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Datasheet for the decision of 24 October 2023

Case Number: T 1638/21 - 3.3.08

Application Number: 14845082.8

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Title of invention:
Improved methods of genetically modifying animal cells

Patent Proprietor:
Wilson Wolf Manufacturing Corporation

Opponent:
European Oppositions Limited

Headword:
Methods of genetically modifying T cells/WILSON WOLF

Relevant legal provisions:
EPC Art. 123(2), 56
RPBA 2020 Art. 12(3), 12(5)

Keyword:
Amendments - extension beyond the content of the application as filed (yes)
Inventive step - combination invention (no) - obvious alternative
Reply to statement of grounds of appeal - reasons set out clearly and concisely (no)
Discretion not to admit submission - submission admitted (no)

Decisions cited:
G 0002/21, G 0002/10

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Case Number: T 1638/21 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 24 October 2023

Appellant: (Opponent)	European Oppositions Limited Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Representative:	Maiwald GmbH Elisenhof Elisenstraße 3 80335 München (DE)
Respondent: (Patent Proprietor)	Wilson Wolf Manufacturing Corporation 33-5th Avenue NW Suite 700 New Brighton, MN 55112 (US)
Representative:	Barker Brettell LLP 100 Hagley Road Edgbaston Birmingham B16 8QQ (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 5 July 2021 concerning maintenance of the European Patent No. 3049515 in amended form**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	R. Morawetz
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 3 049 515 ("the patent") is based on European patent application No. 14 845 082.8, which was filed as an international application published as WO 2015/042595 ("the application as originally filed"). The patent is entitled "*Improved methods of genetically modifying animal cells*".

II. One opposition to the granted patent was filed. The patent was opposed in its entirety under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC), and under Article 100(b) and (c) EPC.

III. By way of an interlocutory decision, the opposition division decided that the patent in amended form on the basis of the main request submitted during oral proceedings and the invention to which it relates met the requirements of the EPC.

IV. The opponent (appellant) filed an appeal against the opposition division's decision.

V. In its statement setting out the grounds of appeal, the appellant submitted arguments, *inter alia*, to the effect that the claims of the main request underlying the decision under appeal did not comply with the requirements of Articles 123(2), 56 and 83 EPC. It furthermore submitted arguments against all auxiliary requests on file.

VI. In reply to the appeal, the patent proprietor (respondent) maintained its main request from the opposition proceedings and submitted auxiliary

requests 1 to 12 and arguments, *inter alia*, to the effect that claims 1 and 7 of the main request met the requirements of Article 56 EPC.

Claims 1 and 7 of the main request read as follows:

"1. A method of transducing T cells comprising:
adding a media, T cells, and genetic modification agents comprised of lentivirus into a device with rigid walls and a bottom comprised of gas permeable, liquid impermeable material, said T cells are at a concentration of greater than 2 million and up to 30 million cells per millilitre of media, with said gas permeable, liquid impermeable material being in contact with ambient gas, and
allowing a period of time whereby said genetic modification agents act to transduce at least a portion of said cells."

"7. A method of transducing T cells comprising:
a) adding media and a quantity of T cells into a gas permeable device with rigid walls and includes a horizontal cell growth surface comprised of gas permeable, liquid impermeable material, and allowing T cells to gravitate to the gas permeable, liquid impermeable material, whereby the T cells are at a first cell concentration, media is a first media height, and media is at a first media volume, said first cell concentration being the quantity of T cells divided by said first media volume, said first media height being defined by the distance from the uppermost location of said media to the lowest location of said media when said cell growth surface is in a horizontal position,
b) removing a portion of said first media volume from said device leaving a second media volume in said

device wherein T cells are at a second cell concentration, said second cell concentration is greater than said first cell concentration, media is at a second media height which is defined by the distance from the uppermost location of said media to the lowermost location of said media when said cell growth surface is in a horizontal position,
c) adding lentivirus into said device,
d) allowing a period of time for said genetic modification agents to transduce at least a portion of said T cells,
e) adding a volume of media into said device, and
f) allowing a period of culture time for T cells to be expanded in quantity when said device is oriented in a position such that at least a portion of said T cells reside upon said cell growth surface and said cell growth surface is oriented in a horizontal position and ambient gas suitable for cell culture is in contact with said gas permeable liquid impermeable material."

Claim 1 of auxiliary request 1 differs from claim 1 of the main request by the insertion of the feature "*said media is in contact with said gas permeable, liquid impermeable material*".

Claim 1 of auxiliary request 2 differs from claim 1 of the main request in that it includes the amendment made in claim 1 of auxiliary request 1 and further specifies that the device has a "*bottom growth surface comprised ...*" (amendments compared to claim 1 of the main request are shown by underlining).

