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Datasheet for the decision of 8 April 2025

Case Number: T 0936/22 - 3.3.04

Application Number: 15782739.5

Publication Number: 3134432

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Language of the proceedings: EN

Title of invention:
MND promoter chimeric antigen receptors

Patent Proprietor:
2seventy bio, Inc.

Opponent:
Patent Boutique LLP

Headword:
MND promoter CARs/2SEVENTY BIO

Relevant legal provisions:
EPC Art. 100(a)
RPBA 2020 Art. 12(4), 12(6), 13(1)

Keyword:

Late-filed evidence - admitted (no) - circumstances of appeal case justify admittance (yes)
Amendment to case - amendment admitted (no)
Inventive step - (no)

Decisions cited:

G 0002/21

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Case Number: T 0936/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 8 April 2025

Appellant: (Opponent)	Patent Boutique LLP 10A Printing House Yard Hackney Road London, E2 7PR (GB)
Representative:	Boult Wade Tennant LLP Salisbury Square House 8 Salisbury Square London EC4Y 8AP (GB)
Respondent: (Patent Proprietor)	2seventy bio, Inc. 60 Binney Street Cambridge, MA 02142 (US)
Representative:	Forresters IP LLP Skygarden Erika-Mann-Straße 11 80636 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 1 February 2022 rejecting the opposition filed against European patent No. 3134432 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairwoman	M. Blasi
Members:	O. Lechner
	A. Chakravarty

Summary of Facts and Submissions

I. The opponent (appellant) filed an appeal against the opposition division's decision to reject the opposition against European patent No. 3 134 432.

II. The patent was granted on European patent application No. 15 782 739.5. The application was filed as an International patent application that was published as WO 2015/164759 ("application as filed").

III. In its decision, the opposition division *inter alia* considered and dismissed objections under Articles 100(a) and 56 EPC, including the objection of lack of inventive step when assessed starting from document D16 representing the closest prior art.

IV. In its statement of grounds of appeal of 10 June 2022, the appellant contested the opposition division's findings on inventive step and maintained its inventive step objection starting from document D16.

V. A first set of third-party observations under Article 115 EPC were received by the board on 18 July 2022, along with new document "D17" (now D19, see below). They contained submissions on lack of inventive step, *inter alia* based on document D16 combined with document D1.

VI. On 12 August 2022, the appellant referred to these third-party observations, stating that it agreed with them. It also re-filed them as document D18.

VII. By letter of 27 October 2022, the patent proprietor (respondent) replied to the statement of grounds of

appeal and resubmitted declaration D17. It provided arguments concerning the admittance of document D16 and on inventive step when assessed starting from document D1 as the closest prior art.

VIII. By letter of 5 December 2022, the respondent requested that the third-party submissions and enclosed document "D17" (D19 in the present proceedings) not be admitted and commented on the third-party observations and the inventive step objections.

IX. Further third-party observations under Article 115 EPC were received by the board on 7 May 2024, together with new documents TPO1 and TPO2. The letter contained submissions on lack of inventive step when assessed starting from document D16, *e.g.* when combined with document D1.

X. On 12 June 2024, the respondent commented on the third-party observations, requesting that they be disregarded or not admitted.

XI. On 30 July 2024 and 19 August 2024, the third party that had submitted observations on 7 May 2024 made further submissions including arguments relating to the issue of admittance of its observations.

XII. Further substantive submissions by the respondent and appellant were filed on 1 November 2024, 18 December 2024, and 7 March 2025, respectively. With the letter dated 1 November 2024, the respondent filed new experimental evidence.

XIII. The board issued a summons to oral proceedings as requested and subsequently a communication under Article 15(1) RPBA.

XIV. Oral proceedings before the board took place on 8 April 2025. During the oral proceedings, the appellant stated that it did not intend to rely on document D19.

At the end of the oral proceedings, the Chairwoman announced the board's decision.

XV. Reference is made to the following documents:

D1: De Oliveira *et al.*, Human Gene Therapy (2013); 24(10):824-839

D16: WO 2012/079000 A1

D17: Declaration of Alexander Astrakhan (undated; filed by letter dated 18 November 2021)

D18: Third-party observations of 18 July 2022

XVI. The appellant's arguments, relevant to the decision, are summarised as follows:

(a) *Consideration/Admittance of document D16*

There was no legal basis for excluding document D16 from the proceedings. It was filed before the final date set under Rule 116 EPC in reaction to the reasoning provided in the opposition division's preliminary opinion.

Since document D16 was the document having most technical features in common with the claimed subject-matter of the patent, it was *prima facie* relevant. Moreover, the opposition division's decision on inventive step was based on document D16 as closest

prior art, thus, said document had become part of the decision under appeal and consequently had to be taken into account in the appeal proceedings.

