clarity (Article 84 EPC)

2. The amendments to the claims, as compared to claims pending before the examining division, have rendered moot the objections raised in an *obiter dictum* by the examining division in the decision under appeal. The board decides that the claims meet the requirement of clarity provided for in Article 84 EPC.

Novelty (Article 54 EPC)

3. The board decides that the subject-matter of the claim is novel as it is not disclosed in any of the available documents belonging to the prior art, in particular in documents D1 and D3. The differences relevant for the assessment of novelty are identified below in the context of the assessment of inventive step (see points 7 to 16).

Inventive step (Article 56 EPC)

Relevant prior art

4. The claim is for a composition for use in a method for treating or preventing cancer. The method entails the systemic injection of the composition. The composition is further defined to comprise cells consisting of a population of CD4+ T cells and a population consisting of CD8+ T cells, whereby each population comprises

T cells engineered to express a molecule capable of binding to an antigen on a target cell of the cancer and in which the ratio of engineered CD4+ T cells to engineered CD8+ T cells in the composition is greater than 1:3 and less than 3:1.

5. Accordingly, the cellular compound of the composition as claimed consists of two particular T cell populations, each of which comprises a fraction of engineered cells with a defined ratio of the number of engineered cells in the first population over the second population.
6. Two documents have been considered by the examining division to be of primary relevance for the assessment of inventive step, i.e. documents D1 and D3.
7. Document D1 discloses adoptive immunotherapy with a composition comprising genetically engineered human CD4+ and CD8+ T cells expressing the product of a transduced scFv-CD28- ζ chimera recognising the ErbB-2 receptor. An attempt was made to systemically treat two human ErbB2+ tumours, subcutaneously injected in irradiated NOD:SCID mice, by intravenous injection of the transduced human T cells (page 701, right-hand column, last paragraph). The treatment reportedly led to a significant inhibition of tumour growth in both cases (page 704, right-hand column). Despite the significant tumour growth inhibition, no mice treated in the experiments disclosed in document D1 were reported to be cured of the cancer, and no prolonged survival over control was observed (page 706, right-hand column).
8. The nature of the pre-activated and transduced T cell composition used for the adoptive immunotherapy

disclosed in document D1 (see page 701, right-hand column, lines 40 to 50) is addressed in the paragraph bridging the columns on page 702, where it is stated that "[the receptor] was routinely detected in both $CD8^+$ T cells (25-40%, $n = 4$) (Fig. 1D) and $CD4^+$ T cells (15-20%, $n = 4$) (Fig. 1E)." and "After transduction/selection in G418, the culture largely consisted of T cells ($CD3^+CD8^+$, $70 \pm 15\%$; $CD3^+CD4^+$, $25 \pm 13\%$, $n = 3$) with only a small proportion of $CD56^+CD3^-$ cells ($4 \pm 1\%$, $n = 3$)".

9. The appellant has submitted, also based on the declaration D10 - and the board agrees - that the skilled person would have understood both sentences to refer to the composition as obtained after the transduction and the selection process disclosed on page 701 (left-hand column, lines 6 to 29). It can accordingly be calculated that the composition disclosed in document D1 contained approximately 17.5 to 28% engineered $CD8^+$ T cells (i.e. 70% of 25 to 40%, see point 8) and 3.75 to 5% engineered $CD4^+$ T cells (i.e. 25% of 15 to 20%) expressing the receptor, which is outside the 1:3 to 3:1 ratio specified in the claim.

10. The disclosure in document D1 accordingly differs from the claimed subject-matter in that the intravenously injected composition is not devoid of cells other than $CD4^+$ and $CD8^+$ T cells (see claim 1 which provides "the composition comprising cells, wherein the cells consist of"; emphasis by the board). In fact, the composition disclosed in document D1 comprises a small portion of $CD56^+CD3^-$ cells (see citation referred to in point 8 above). Moreover, the disclosure in document D1 differs from the claimed subject-matter in that the intravenously injected composition has a ratio of receptor expressing $CD4^+$ T cells to receptor expressing

CD8+ T cells not within the 1:3 to 3:1 ratio of the claim.