Claim 1 of auxiliary request 3 differs from claim 1 of the main request by the insertion of the feature "*at least a portion of said T cells are in contact with said gas permeable, liquid impermeable material*".

Claim 1 of auxiliary request 4 combines the amendment made in claim 1 of auxiliary requests 2 with respect to the growth surface with the amendment of claim 1 of auxiliary request 3.

Claim 1 of auxiliary request 5 differs from claim 1 of the main request by the insertion of the feature "*said T cells are in contact with said gas permeable, liquid impermeable material*".

Claim 1 of auxiliary request 6 combines the amendment made in claim 1 of auxiliary requests 2 with respect to the growth surface with the amendment of claim 1 of auxiliary request 5.

Claim 1 of auxiliary request 7 differs from claim 1 of the main request in that it specifies that "*said T cells are at a concentration of greater than 2 million and up to ~~30~~5 million cells per millilitre of media*" (amendments compared to claim 1 of the main request are shown by underlining and strike-through).

Claim 1 is the same in auxiliary request 8 and auxiliary request 9 and combines the amendments made in claim 1 of auxiliary requests 2 and 7.

Claim 1 of auxiliary request 10 combines the amendment made in claim 1 of auxiliary request 2 with respect to the growth surface with the amendments made in claim 1 of auxiliary requests 5 and 7.

Claim 1 of auxiliary request 11 is identical to claim 7 of the main request.

Claim 1 of auxiliary request 12 differs from claim 1 of auxiliary request 11 in that step b) is amended to

indicate that "*T cells are at a second cell concentration* *of greater than 2 million and up to 5 million cells per millilitre of media*" (amendments compared to claim 1 of auxiliary request 11 are shown by underlining).

VII. In a further letter, the appellant gave, *inter alia*, additional reasons as to why claims 1 and 7 of the main request did not comply with the requirements of Article 56 EPC.

VIII. The board scheduled oral proceedings, in accordance with the parties' requests, and subsequently issued a communication under Article 15(1) RPBA setting out its preliminary opinion on matters relevant for the decision to be taken.

IX. In reply, the respondent provided arguments for the admittance of auxiliary requests 1 to 12 into the appeal proceedings.

X. The oral proceedings before the board took place as scheduled. At the end of the oral proceedings, the Chairwoman announced the board's decision.

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

D1 Lamers C.H.J. *et al.*, Cancer Gene Therapy 9, 2002, 613-23

D15 Vera J.F. *et al.*, Curr Gene Ther. 9(5), 2009, 396-408

D17 Costello E. *et al.*, Gene Therapy 7, 2000, 596-604

D20 WO 00/56870

D21 Gagliardi C. *et al.*, Cytotherapy 21, 2019, 1246-57

XII. The parties' arguments relevant to the decision are reflected in the Reasons below.

XIII. The appellant requested that the decision under appeal be set aside and the patent be revoked. It also requested that auxiliary requests 1 to 12 filed with the reply to the statement of grounds of appeal not be admitted into the appeal proceedings.

The respondent requested that the decision under appeal be upheld (implying that the appeal be dismissed) or, alternatively, that the patent be maintained in amended form on the basis of one of auxiliary requests 1 to 12 filed with the reply to the statement of grounds of appeal.

Reasons for the Decision

Main request

Amendments (Article 123(2) EPC) - claim 1

1. The opposition division held that claim 1 met the requirements of Article 123(2) EPC. On appeal, the appellant maintained that the subject-matter of the claim extended beyond the content of the application as filed as a result of the omission of the features "*said animal cells in contact with said gas permeable, liquid impermeable material*" and "*said gas permeable, liquid impermeable material being in a horizontal position*" and the addition of the feature "*bottom comprised of*

gas permeable, liquid impermeable material".

2. The sole issue considered in this decision on the main request is whether the omission of the feature "*said gas permeable, liquid impermeable material being in a horizontal position*" results in subject-matter which extends beyond the content of the application as filed within the meaning of Article 123(2) EPC.

3. The standard for assessing compliance with the requirements of Articles 123(2) EPC is the standard set out in G 2/10 (OJ EPO 2012, 376, Reasons 4.3). Amendments are only permitted within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of the application as filed. The amendment cannot provide the skilled person with new technical information.

4. It is undisputed that claim 1 of the main request is based on claim 1 as filed. That claim relates to a method of transducing animal cells in a device that includes a gas permeable, liquid impermeable material in a horizontal position and reads as follows:

"1. A method of transducing animal cells comprising: adding a media, animal cells, and genetic modification agents into a device that includes gas permeable, liquid impermeable material, said animal cells are at a concentration of 3 million to 20 million cells per milliliter of media, said animal cells in contact with said gas permeable, liquid impermeable material, said gas permeable, liquid impermeable material being in a horizontal position, and

allowing a period of time whereby said genetic modification agents act to transduce at least a portion of said cells."