There was no legal basis for excluding a document during appeal proceedings if that document had already been admitted by the opposition division and considered in its decision.

(b) *Admittance of the respondent's new evidence and the associated arguments to support inventive step in the letter dated 1 November 2024 - Article 13(1) RPBA*

The new evidence filed by the respondent should not be admitted, as it constituted a late filed amendment to the respondent's appeal case under Article 13(1) RPBA. The respondent had failed to identify the new data as an amendment and had not provided adequate justification for its filing at this stage of the proceedings. Moreover it had not offered any explanation for its late submission. The stated justification - aligning the appeal with a corresponding divisional case - was not a valid reason under Article 13(1) RPBA.

Moreover, the purported *prima facie* relevance of the new evidence was flawed by the lack of sufficient information about the experimental setup, such as details about the CAR domains used.
Contrary to the respondent's assertion, decision G 2/21 was not applicable to the present case and did not have precedence over the requirements of Article 13(1) RPBA.

Accordingly, the late-filed new evidence should not be admitted under Article 13(1) RPBA.

(c) *Admittance/exclusion of the appellant's arguments adopted by letter dated 12 August 2022 and the respondent's arguments on inventive step starting from document D16 as closest prior art as filed by letter dated 5 December 2022*

Contrary to the requirements of Article 12(3) RPBA, the respondent did not present its complete appeal case in the reply to the statement of grounds of appeal. Document D16 was addressed under inventive step only in reaction to the appellant's adoption of the third party observations (document D18). However, the decision under appeal as well as the statement of grounds of appeal already considered the issue of inventive step starting from document D16 taken as the closest prior art. The respondent's reasoning under inventive step starting from document D16 thus represented an amendment to its appeal case under Article 13(1) RPBA. Either the appellant's letter dated 12 August 2022 including the submissions in document D18 and the respondent's submission of 5 December 2022 in reaction thereto were all to be admitted into the proceedings or none of them.

At the oral proceedings, the appellant stated that it did not object to the admittance of the respondent's inventive step reasoning based on a combination of documents D16 and D1, as submitted in the letter dated 5 December 2022.

(d) *Inventive step - Article 100(a) EPC - main request - claim 1*

Document D16 represented the closest prior art.

Difference and its technical effect

The subject-matter of claim 1 differed from the lentiviral vector shown in Figure 1A and Figure 12A of document D16 only in that the MND promoter is used and not an EF-1α promoter.

Contrary to the respondent's assertion, the presence of a woodchuck post-transcriptional regulatory element (WPRE) element was not a difference, since it was not excluded by the wording of claim 1 and was a feature of dependent claim 7(c).

As evidenced, e.g. by the data in Example 2 on page 80 of document D16, consistent expression for at least 6 months and a complete remission were also achieved with a CAR having the claimed architecture expressed under the EF-1α promoter.

The patent failed to show any surprising technical effect for the MND promoter in comparison with the EF-1α promoter. The only comparative example (Example 5) actually showed that a higher percentage of CAR expressing T cells could be obtained using the EF-1α promoter (Figure 6).

No persistent *in vivo* expression could be inferred from Example 7 of the patent, actually Figure 8 showed that after 20 days the CAR T cell treated mice also developed tumours.

Thus, the opposition division was wrong to rely solely on the speculative passage at paragraph [0072] of the patent (page 9, lines 23 to 27 of the application as filed) when considering the technical effect of the difference between document D16 and the claims, without

also considering the comparative data provided in the opposed patent.

Objective technical problem

The objective technical problem was the provision of an alternative vector to drive the expression of the CAR disclosed in document D16. The claimed solution was the use of the MND promoter.

Obviousness

The MND promoter was a viable and obvious choice for expressing CARs like those in document D16, as it was known to provide expression of proteins in haematopoietic cells including CARs. This was evidenced by document D1. When seeking an alternative promoter for driving the expression of a CAR of document D16, the skilled person would have been motivated to use MND as disclosed in document D1 because document D1 clearly demonstrated that the MND promoter effectively drives expression of second-generation CARs with potent and sustained activity, both *in vitro* and *in vivo*, providing a reasonable expectation of success when used as an alternative to the EF-1α promoter in document D16. The subject-matter of claim 1 was obvious over the combination of the teaching in documents D16 and D1.

If architecture of e.g. the hinge, transmembrane and costimulatory regions of a CAR truly required fine-tuning, as stated in document D17, then the claims should be limited to the specific construct tested in the patent. However, since the CAR constructs of claim 1 and of document D16 shared the same structural backbone and differed only in the target specificity of their N-terminal scFvs, the observed effect of the MND

promoter should be considered applicable to all these constructs. No evidence was provided to show that the promoter behaved differently depending on the CAR architecture.