11. Document D3 discloses adoptive immunotherapy of tumours grown from subcutaneously transplanted HC11 R2 cells (mouse cells expressing human activated ErbB-2) in BALB/c mice by intra-tumoural injection of genetically modified mouse T cells expressing the product of a transduced chimeric scFv(FRP5)- ζ fusion gene recognising the ErbB-2 receptor. Injection of 10^7 of these transduced mouse T cells caused total tumour regression within 1 week and no tumour re-occurrence was observed for 30 days after treatment termination (see page 5512, paragraph bridging both columns).
12. The cellular contents of the genetically modified mouse T cell composition expressing the product of the transduced chimeric fusion gene used for the intra-tumoural administration is addressed on page 5510 in the paragraph entitled "*Transduction of T cells with chimeric TCR genes*" and on page 5511 (left-hand column, lines 3 to 13).
13. The first passage referred to, i.e. on page 5510, explains that the T cell enriched population of cells used for the transduction contained > 85% T cells (TCR +). It is then further stated in the passage that: "*The T cells were polyclonally activated and cocultured for 48 h with the retrovirus-producing packaging cells ΩE as described by Altenschmidt et al. (29). After the coculture, the T lymphocytes were separated from the packaging cells. The T cell culture was placed into a 1-cm plastic dish for 3 h to allow ΩE cells to adhere to the surface; then **T cells were washed** in T cell medium or PBS **and used for in vitro and in vivo assays.*** The ratio of CD4⁺/CD8⁺ T cells and the expression of

the ζ fusion proteins on the surface of the modified T lymphocytes was analyzed by indirect immunofluorescence." (Emphasis added by the board).

14. The second passage referred to, i.e. on page 5511, reports on the results obtained from this analysis and discloses that: "*The expression of the fusion proteins on the surface of the T lymphocytes was determined by FACS analysis (Fig. 2). The cells were reacted with the mAb Mycl-9E10, directed against the myc-tagged epitope in the fusion protein. No expression of the fusion protein was detected in T lymphocytes transduced with the retro-viral vector pLXSN (Fig. 2A). The majority (>75%) of the T cells infected with the vector encoding the fusion proteins, directed against the ErbB-2 receptor (Fig. 2B) or the viral surface protein (Fig. 2C), were recognized by the tag-specific Ab. The relative phenotype of the transduced T lymphocytes was about 40% CD4⁺ and 60% CD8⁺ T cells (data not shown).*" (see page 5511, left-hand column, lines 3 to 13; emphasis added by the board).

15. From the above data, the ratio of "engineered CD4+ T cells to engineered CD8+ cells" cannot be calculated for the T cell compositions which are used for the disclosed *in vitro* and *in vivo* assays. In particular, the intra-tumour injection study reported on and disclosed in the section entitled "*Transduced T lymphocytes cause total tumor regression in vivo*" (bridging pages 5512 and 5513). Indeed, although document D3 states that >75% of the T cells produced the fusion protein encoded by the chimeric gene, this value applies in fact to the totality of T cells in the composition. In these T cells the relative phenotype is about 40% CD4⁺ and 60% CD8⁺.

16. The disclosure in document D3 accordingly differs from the claimed subject-matter in that the claimed cellular composition consists of - and thus is limited to - CD4+ and CD8+ T cells and that it defines a ratio of "engineered CD4+ T cells to engineered CD8+ cells". It differs further in the mode of administration of the composition, i.e. intra-tumoural *versus* systemic injection.