5. The orientation of the device - and hence the orientation of the bottom comprised of gas permeable, liquid impermeable material - is no longer defined in claim 1 of the main request, which reads as follows:

"A method of transducing ~~animal~~ T cells comprising:
adding a media, ~~animal~~ T cells, and genetic modification agents comprised of lentivirus into a device ~~that includes~~ with rigid walls and a bottom comprised of gas permeable, liquid impermeable material, said ~~animal~~ T cells are at a concentration of ~~3~~ greater than 2 million and up to ~~20~~ 30 million cells per milliliter of media, ~~said animal cells in contact with said gas permeable, liquid impermeable material, said gas permeable, liquid impermeable material being in a horizontal position,~~ with said gas permeable, liquid impermeable material being in contact with ambient gas and
allowing a period of time whereby said genetic modification agents act to transduce at least a portion of said cells." (amendments compared to claim 1 as filed are shown by underlining and strike-through)."

6. Claim 1 therefore also embraces methods in which the gas permeable, liquid impermeable material of the device is not in a horizontal position.

7. At issue is whether this results in new technical information not included in the application as filed.

8. The respondent asserted that the skilled person recognised from the disclosure in the application as

filed that the device has a bottom surface comprised of gas permeable, liquid impermeable material but that a horizontal position was not an essential feature of the method.

9. First, the board notes that the test for compliance with Article 123(2) EPC has been set out in point 3. above and that the so-called essentiality test cannot take the place of the standard set out in G 2/10. Furthermore, in the more recent, and now well-established, case law of the boards, the essentiality test is no longer considered appropriate (see Case Law of the Boards of Appeal of the European Patent Office, 10th edition 2022 ("CLBA"), II.E.1.4.4 c)).

10. Second, the board agrees with the appellant that the passages in the application as filed relied on by the respondent actually disclose a horizontal position of the device.

11. These passages read as follows:

"*Figure 2 shows a cross-sectional view of gas permeable device 100, for example such as described within Wilson '814, Vera '700, Vera '768, Wilson '848, Welch '702 and the commercially available G-Rex® devices, which advocate and/or allow media to reside at a height well beyond conventional devices and allow cells to reside at a higher surface density than conventional culture devices. In this example, cells 40 (shown as circles) are in a state of static culture and have gravitated to the bottom of the device, which is comprised of gas permeable, liquid impermeable cell growth surface 160.*" (page 8, lines 8 to 14).

"*The genetic modification agents are at a lower specific gravity than that of cells, and at a specific gravity that prevents them from gravitating to the bottom of the device as the cells do.*" (page 9, lines 5 to 7)

"*To further increase transduction efficiency, it may be advantageous to move the cells out of their resting position, which is a result of the static state of the media and gravity acting on the cells to move them to the bottom of the device.*" (page 10, lines 1 to 3)

"*Stated differently, by putting the media into a state of forced motion, as opposed to a static state that allows cells to gravitate to the device bottom, cells are moved from the bottom and into a state of distribution throughout the media.*" (page 10, lines 9 to 13)

"*Preferably the bottom of the device is comprised of a gas permeable cell growth surface that is in a planar and horizontal state when the media height is being reduced and/or animal cells are being cultured.*" (page 20, lines 13 to 15)

12. The board agrees with the appellant that the disclosure that cells gravitate to the bottom of the device (see previous point) is indicative of a horizontal position of the device and hence also of a horizontal orientation of its bottom comprised of gas permeable, liquid impermeable material.

13. Furthermore, as also noted by the appellant, Figure 2 of the application as filed depicts the device with the bottom of the device, which is comprised of gas permeable, liquid impermeable cell growth surface 160,

exclusively in a horizontal position (Figures 2, 2A, 2B), even when the media is in a state of forced motion within the device (Figure 2C; page 10, lines 3 to 5).

14. The respondent's argument that from the passage on page 20, lines 13 to 15 (see point 11. above) it could be derived that the planar and horizontal position was only a requirement when the media height was being reduced, or when animal cells were being cultured, or both, is not persuasive. The passage on page 20, lines 13 to 15 is not about the method of claim 1 as filed but a different method, which is the subject of claim 9 as filed. The skilled person would therefore not derive from the passage on page 20, lines 13 to 15 any indication that in the method according to claim 1, the gas permeable, liquid impermeable material of the device was not in a horizontal position.

15. The board therefore also agrees with the appellant that the technical information conveyed to the skilled person in the application as filed in all instances relating to the method of claim 1 is that the bottom of the device, comprised of the gas permeable, liquid impermeable material, is in a horizontal position.

16. In a further line of argument, the respondent submitted that the disclosure in the application as filed as regards the possibility of moving media out of a static state into a non-static state by shaking the device (page 10, lines 4 to 5) implied that the device would not be in a horizontal position.