(e) *Remittal - Article 111 EPC, Article 11 RPBA*

The respondent had not provided any specific reasoning within the meaning of Article 11 RPBA to justify a remittal in the present case. Accordingly, the case should not be remitted.

XVII. The respondent's arguments, relevant to the decision, are summarised as follows:

(a) *Consideration/Admittance of document D16*

Document D16 should not be taken into account. The opposition division's decision to admit document D16 should be overturned. Document D16 should not have been admitted by the opposition division because it had been filed by letter dated 5 November 2021, shortly before the oral proceedings before the opposition division, without any justification, despite having been available to the opponent before expiry of the opposition period. The late submission was a procedurally unfair attempt to ambush the respondent.

The opposition division's decision to admit document D16 based on the argument that one or two months were ample time to review it was not a proper justification for its admittance. In line with Article 99(1) and Rule 76(2)(c) EPC, the relevant time limit for filing all relevant facts and evidence was the nine-month opposition period.

Admitting document D16 solely based on its relevance encouraged late filing and disadvantaged the respondent, undermining fair and equitable proceedings. Allowing such late submissions without proper justification set a precedent that encouraged procedural abuse and negatively impacted the integrity of the appeal proceedings.

(b) *Admittance of the new evidence and the associated arguments to support inventive step in the letter dated 1 November 2024 - Article 13(1) RPBA*

The additional experimental evidence provided with the letter dated 1 November 2024 in point 3.34 - showing the sustained anti-leukaemia activity associated with anti-CD19 CAR T cells driven by the MND promoter - was entirely consistent with what is provided in paragraph [0072 of the patent (page 9, lines 19 to 27 of the application as filed) which clearly stated that a benefit of using the MND promoter was persistent, sustained expression of CAR polypeptides.

The additional experimental evidence had been submitted as early as possible. Decision G 2/21 (Reasons 88 to 91 and 93) enshrined the principle of free evaluation of evidence under the EPC, as outlined in Article 113(1) and Article 117(1) EPC, allowing any means of evidence to be assessed, regardless of its filing date. This principle ensured that evidence crucial for demonstrating a technical effect relevant to inventive step cannot be disregarded merely because it was submitted after the filing date. The relevant standard for inventive step assessment was what the skilled person, using common general knowledge, would understand from the application as filed. The technical effect had to be encompassed by the original teaching

and embodied by the same invention, even if considered later.

In the present case, the MND promoter had always been central to the invention, as evidenced by paragraph [0072] of the patent stating: "*The improved compositions and methods of adoptive cell therapy disclosed herein* [...] *the surprising finding that the MND promoter directs persistent expression of CAR polypeptides in resting, activated, and expanded T cells, and that such expression is sufficient to efficiently redirect the genetically modified immune effector cells contemplated herein to elicit cytotoxic activity against the tumour or cancer cell.*" Thus, the improved effect of the MND promoter was clearly embodied by the patent's teaching. The additional evidence did not alter the invention's framework.

(c) *Admittance of the appellant's arguments adopted by letter dated 12 August 2022 and the respondent's arguments on inventive step starting from document D16 as closest prior art as filed by letter dated 5 December 2022*

The submissions of 5 December 2022, which included inventive step arguments based on document D16 alone and *inter alia* in combination with document D1, were filed in direct response to the third-party observations of 18 July 2022 (document D18), which were adopted by the appellant on 12 August 2022. These submissions were explicitly presented under the heading "*Comments on the third-party observations*" and were conditional on the admittance of those observations.

These arguments were a reaction to new arguments introduced by the appellant.

The submissions should be admitted if the third-party observations or the appellant's adoption of them (D18) were to be admitted. Either both parties' related submissions should be admitted or none.

(d) *Inventive step - Article 100(a) EPC - main request - claim 1*

Since document D16 was admitted, it was a suitable starting point for the assessment of inventive step.

Difference and its technical effect

The subject-matter of claim 1 differed from the constructs used in Figure 1A of document D16 by the use of the MND promoter instead of the EF-1α promoter and the lack of a woodchuck post-transcriptional regulatory element (WPRE) as an essential element in the lentiviral vector.

It was important to emphasise that the lentiviral vector disclosed in document D16 used a WPRE which increases expression. Since it was not essential for driving persistent expression in the context of the invention, the WPRE element was not part of the subject-matter of claim 1.

The patent in paragraph [0072] reported the surprising finding that the MND promoter directs persistent expression of CAR polypeptides in resting, activated and expanded T cells, and that such expression is sufficient to efficiently redirect the genetically modified immune effector cells contemplated herein to elicit cytotoxic activity against the tumour or cancer cell. Examples 7 and 8 and Figure 8 of the patent

provided *in vivo* and *in vitro* evidence that the claimed CAR is suitable for treating cancer.