Closest prior art

17. For assessing whether a claimed invention meets the requirements of Article 56 EPC, the boards of appeal normally apply the "problem and solution" approach. This requires first identifying of the closest prior art. This is generally a prior art document disclosing subject-matter conceived for the same purpose, i.e. 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 (see also Case Law of the Boards of Appeal, 8th edition 2016, I.D.3.1).
18. In relation to the subject-matter of claim 1 of the main request dealt with in the decision under appeal, the examining division held the disclosure in document D3 to represent the closest prior art. However, on the basis of the analysis given in points 10 and 16, above the board can concur with the appellant that, also for the subject-matter of the claim now under consideration, rather than the disclosure in document D3, the disclosure in document D1 represents the closest prior art.

The technical problem and the solution

19. The technical effect resulting from the technical differences identified in point 10 above is that whereas the *in vivo* adoptive immunotherapy experiments disclosed in document D1, similarly involving intravenous injection, did not lead to the curing of mice of the cancer and did not result in a prolonged survival of these mice, the *in vivo* adoptive immunotherapy experiments disclosed in Example 4 and Figure 3 of the application as filed demonstrate a substantial tumour-free survival rate of the mice treated with the composition defined in the claim.

20. The technical problem to be solved by the claimed invention can therefore be formulated as the provision of an *in vivo* adoptive immunotherapy resulting in total tumour-free survival of subjects suffering from cancer.

Obviousness

21. It has to be established whether the skilled person, starting from the disclosure in document D1 and faced with the technical problem defined above, would arrive in an obvious manner at the composition defined in the claim for use in adoptive immunotherapy of cancer in a subject involving systemic administration (injection).

22. Document D1 itself is silent on the ratio of engineered CD4+ T cells to engineered CD8+ T cells in the composition used for systemic injection, and the board is satisfied that, even if the skilled person had calculated this ratio from the disclosed data, values are obtained which consistently fall outside the 1:3 to 3:1 ratio specified in the claims (see point 10 above). Similarly, document D1 would not have prompted the

skilled person to restrict the cellular compounds contained in the systemically injected composition to CD4+ and CD8+ T cells.

23. Also, none of the further cited documents on file would have suggested the composition as claimed to the skilled person. Even when additionally consulting the disclosure in document D3, the skilled person's attention would rather have been drawn to the different mode of administration of the composition, i.e. intratumoural, than to the exact nature of the cellular compound in the composition used, let alone to the ratio of "engineered CD4+ T cells to engineered CD8+ cells" which could not even have been calculated from the available data.
24. In view of these considerations the board concludes that the skilled person would not arrive in an obvious manner at the composition defined in the claim when starting from the disclosure in document D1.
25. For the sake of completeness the board notes that also when starting from document D3 as representing the closest prior art, none of the further cited documents on file would have prompted the skilled person to provide as a solution the composition with the cellular compound as now defined in the claim and to systemically inject it in subjects suffering from cancer.
26. Accordingly, the subject-matter of claim 1 of the main request complies with the requirements of Article 56 EPC.

Conclusion

27. The decision under appeal has only addressed the requirements of Article 56 EPC in relation to claim 1 of all then pending requests and further contains an *obiter dictum* relating to Article 84 EPC concerning those requests.
28. The board decided that claim 1 of the present main request was clear (Article 84 EPC) and that its subject-matter was novel and inventive (Articles 54 and 56 EPC).
29. Pursuant to Article 111(1) EPC, following the examination as to the allowability of the appeal, the board will decide on the appeal, and in that respect it may either exercise any power within the competence of the department which was responsible for the decision appealed or remit the case for further prosecution to that department.
30. In view of the appellant's request (see section IX) and also considering that the examining division in the decision under appeal has not dealt with all requirements of the EPC for the grant of a patent, the board, exercising its discretion under Article 111(1), second sentence, EPC, decides to remit the case to the examining division for further prosecution on the basis of the main request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the examining division for further prosecution on the basis of the set of claims of the main request filed with letter dated 17 December 2018.

The Registrar:

The Chair:



S. Lichtenvort

G. Alt

Decision electronically authenticated