17. Contrary to the respondent's assertion, the application teaches that the device is in a horizontal position, even when media is moved into a non-static state. As set out above, Figure 2C, mentioned in this context in

the application as filed, depicts the device in a horizontal position. The skilled person also knows that the equipment mentioned in the application as filed in this context, i.e. the "*orbital shaker*" and "*shaker plate*" (page 10, line 8 of the application), performs a horizontal movement.

18. The board therefore also agrees with the appellant that the skilled person would not derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of the application as filed that in a method according to claim 1 the device is in any other position but horizontal.

19. In these circumstances, the skilled person would need to reflect if the device could be positioned differently such that the gas permeable, liquid impermeable material is no longer in a horizontal position, e.g. whether the device could be tilted at an angle. However, what the skilled person might do upon reflection is not part of the content of the application as filed but concerns obviousness (see also CLBA, II.E.1.9.3). The board is therefore not persuaded by the respondent's argument that, based on their common general knowledge, the skilled person would realise that there was no requirement for a particular orientation of the device.

20. Finally, with respect to the respondent's submission that the embodiment described on page 5, lines 9 to 14 of the application as filed has no requirement for a horizontal position, the board recalls that the feature in question is disclosed as an explicit requirement of the method which provides the basis for claim 1 of the main request, i.e. claim 1 as filed. It is moreover

disclosed in the passages of the application and Figure 2 relied on by the respondent as providing a basis for claim 1 of the main request (see points 11. to 15. above). The embodiment on page 5, lines 9 to 14 differs in several features from claim 1 of the main request, and the respondent has provided no argument why the skilled person would derive the subject-matter of claim 1 of the main request directly and unambiguously from that embodiment. Indeed, the respondent confirmed during the oral proceedings before the board that it was relying on claim 1 as filed as providing the basis for claim 1 of the main request and not on the embodiment on page 5, lines 9 to 14 of the application as filed.

21. For these reasons, claim 1 of the main request contravenes Article 123(2) EPC.

Auxiliary requests 1 to 10

Admittance and consideration

22. Auxiliary requests 1 to 10 were submitted in reply to the appeal. The respondent submitted that they are identical to auxiliary requests 14 to 23 submitted on 14 April 2021, except that granted claim 5 was deleted, where present. The appellant requested that auxiliary requests 1 to 10 not be admitted on the grounds that they had not been substantiated in appeal (Article 12(3) and (5) RPBA).

23. In view of the board's conclusions on added subject-matter in claim 1 of auxiliary requests 1 to 10 (see point 24. below), the question of whether these requests should be considered in substance need not be

addressed.

Amendments (Article 123(2) EPC) - claim 1

24. Claim 1 of each of auxiliary requests 1 to 10 is based on claim 1 as filed but omits the requirement that the gas permeable, liquid impermeable material be in a horizontal position (see section VI. above). The respondent conceded during oral proceedings before the board that it was not a requirement of claim 1 of any of these claim requests that the gas permeable, liquid impermeable material be in a horizontal position. The objection set out above for claim 1 of the main request therefore applies, *mutatis mutandis*, to claim 1 of each of auxiliary requests 1 to 10. This was not disputed by the respondent. Claim 1 of each of auxiliary requests 1 to 10 therefore does not comply with Article 123(2) EPC.

Auxiliary request 11

Admittance and consideration

25. Auxiliary request 11 is limited to a single claim which is identical to claim 7 of the main request.

26. The appellant submitted that auxiliary request 11 should not be considered in the appeal proceedings on the grounds that it had not been substantiated in appeal.

27. In the reply to the appeal, the respondent did not provide any reasons why the patent should be upheld on the basis of auxiliary request 11 if the main request was rejected (Article 12(3) RPBA). The respondent did, however, provide reasons for the allowability of

claim 7 of the main request.

28. Since claim 1 of auxiliary request 11 is identical to claim 7 of the main request, these reasons apply necessarily to claim 1 of auxiliary request 11. The board therefore concurs with the respondent that the reasons for presenting auxiliary request 11 in reply to the appeal can be considered self-explanatory, and the requirements of Article 12(3) RPBA are met.

29. The board therefore decided to consider auxiliary request 11 to be part of the appeal proceedings.

Inventive step - claim 1

Claim construction - the claimed invention

30. Claim 1 relates to a method of transducing T cells in a gas permeable device with rigid walls and a horizontal cell growth surface comprised of gas permeable, liquid impermeable material (for the complete wording of the claim, see section VI. above). Claim 1 does not define the device in terms of its dimensions, nor does it specify the amount of T cells added to the device or the concentration of T cells at any stage of the method.