Example 5 did not cast any doubt on the effect of treating cancer being achieved. It was important to understand that the expression analysed in Example 5 was not to be considered identical to a therapeutic effect.

Thus, the MND promoter enabled persistent CAR expression without requiring a WPRE.

Objective technical problem

The objective technical problem was the provision of an alternative CAR expressing lentiviral vector for use in cancer treatment. The claimed solution was the use of the MND promoter.

Obviousness

The question on obviousness was whether the skilled person starting from the disclosure in document D16 and faced with the technical problem above, would have arrived at the claimed method without relying on *ex-post facto* analysis.

Promoter performance was highly context-dependent. Designing a CAR-encoding vector was not a "plug and play" exercise; simply swapping promoters or CAR components from different sources did not guarantee functionality. Even when using the same promoter and scFv, different CAR architectures yielded drastically different results, as shown in document D1.

Thus, the effect of a promoter on CAR expression could not be predicted in advance, as it depended on the specific CAR architecture and cellular environment. Accordingly, the skilled person would not have expected that replacing the EF-1α promoter in document D16 with the MND promoter from document D1 would result in a functional CAR for cancer treatment.

Document D16 focused on CAR architecture, as evidenced by page 24, first full paragraph, but not on promoter selection. It provided a list of diverse promoters on page 36, first full paragraph, none of which included MND.

Faced with the objective technical problem, the skilled person starting from document D16 had a list of alternative promoters to test. However, they would have had no motivation to consider document D1, which focused on modifying haematopoietic stem/progenitor cells (HSPCs), not T cells, with a CD19-specific CAR, and did not address expression vector design. Moreover, document D1 did not demonstrate therapeutic efficacy in T cells, which was the relevant context for the claimed invention.
D1 also confirmed that CAR architecture — such as hinge, transmembrane (TM), and signalling domains — was critical, and that the CAR disclosed in D1 differs substantially from that in D16.

Document D17 further confirmed that CAR components like hinge and TM domains are not interchangeable and must be empirically optimised for each construct, as CAR functionality depends on specific configurations, cellular context, and immunogenicity. Therefore, not only the promoter but the entire CAR structure needed to be tailored to achieve functionality.

The disclosures of documents D16 and D1 were technically incompatible. The skilled person could, in theory, have combined them, but would not have done so with a reasonable expectation of success of achieving a persistent expression of CAR in T cells sufficient to effectively redirect the T cells cytotoxic activity against tumours, and only hindsight would suggest otherwise.

(e) *Remittal - Article 111 EPC, Article 11 RPBA*

The case should be remitted to the opposition division for further prosecution, leading to maintenance of the patent in amended form, should the board not allow the main request, i.e. maintenance of the patent as granted. Remittal was justified because the decision of the opposition division had not decided on maintenance of the patent in amended form. The respondent should be given the opportunity to present amendments before the opposition division.

XVIII. The parties' requests relevant to the decision were as follows.

(a) The appellant requested that
- the decision under appeal be set aside and that the patent be revoked;
- the new evidence filed under item 3.34 of the respondent's letter dated 1 November 2024 and the associated arguments not be admitted;
- document D18 be admitted;
- document D16 not be excluded from the proceedings;
- the respondent's arguments pertaining to the disclosure of D16 and the combination of D16 with D1 - contained in the letter of 5 December 2022 - not be admitted insofar as the corresponding

arguments of 18 July 2022 and 12 August 2022 regarding these issues were not also admitted;
- the case not be remitted to the opposition division.

(b) The respondent requested that
- the appeal be dismissed, implying that the opposition be rejected and the patent be maintained as granted;
- documents D16 and D18 not be admitted;
- the third-party observations filed on 18 July 2022 and 7 May 2024 and accompanying documents TPO1 and TPO2 be disregarded or not admitted;
- the new experimental evidence as filed by letter dated 1 November 2024 and the related submissions be admitted; and
- the case be remitted to the opposition division should the main request not be found allowable.

Reasons for the Decision

Ground for opposition pursuant to Article 100(a) and Article 56 EPC - Inventive step

Consideration of document D16

1. Document D16 was filed in the proceedings before the opposition division by letter dated 5 November 2021, after the 9-month time-limit under Article 99(1) EPC but before the date set under Rule 116 EPC for making final written submissions. The opposition division decided to admit the document, finding it relevant (see point 7.2 of the decision under appeal). Document D16 was considered to represent the closest prior art in the assessment of inventive step and the decision under appeal is thus based on document D16 within the meaning

of Article 12(2) RPBA. On appeal, the appellant maintained its objection of lack of inventive step based on document D16 representing the closest prior art.

2. The respondent argued that, because the opposition division erred in admitting the document into the opposition proceedings, the opposition division's decision to admit document D16 should be overturned by the board and this should have the result of that document not being considered in the appeal proceedings.

3. The board confirms that the opposition division's decision to admit document D16 can, as such, be reviewed. Such a review must be conducted in accordance with the principles established for reviewing decisions taken by opposition divisions in exercise of their discretion.

However, in the present case, the board sees no legal basis, and none was relied upon by the respondent, which would allow document D16, which had been admitted by the opposition division and considered in the decision under appeal to represent the closest prior art, to be excluded from the appeal proceedings. In this context, the board notes that the opposition division has far-reaching powers to consider facts and evidence of its own motion under Article 114(1) EPC, including those which constitute grounds for opposition not invoked by an opponent (see Rule 81(1) EPC) and proceedings may be continued even in case of withdrawal of the opposition (see Rule 84(2) EPC). The rights of the patent proprietor in this situation are safeguarded via Article 113 EPC.

4. Accordingly, document D16 is part of the appeal proceedings under Article 12(2) RPBA.

5. Moreover, as far the opposition division's decision to admit document D16 is concerned, the board sees no error in the manner in which the opposition division exercised its discretion.

6. According to established case law of the Boards of Appeal (see G 7/93, reasons 2.6 and Case Law of the Boards of Appeal of the European Patent Office, 10th edition 2022, V.A.3.4.1, IV.C.4.5.2), the board's review of decisions taken by an opposition division in exercise of its discretion is limited. The board only considers whether the opposition division exercised its discretion according to wrong principles, or without taking into account the right principles, or in an unreasonable way, and has thus exceeded the proper limits of its discretion.

7. As can be derived from the opposition division's reasoning in point 7.2 of the decision under appeal, the opposition division admitted document D16 which had been filed prior to the final date set under Rule 116 EPC based on the *prima facie* relevance of its content and, hence, based on right principles. The board thus sees no error in this decision.

8. In these circumstances, where the decision under appeal was based on the disputed document, the board does not see on which basis the document could be excluded from the proceedings.

In addition, even if the opposition division had exercised its discretion wrongly, the board would not have excluded document D16 from the proceedings. In the

event that the admittance had been associated with a violation of the respondent's right to be heard for the reason that it had no an adequate opportunity to respond, it would have been this procedural deficiency which would have had to be remedied, e.g. by remitting the case to the opposition division under Article 11 RPBA. The respondent, however, did not complain that its right to be heard had been violated by the opposition division.

In view of the above considerations the board decided that document D16 is part of the appeal proceedings under Article 12(2) RPBA.

Admittance of the respondent's new evidence and the associated arguments to support inventive step presented in the respondent's letter dated 1 November 2024 - Article 13(1) RPBA

9. In the letter dated 1 November 2024, filed more than two years after filing the reply to the statement of grounds of appeal, the respondent filed new evidence in the form of a direct comparative example (presented in point 3.34 of the letter dated 1 November 2024). Based on these data, the respondent argued (see point XVII.(b) above) that MND-transduced CAR-T cells had a higher transduction efficiency. It also argued that the new evidence showed improved *in vivo* benefits of the MND promoter compared to the EF-1α promoter.

10. The respondent argued that the principle of free evaluation of evidence confirmed in decision G 2/21 meant that subsequently filed evidence had to be admitted by the board because the ruling in decision G 2/21 had precedence over the Rules of Procedure of the Boards of Appeal, especially over Article 13 RPBA, such that evidence to prove a technical effect relied

upon for acknowledgement of inventive step of the claimed subject-matter could be filed by the respondent at any stage of the proceedings and had to be admitted and considered by the board under all circumstances.

11. The respondent's approach is, however, incorrect. While decision G 2/21 confirms the principle of free evaluation of evidence, the issues of whether evidence filed at a particular stage in the proceedings before the board forms part of the proceedings or is subject to admittance by the board are distinct issues. The latter issues are to be decided upon on the basis of the provisions governing the proceedings before the boards, in particular Article 114(2) EPC and the RPBA.

12. As the evidence and related submissions were first presented after the respondent's reply to the grounds of appeal and before notification of the board's communication under Article 15(1) RPBA drawing attention to matters likely to be dealt with at the oral proceedings, Article 13(1) RPBA applied.

The respondent did not provide any arguments as to why the new evidence was submitted only at this late stage of the appeal proceedings even though the comparative evidence in Example 5 of the patent was already disputed from the onset of the opposition proceedings (notice of opposition, point 28) and inventive step continued to be an issue on appeal. Moreover, as submitted by the appellant, the respondent provided no details on how the additional experiments submitted by letter dated 1 November 2024 were performed or of the exact structure of the CAR used therein. Thus, the admittance of the experimental data would have raised further issues and admitting them, and the related arguments, would have been detrimental to procedural

economy.