31. Accordingly, no conclusion can be drawn from the technical features recited in the claim as to the concentration of the T cells (cells/ml) or their density (cells/cm^2 bottom surface) at any stage of the claimed method.

Closest prior art

32. As set out above, claim 1 of auxiliary request 11 is identical to claim 7 of the main request underlying the decision under appeal. The opposition division held for the subject-matter of that claim that document D1 was the closest prior art. On appeal, it was common ground that document D1 represented the closest prior art.

33. Document D1 concerns a protocol for gene transduction and expansion of human T cells. Specifically, document D1 discloses a process for T cell transduction involving Retronectin™-coated tissue culture 24-well plates or Lifecell® X-fold® cell culture bags (document D1, page 615, left-hand column, last paragraph to right-hand column, second paragraph). Document D1 reports that activated T lymphocytes were resuspended in retrovirus-containing culture supernatant (RTVsup) supplemented with 100 IU/mL IL-2 and plated on Retronectin™-coated 24-well plates or cell culture bags. Gene transductions were performed using cell concentrations varying from 0.25 to 1.0 x 10^6 cells/cm^2 and RTVsup volumes of 0.25 to 1.0 mL/cm^2. Plates and bags were incubated at 37°C and 5% CO_2 for 6 hours. Next, the transduction medium was replenished or completely replaced with various types of medium. The following day, a second, identical cycle of gene transduction was performed. Human T-lymphocyte transductants were then expanded by seeding 0.5 x 10^6 cells/ml in various test media. According to document D1, lymphocyte density per surface unit affected gene transduction efficiency of human T cells, and the maximal number of T cells that could be used per cm^2 without lowering gene transduction efficiencies was 0.5 x 10^6 T lymphocytes/cm^2 (page 618, left-hand column, second paragraph and Figure 4). Document D1

furthermore concludes that gene transduction was independent of the geometry of the system used, i.e. bags or plates, since the results of 12 independent experiments showed comparable transduction efficiencies (page 620, left-hand column, third paragraph and Figure 7).

34. Lifecell® X-fold® cell culture bags are gas permeable bags with a protein-coatable polystyrene inner surface layer (document D1, page 614, right-hand column, last paragraph). In agreement with the respondent, the board considers that the method of transducing T cells using the Lifecell® X-fold® gas permeable cell culture bags (the bag-based method) is a suitable starting point for the assessment of inventive step.

Distinguishing features, technical effect and objective technical problem

35. The board agrees with the appellant that the claimed subject-matter differs from the bag-based method of document D1 on account of (i) the rigid walls of the gas permeable device, (ii) the removal of a portion of the media before transduction and (iii) the use of a lentivirus for transduction of the T cells.

36. As set out above (see point 30.), claim 1 does not define any cell concentrations, either explicitly or implicitly. The board therefore also agrees with the appellant that the respondent's assertion that the claimed subject-matter additionally differed from the disclosure in document D1 on account of "cell concentrations exceeding conventional concentrations" (see reply, page 8, last paragraph and page 12, second paragraph) is not correct.

37. While the application as filed asserts that reducing the distance between gene modifying agents and cells would enhance T cell transducing efficiency (page 8, line 22 to page 9, line 23 of the application as filed), it was common ground during opposition proceedings and on appeal that the application provides no evidence to support this assertion. The opposition division moreover held that it had not been shown by the respondent that the transduction efficiency was improved when applying the claimed method.

38. The opposition division was, however, persuaded that distinguishing features (i) and (ii) allowed "*generate*[ing] *higher viable cell densities* (...) *due to the structure of the device, i.e. a small defined gas permeable bottom surface with a column above structured by the rigid walls.* (...) *this allows cell densities of 20 million cells per* cm^2 *or even 20 million cells per ml when the medium above the cells was removed. The flexible device of D1 does not allow for such high cell surface density, here the upper concentration is rather 2 million cells/ml*" (decision under appeal, Reasons 6.4). On this basis, the opposition division formulated the technical problem to be solved as the provision of a transduction method of T cells allowing the generation of high cell densities.

39. However, the invention which is the subject of claim 1 does not include any feature defining the size of the bottom surface of the device, the cell concentration or density, or the amount of media removed (see points 30. and 31. above).

40. Indeed, the opposition division's considerations were not based on the subject-matter of claim 7 of the main request (identical to current claim 1). Instead, they

were based on the cell concentration recited in a different claim (claim 1 of the main request) and a scenario discussed in the application as filed: the G-REX® device having a cell growth surface area of 100 cm^2, cells having gravitated to the bottom of the device and residing there at a surface density of 20 x 10^6 cells/cm^2 (see page 8, lines 8 to 21 of the application as filed). None of these technical features are reflected by any of the technical features recited in the claim at issue. The board therefore agrees with the appellant that the opposition division's reasoning does not apply to claim 1 at issue and, further, that the objective technical problem to be solved was not correctly formulated in the decision under appeal.