Finally, the aim of filing these submissions as stated by the respondent, namely to align this case with case T 250/24 relating to a divisional application was also no convincing justification for submitting them at this late stage of the current proceedings.

13. In view of the above considerations, the board decided not to admit the experimental evidence and the associated arguments in point 3.34 ff. of the respondent's letter dated 1 November 2024 into the proceedings (Article 13(1) RPBA).

Admittance of the appellant's arguments filed by letter dated 12 August 2022 and the respondent's arguments as filed by letter dated 5 December 2022 on the disclosure of document D16 and on inventive step starting from document D16 as closest prior art

14. With letter dated 12 August 2022, i.e. after the statement of grounds of appeal was filed, the appellant adopted the third-party observations which had been filed on 18 July 2022 (document D18). These letters *inter alia* contained submissions on the disclosure content of document D16 and on the inventive step objection starting from document D16 in combination with document D1.

15. The respondent replied to these submissions with its letter dated 5 December 2022.

16. Pursuant to Article 13(1) RPBA, the board decided to admit both parties' submissions, in their respective letters, concerning the disclosure of document D16 and

the inventive step objection starting from document D16 in combination with document D1.

17. This decision was the result of the considerations that the further submissions were presented at an early stage of the appeal proceedings, that inventive step considerations based on the teaching of documents D16 alone or in combination with the teaching of document D1 were already part of the decision under appeal and that, at the oral proceedings, there was agreement that the board proceed by way of taking these submissions into consideration.

Inventive step - Article 100(a) EPC and Article 56 EPC - claim 1

Closest prior art

18. In the decision under appeal, document D16 was considered as the closest prior art for assessing inventive step.

Document D16 discloses a lentiviral vector (designated pELPs l9BBz) comprising the anti-CD19 scFv FMC63 linked to a human CD8α hinge, a human CD8α transmembrane (TM) domain, and a 4-1BB (= CD137) and a CD3ζ signalling domain. The expression is driven by an EF-1α promoter (see Figure 1A and page 5, last paragraph ff.). Example 1 shows the successful treatment of patients with advanced leukaemia.

Page 77, lines 9 to 25 also reports that limited *in vivo* expression and effector function of CARs has been a central limitation in the trials testing first generation CARs and that second generation CARs including a 4-1BB (CD137) signalling module

demonstrated improved expansion, enhanced persistence, and *in vivo* tumour cell killing.

Page 78, paragraphs 3 and 4 mention that signalling of 4-1BB (CD137) has been reported to promote the development of memory in the context of T-cell receptor (TCR) signalling. The mechanism of the extended survival of anti-CD19 CAR T cells (CART19) may relate to the aforementioned incorporation of the 4-1BB domain or to signalling through the natural TCR and/or CAR.

Example 1 of document D16 reports successful treatment of patients with chronic lymphocytic leukaemia (CLL) with the anti-CD19 CAR who achieved a rapid and complete response (page 66 ff.; Figure 5).

Difference and its technical effect

19. The subject-matter of claim 1 differs from the lentiviral vector disclosed in Figure 1A of document D16 only by the promoter used, an MND promoter instead of an EF-1α promoter.

20. With reference to Examples 7 and 8 of the patent, the respondent argues that the technical effect of using the MND promoter was to allow expression of CAR at sufficient levels over a longer period of time, i.e. persistent expression, and particularly without the need for a WPRE which is used in the lentiviral vector disclosed in document D16. Example 5 of the patent did not measure the persistence of CAR expression when comparing the promoters.

21. The patent (or the application as filed, respectively) shows in Example 5 and Figure 6 that MND promoter driven CD19 CAR expression and vector copy numbers

(VCN) in transduced T cells is comparable to an EF-1α promoter driven expression of the same CAR. It is also shown that the tumour burden was reduced in mice administered the modified CAR T cells (Example 7 and Figure 8) using the specific lentiviral vector of Example 1.

The patent does not compare the lentiviral constructs of claim 1 with those disclosed in Figure 1A of document D16, and from the data in the patent (or the application as filed, respectively) it cannot be concluded that the claimed constructs are improved in terms of (persistent) levels of expression of the CAR in amounts suitable to achieve a therapeutic effect or in terms of therapeutic efficacy.

Examples 7 of the patent determines the anti-tumour function of CAR T cells engineered to express a pMND-anti-κLC CAR in NOD SCID IL-2 receptor gamma chain knockout mice or of CAR T cells engineered to express a pMND-anti-BCMA CAR T cells *in vitro*. However, these experiments do not compare the effect of using an MND promoter with the effect of using an EF-1α promoter.

Example 8 of the patent mentions that anti-BCMA expressing CAR T cells, manufactured as described in Example 1, show antigen specific tumour clearance and that anti-BCMA expressing CAR T cells killed BCMA expressing K562 cells (Figure 9A) and released IFN-γ (Figure 9B). These data support the conclusion that the lentiviral vector with the MND promoter drives functional expression of the CAR enabling antigen-specific cytotoxicity and functional activation *in vitro*.

In view of the above, it must be concluded that the data in the patent (or the application as filed, respectively) do not support the respondent's allegation that the claimed lentiviral vector represents an improvement over the one described in document D16.

22. In support of a technical effect over the EF-1α promoter used in document D16, the respondent also referred to the passage in paragraph [0072] of the patent reporting "*the surprising finding that the MND promoter directs persistent expression of CAR polypeptides in resting, activated, and expanded T cells, and that such expression is sufficient to efficiently redirect the genetically modified immune effector cells contemplated herein to elicit cytotoxic activity against the tumor or cancer cell*".

However, document D16 also discloses a more than thousand-fold expansion of the engineered CAR T cells, trafficking of these cells to the bone marrow and persistent expression of functional CARs at high levels for at least 6 months. A CD19-specific immune response was demonstrated in the blood and bone marrow, accompanied by complete remission in two of three patients. A portion of the cells persisted as memory CAR+ T cells (document D16, Example 1).

Thus, persistent expression of the CAR and an *in vivo* therapeutic anti-cancer effects have also been shown for the claimed CAR expressed under the EF-1α promoter.

23. The respondent further argued that the EF-1α promoter alone was insufficient to ensure sustained and persistent expression of the claimed CAR, and that the

lentiviral vectors in Example 1 of document D16 included a WPRE element to achieve this effect.

The presence or absence of a WPRE cannot however be considered as a difference between the lentiviral vector according to claim 1 and that disclosed in document D16, given the (open-ended) comprising language of claim 1 and the fact that a WPRE is clearly optional in claim 1, since it is the subject-matter of dependent claim 7(c).

24. Consequently, no improvement can be ascribed to using the MND promoter instead of the EF-1α promoter on the basis of the application as filed.

Objective technical problem

25. The objective technical problem must therefore be defined as the provision of an alternative CAR expression vector.

Obviousness

26. The skilled person, starting from the lentiviral vector, EF-1α promoter based vector construct disclosed in Figure 1A of document D16 and faced with the objective technical problem of providing an alternative CAR expression vector, would have consulted the literature for suitable alternative promoters and would thereby have turned to document D1 which belongs to the same field of engineering cells to express CARs for immune cell-based immunotherapy.

27. Document D1 discloses lentiviral vectors carrying the genes encoding CD19-specific CAR driven by the MND LTR U3 region (MNDU3) as internal enhancer/promoter, which

are reported to successfully modify haematopoietic stem/progenitor cells (HSPCs) with persistent transgene expression (page 828, left-hand column, last full paragraph). The promoter can drive expression of first-generation (CD19R) as well as of second-generation (CD19RCD28) CARs in primary T cells and myeloid cells (Figure 1a and b). The transduced T cells are also shown to lyse CD19+ target cells (Figure 1c).

Figure 7c shows *inter alia* that 32 weeks after intrahepatic injection into pups of CAR-transduced human HSPCs in humanised NSG mice T cells (CD3+) expressing the first- and second-generation CAR can be detected in the bone marrow (BM), spleen (SP), and peripheral blood (PB). Figure 8b and c show improved survival of mice in the CD19RCD28 arm compared to animals in the CD19R arm and controls.

Document D1 also states on page 837, left-hand column, end of first full paragraph that it is known that second-generation CARs are more efficient than first-generation constructs for target-specific activation of modified T-cells *in vitro* and *in vivo*.

Thus, it shows that using an MND promoter, a second-generation CAR can be successfully expressed in various cell types — including T cells (CD3+) — resulting in a functional immunotherapeutic anti-cancer effect.

28. There is no technical reason why the skilled person would have limited themselves to the set of promoters exemplified on page 36 of document D16 as suggested by the respondent. Faced with the objective technical problem of identifying an alternative promoter suitable for CAR expression in T cells, the skilled person would

also have consulted the broader body of relevant literature in the field.

In doing so, the skilled person would also have been aware of those promoters already known to be effective for CAR expression in T cells and shown to be effective *in vivo*. One such promoter was the MND promoter, disclosed in document D1 as having been successfully employed to achieve persistent expression of CAR constructs in HSPCs and T cells, with sustained *in vivo* activity.

29. The respondent argued that the skilled person could have selected the MND promoter but would not have contemplated to do so, especially in view of the fact that document D16 proposes on page 36, first full paragraph several suitable promoters, but not the MND promoter.

30. In the case at hand, the objective technical problem is merely the provision of an alternative CAR expression vector and the skilled person would have modified the lentiviral vector as used in the examples of document D16 in any manner within the framework of routine experimentation and arbitrary choice. For applying routine measures and making arbitrary choices, the skilled person does not need any specific pointer in the closest prior art.

31. The respondent argued that document D1 focuses on modifying HSPCs, which was fundamentally different from the T cells transduced in document D16. Therefore, document D1 was not relevant to the invention's context and could not support an inventive step objection. No teachings regarding the anti-cancer properties of T cells transduced with the vector was derivable from

document D1 and the skilled person would not have considered to use the MND promoter disclosed in document D1.

32. The respondent is correct that document D1 focusses on the transduction of HSPCs with the lentiviral vector. However, while document D1 states that "*in vitro differentiation of modified HSPC to T-cells was not performed, as the resulting cells are not fully mature and may lack effector function*" (page 837, paragraph left-hand column, second full paragraph), this does not preclude its relevance to T-cell applications. In fact, document D1 provides direct evidence that mature primary human T cells were efficiently transduced with CD19-specific CARs and exhibited potent, antigen-specific cytotoxicity against CD19+ targets (page 828, paragraph bridging the left-and right-hand column; Figure 1c). Furthermore, *in vivo* data from humanised NSG mice show that CAR-modified HSPCs gave rise to CD3+ T cells expressing the CAR transgene (page 835, chapter "*In vivo studies in humanized NSG*"; Figure 7), confirming the feasibility of CAR expression in T cells derived from HSPCs.

33. The respondent further argued, with reference to expert declaration D17, that, in addition to the promoter, the architecture of the CAR played an important role. This was, for example, evidenced by the different results obtained for the first- and second-generation CAR in document D1.

34. While it is apparent from the cited literature that CAR architecture can influence expression and function, particularly depending on how domains such as the hinge, transmembrane, and signalling regions are combined, this does not detract from the fact that the

CAR construct disclosed in document D16 is identical to the one according to claim 1 of the patent.

Therefore, the argument that CAR architecture plays a role does not undermine the relevance of document D16 as closest prior art, since it discloses the exact same CAR configuration as claimed, meaning any effect attributed to promoter differences can be assessed in this context.

35. The respondent referred to differing results in document D1 to argue that promoter performance was architecture-dependent. However, document D1 itself explains that this variability was expected and context-specific. The skilled person, faced with the objective technical problem of identifying an alternative promoter for the CAR of D16, would have recognised from document D1 that the MND promoter had successfully been used in lentiviral vectors for CAR expression and was known to drive strong transgene expression in human cells.
Therefore, given the known utility of the MND promoter in similar contexts and the structural identity between the CARs in document D16 and the claimed invention, the skilled person would have considered the use of the MND promoter as an obvious and reasonable alternative to the EF-1α promoter.

36. As already set out in point 27. above, the skilled person would have expected that second-generation CARs would be more efficient than first-generation constructs for target-specific activation of modified T-cells *in vitro* and *in vivo* (D1, page 837, left-hand column, end of first full paragraph; D16, page 77, lines 9 to 25).

Conclusion on inventive step

37. The board concludes that the subject-matter of claim 1 is obvious in view of a combination of the teaching in documents D16 and D1. Thus, the ground of opposition under Article 100(a) and Article 56 EPC prejudices the maintenance of the patent as granted.

Remittal – Article 111 EPC, Article 11 RPBA

38. The respondent requested that the case be remitted to the opposition division "*for discussion regarding maintenance of the patent in amended form*" should the main request not be granted.

No auxiliary requests had been filed in appeal, since the goal was that the patent as granted be upheld and in view of the fact that the filing of an auxiliary request would have been an amendment to the case under Article 12(4) RPBA.

Remittal was justified since the decision of the opposition division did not discuss maintenance of the patent in amended form. As the appeal procedure was a judicial review of the opposition division's decision, the respondent should be given the opportunity to present amendments before the opposition division.

39. The board notes that a set of claims of an auxiliary request had been filed during the opposition proceedings. However, in the appeal proceedings, the respondent did not pursue maintenance of the patent in amended form on the basis of that auxiliary request, nor did it file any other auxiliary requests relating to an amended version of the patent which could be considered by the board in the event that the decision

under appeal was to be set aside. The only request presented for consideration and decision in appeal proceedings was the patent as granted. In the absence of any auxiliary request, there is no basis for remitting the case to the opposition division.

Consequently, the board decided to not remit the case to the opposition division.

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:

I. Aperribay M. Blasi

Decision electronically authenticated