41. The respondent maintained on appeal that the technical effect of distinguishing features (i) and (ii) was the production of high cell densities. Its argument, submitted in writing, hinged on the claimed method relating to cell concentration being beyond 2 million cells per ml, the claimed device having a small defined bottom surface, and much of the media being removed from above the cells. The respondent's argument is thus similar to the argument of the opposition division (see point 38. above) and fails to convince for the same reasons (see point 40. above).

42. It also follows from the observations above that distinguishing features (i) and (ii) are not functionally interdependent. That feature (iii) is functionally unrelated to the other distinguishing features was already established in the decision under appeal and not contested by the respondent on appeal.

43. The board therefore agrees with the appellant that the effect of each distinguishing technical feature (see

point 35. above) must be considered separately and each difference must be considered to constitute a solution to a partial technical problem to be solved (CLBA, I.D.9.3.2).

Feature (i)

44. The respondent submitted during oral proceedings before the board that there was synergy between the rigid walls and the gas permeable bottom of the device in that the gas exchange via the gas permeable bottom of the device ensured higher viability of the cells during expansion resulting in higher numbers of transgenic cells and hence higher cell densities compared with the bag-based method disclosed in document D1.

45. In this context, the respondent relied on post-published document D21 as providing evidence that significantly more transduced cells were produced in a method according to claim 1 compared to the bag-based method of document D1.

46. Document D21 reports that significantly more transduced cells were harvested when cells were activated, transduced and expanded in a G-Rex® device compared with cell culture bags (document D21, page 1252, paragraph bridging columns; page 1256, left-hand column, third paragraph; Figure 6F). However, while it is undisputed that the device used in document D21 falls within the terms of claim 1 at issue, the board agrees with the appellant that the method does not. In document D21, Vectofusin-1 was added as transducing-enhancing reagent for transduction in the G-Rex® device yielding a transduction efficiency of 8 to 25% at MOI 1 and greater than 80% at MOI 10 (document D21, page 1255, paragraph bridging columns). By contrast,

document D21 also reports that without transduction-enhancing reagent and hence in a method corresponding to claim 1 at issue, transduction efficiency was less than 1% (*ibid.*). The number of transfected cells obtained after transduction and expansion in a G-Rex® device without using a transduction-enhancing reagent is not disclosed in document D21.

47. Accordingly, the board agrees with the appellant that document D21 cannot constitute evidence for the achievement of a higher number of transduced cells by a method according to claim 1 compared with the bag-based method of document D1.

48. The respondent's additional argument that Figure 6F of document D21 was self-contained and allowed the conclusion that it was the gas exchange via the gas permeable bottom of the device that enhanced the viability of the cells compared to bags likewise fails. As noted by the appellant, the bag of document D1 has a gas permeable bottom. Any advantage attributed to the gas permeable bottom of the device, i.e. enhanced viability, therefore equally applies to the bag of document D1.

49. In sum, the effect seen in document D21 (page 1252, paragraph bridging columns; page 1256, left-hand column, third paragraph; Figure 6F) cannot be ascribed to have its origin in the distinguishing feature of the invention compared with document D1, the closest state of the art. The respondent's argument regarding the achievement of a higher number of transgenic cells as a consequence of higher cell viability in the claimed method compared to the bag-based method of document D1 thus fails.

50. Accordingly, the question of whether the skilled person would have derived the purported effect of higher numbers of transgenic cells and therefore higher cell densities as being encompassed by the technical teaching and embodied by the same originally disclosed invention (G 2/21, OJ EPO 2023, 85, Order 2) need not be addressed.

51. In view of the above, the board agrees with the appellant that achieving a "high cell density" is not a technical effect associated with distinguishing feature (i). Bearing in mind that no other technical effect has been shown by the respondent to have anything to do with the device and, specifically, its rigid walls, which are the only structural difference compared to the cell culture bag of document D1, the technical effect provided by the differentiating feature (i) needs to be formulated in a less ambitious manner as merely the provision of an alternative. The technical effect of feature (i) is that it provides an alternative device for T cell transduction.

Feature (ii)

52. The respondent has not presented the board with any evidence of any technical effect associated with feature (ii). The respondent argued, however, that feature (ii) would lead to high cell density, which would in turn, as established in the art (document D17), result in an increased transduction of T cells.

53. Document D17 reports that in lentiviral vector-mediated gene transfer to T cells, centrifugation of vector supernatant and cells during infection leads to a five-fold increase in transduction (page 597, paragraph bridging columns). Centrifugation in document D17 has

the consequence that the cells and the agent are brought in very close contact.

54. The board recalls that neither the amount of media removed nor any cell concentration is defined in claim 1 (see points 30. and 31. above). It is *prima facie* highly unlikely that the removal of an undefined amount of media, which, as submitted by the appellant, could be as little as 1 nl, from a solution comprising an undefined number of cells would necessarily result in the same close contact of cells and lentivirus as achieved in document D17. Accordingly, the board does not accept that feature (ii) has any effect on T cell transduction. The respondent has not argued that any other technical effect would be attributable to distinguishing feature (ii).

55. The board therefore agrees with the appellant that feature (ii) does not establish any technical effect, i.e. it is arbitrary, and need not be considered further for the assessment of inventive step of claim 1.

Feature (iii)

56. The respondent did not provide any evidence or argument regarding this feature. It is also not self-evident that the use of a lentivirus would result in any surprising technical effect not already achieved by the use of the retrovirus in the method of document D1. The technical effect provided by the differentiating feature (iii) is therefore formulated as the provision of an alternative transducing agent.

57. In sum, starting from the teaching in document D1, the objective technical problem can be expressed as two

unrelated partial problems, one being the provision of a further T cell transduction method using an alternative device, the other being the provision of a further T cell transduction method using an alternative transducing agent.

Obviousness

58. It remains to be assessed whether the skilled person starting from the disclosure in document D1 and seeking a solution to the technical problem formulated above would, in view of the closest prior art, possibly in combination with other prior art or common general knowledge, have modified the disclosure of document D1 in such a way as to arrive at a method falling within the scope of claim 1 in an obvious manner. In the absence of any synergistic effect arising from the features distinguishing the claimed solution from the closest prior art, the obviousness of each feature, taken alone, has to be assessed separately.

59. Document D1 analysed the transduction efficiency of primary human T cells using either cluster well plates or cell culture bags. Since both showed comparable transduction efficiencies, document D1 concluded that gene transduction is independent of the geometry of the system used, i.e. bags or plates (see point 33. above). The board therefore agrees with the appellant that contrary to what was held in the decision under appeal and argued by the respondent on appeal, document D1 did not motivate the skilled person to use the bag technology for T cell transduction. In agreement with the appellant, the board furthermore considers that from that disclosure in document D1, the skilled person would have understood that any type of known cell culture containers suitable for T cell culture could be

used for T cell transduction and expansion.

60. The skilled person starting from the bag-based method in document D1 seeking a solution to the partial problem of feature (i) and without a requirement to achieve any specific technical effect had at their disposal all known T cell culture containers, *inter alia*.

61. Document D15 discloses the use of a G-Rex® cell culture device - a device with a gas permeable, liquid impermeable bottom and rigid walls - and its advantages for T cell culture including rapid expansion of genetically modified T cells (document D15, page 10, second paragraph).

62. The respondent did not dispute that the G-Rex® device was a device that fell within the ambit of claim 1 and was suitable for carrying out the claimed method. It argued, however, that neither document D1 nor document D15 provided any motivation to use that device.

63. When the objective technical problem lies in the provision of an alternative, no pointer or incentive is required. It suffices that the skilled person would have considered the claimed solution to be a reasonable alternative to the method of the closest prior art. Accordingly, the respondent's argument regarding the lack of motivation to use the G-Rex® device fails.

64. The board agrees with the appellant that the skilled person starting from the bag-based method in document D1 and being aware that different devices could be used for T cell transduction would have understood that the bags of document D1 could be replaced with the G-Rex® device disclosed in

document D15.

65. As regards the use of a lentivirus as the transduction agent, the board notes that document D1 used a retrovirus for transducing T cells (see point 33. above). Not only was the skilled person aware that the Retroviridae family includes lentiviruses, document D15 discloses that the great majority of studies on effective genetic modification of T cells have used retroviral vectors, either Moloney or Lentivirus based (page 3, first paragraph). The use of a lentivirus as the transducing agent instead of the retrovirus used in the bag-based method of document D1 was therefore not only conventional but even suggested to the skilled person in light of the disclosure of document D15.

66. In conclusion, when starting from document D1 and wishing to solve the partial technical problems posed, the skilled person would have arrived at the subject-matter of claim 1 in view of the teaching of document D15 without exercise of an inventive step. Therefore, the subject-matter of claim 1 of auxiliary request 11 does not meet the requirements of Article 56 EPC.

Auxiliary request 12

Admittance and consideration (Article 12(3) and (5) RPBA)

67. Auxiliary request 25 submitted on 14 April 2021 was re-submitted in reply to the appeal as auxiliary request 12. Auxiliary request 12 consists of a single claim, claim 1, which differs from claim 1 of auxiliary request 11 in that step b) has been amended to include a cell concentration range (see section VI. above). The appellant requested that auxiliary request 12 not be

admitted on the grounds that it had not been substantiated in appeal.

68. In the appeal, the appellant raised, *inter alia*, objections under Articles 123(2), 56 and 83 EPC against the claims of the main request and objections under Articles 56 and 83 EPC against claim 1 of auxiliary request 25 on file in the opposition proceedings.

69. Article 12(3) RPBA stipulates that the statement of grounds of appeal and the reply must contain a party's complete appeal case. Claim requests submitted in reply to the appeal must be justified by reasons why the amendments overcome the objections raised in the appeal. Pursuant to Article 12(5) RPBA, the board has discretion not to consider claim requests filed with the reply that do not meet the requirements of Article 12(3) RPBA.

70. In its reply to the appeal, the respondent submitted that auxiliary request 12 was a "genuine attempt to address the opposition [sic]" (see reply, page 17, last line) and referred to submissions made during the opposition proceedings in the context of auxiliary request 25 submitted by letter dated 14 April 2021.

71. In that submission, it was explained that auxiliary request 25 is identical to auxiliary request 12 filed with the letter dated 2 June 2020 (the reply to the notice of opposition), with the exception of a further amendment to clarify the features of the device (letter dated 14 April 2021, page 2, second paragraph). No argument on the cell concentration range was provided in that letter. Instead, reference was made to the earlier submission of 2 June 2020, and it was stated that the arguments made there for the main request

applied equally to auxiliary request 12.

72. In the submission dated 2 June 2020, the basis in the application as filed for the cell concentration range was indicated (item XIII). However, no reasons were provided as to why the cell concentration range was inserted into claim 1 of auxiliary request 12 or which objections the amendment was meant to address and how. Furthermore, if the arguments for auxiliary request 12 were the same as those for the main request (see previous point), they cannot explain what purpose the amendment made in auxiliary request 12 served since the corresponding claim of the main request, claim 8, did not specify any cell concentration range.

73. In its written reply to the board's preliminary opinion, the respondent argued that the reason for auxiliary request 12 being presented was at least implied and derivable from the circumstances. It submitted that auxiliary request 12 should be admitted and considered in the appeal proceedings because it was identical to previous auxiliary request 25 submitted during opposition proceedings "to address allegations [of] added subject matter and lack of sufficiency" (letter dated 3 October 2023, last paragraph of page 1).

74. The board disagrees. First, a mere reference to submissions filed in opposition does not suffice to provide the required substantiation in appeal proceedings. It can also not be expected that the board or the appellant piece together the respondent's arguments for auxiliary request 12 from three different submissions.

75. What is more, in the case at hand, it is evident from points 71. and 72. above that none of the respondent's submissions during opposition proceedings provided any reasons as to which objection the insertion of the concentration range was meant to address and how. Contrary to the respondent's assertion, it is not evident that the amendment was meant to address allegations of added subject-matter and lack of sufficiency.

76. Furthermore, given that the appellant had objected to inventive step and sufficiency of disclosure of claim 1 of auxiliary request 25 (identical to current auxiliary request 12) in the appeal, the respondent should have addressed these objections with appropriate reasons in the reply to the appeal since claim requests submitted in reply to the appeal must be justified by reasons why the amendments made overcome the objections raised in the appeal (Article 12(3) RPBA).

77. However, the reply contains no explanation or reason for the amendment of claim 1 of auxiliary request 12. Nor was any argument submitted in the respondent's written reply to the board's preliminary opinion. In view of the appellant's inventive-step objection, the board is moreover unable to accept the respondent's assertion that the reason for auxiliary request 12 was derivable from the circumstances.

78. During oral proceedings before the board, the respondent additionally argued that the submissions made in the reply for the main request on page 15, fourth full paragraph applied to claim 1 of auxiliary request 12.

79. In that passage, reasons for the inventive step of claim 7 of the main request in view of document D20 are provided. The argument focuses on the reduction of the media height in step b) of claim 7 but does not relate to the concentration range in claim 1 of auxiliary request 12 as this is not a feature of claim 7 of the main request. The board therefore agrees with the appellant that the submissions on page 15, fourth full paragraph of the reply concern a different context and do not address the appellant's objection to claim 1 of auxiliary request 12 (see section V. above).

80. In sum, the board concludes from the above that for auxiliary request 12, there are no facts or arguments concerning any of the objections raised by the appellant, in particular none addressing the objection under Article 56 EPC, raised in the statement of grounds of appeal such that this request is not substantiated.

81. The board therefore decided to not admit and consider auxiliary request 12 in the appeal proceedings (Article 12(5) RPBA).

Conclusion

82. The main request and auxiliary requests 1 to 11 are not allowable, and auxiliary request 12 is not admitted into the proceedings. There is no claim request on the basis of which the patent could be maintained in amended form. Accordingly, the patent has to be revoked.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated