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Datasheet for the decision of 25 April 2024

Case Number: T 1502/22 - 3.3.04

Application Number: 15713513.8

Publication Number: 3126390

IPC: C07K16/28, A61K39/395, A61P35/02

Language of the proceedings: EN

Title of invention:
CD33 specific chimeric antigen receptors for cancer immunotherapy

Patent Proprietor:
Cellectis

Opponent:
Wuesthoff & Wuesthoff Patentanwälte PartG mbB

Headword:
CD33-specific CAR/CELLECTIS

Relevant legal provisions:
EPC Art. 83
RPBA 2020 Art. 12(4), 12(6)

Keyword:
Sufficiency of disclosure - Auxiliary request 5 (yes)
Amendment to case - reasons for submitting amendment in appeal proceedings (no)

Decisions cited:
G 0009/91, T 0019/90, T 0596/96, T 0190/99, T 0063/06, T 0491/08

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Case Number: T 1502/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 25 April 2024

Appellant: (Patent Proprietor)	Cellectis 8 rue de la Croix Jarry 75013 Paris (FR)
Representative:	Simmons & Simmons LLP (Munich) Lehel Carré Thierschplatz 6 80538 Munich (DE)
Appellant: (Opponent)	Wuesthoff & Wuesthoff Patentanwälte PartG mbB Schweigerstrasse 2 81541 Munich (DE)
Representative:	Wichmann, Hendrik Wuesthoff & Wuesthoff Patentanwälte und Rechtsanwalt PartG mbB Schweigerstraße 2 81541 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 19 April 2022 concerning maintenance of the European Patent No. 3 126 390 in amended form**

Composition of the Board:

Chairman	A. Chakravarty
Members:	B. Rutz
	A. Bacchin

Summary of Facts and Submissions

I. The appeals by appellant I (the patent proprietor) and appellant II (the opponent) lie from the decision of the opposition division that European patent No. 3 126 390 (the patent), entitled "*CD33 specific chimeric antigen receptors for cancer immunotherapy*" and amended according to auxiliary request 1, meets the requirements of the EPC. The patent is based on European application 15 713 513.8 which was published under the PCT as international application WO 2015/150526 (the application)

II. The opposition proceedings were based on the grounds for opposition under Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC) and under Article 100(b) and (c) EPC.

III. In the decision under appeal, the opposition division decided, *inter alia*, that the subject-matter of claim 1 of the main request (patent as granted) lacked novelty over the disclosure of document D2.

IV. With its statement of grounds of appeal the patent proprietor filed sets of claims of auxiliary requests 1 to 5. The claims of auxiliary request 2 are identical to the claims of auxiliary request 1 decided upon in the decision under appeal. The claims of auxiliary requests 4 and 5 are identical to the claims of auxiliary request 2 and 4, respectively, filed during the opposition proceedings. The claims of auxiliary requests 1 and 3 were newly filed upon appeal.

V. In its statement of grounds of appeal, the opponent objected that the invention in claims 10 and 12 of

auxiliary request 5 was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

VI. The board summoned the parties to oral proceedings, as they had requested and informed them of its preliminary opinion on the appeals in a communication under Article 15(1) RPBA.

VII. In this communication, the board *inter alia* indicated that it preliminarily considered the invention claimed in auxiliary request 5 sufficiently disclosed, meeting the requirements of Article 83 EPC.

VIII. At the oral proceedings before the board the patent proprietor withdrew the main request and auxiliary requests 1 to 4 and requested the maintenance of the patent on the basis of the set of claims of auxiliary request 5.

IX. Claim 1 of auxiliary request 5 reads as follows:

"1. A CD33 specific chimeric antigen receptor (CAR) having the polypeptide structure V1 as illustrated in Figure 2, wherein said structure V1 comprises (a) an extra cellular ligand binding-domain comprising VH and VL from a monoclonal anti-CD33 antibody, (b) a FcγRIIIα hinge, (c) a CD8α transmembrane domain and (d) a cytoplasmic domain including a CD3 zeta signaling domain and a co-stimulatory domain from 4-1BB."

Claim 5 of auxiliary request 5 reads as follows:

"5. An engineered immune cell expressing at the cell surface membrane a CD33 specific CAR according to any one of claims 1 to 3."

Claim 10 of auxiliary request 5 reads as follows:

"10. The engineered immune cell according to any one of claims 5 to 8 for use in therapy of leukemia, wherein said leukemia is selected from the group consisting of acute myelogenous leukemia (AML), chronic myelogenous leukemia, acute lymphoid leukemia, chronic lymphoid leukemia, and myelodysplastic syndrome."

Claim 12 of auxiliary request 5 reads as follows:

"12. The engineered immune cell according to any one of claims 5 to 8 for use in therapy of lymphoma, wherein said lymphoma is selected from the group consisting of multiple myeloma, non-Hodgkin's lymphoma, Burkitt's lymphoma, and follicular lymphoma (small cell and large cell)."

X. At the end of the oral proceedings the Chairman announced the board's decision.

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

D15 M. Sadelain et al., "*The promise and potential pitfalls of chimeric antigen receptors*", Current Opinion Immunology 21(2), 2009, 215–223

D16 M. V. Maus et al., "*Antibody-modified T cells: CARs take the front seat for hematologic malignancies*", Blood 123(17), 2014, 2625-2635

D40 JEK0-1 ACC 553, German Collection of Microorganisms and Cell Cultures GmbH, https://www.dsmz.de/collection/catalogue/details/culture/ACC-553

XII. The patent proprietor's submissions, as far as relevant to the decision, are summarised as follows:

Admission of document D40 (Article 12(4)(6) RPBA)

Document D40 was submitted as further evidence that the cell line, which the patent describes as CD33-negative, was derived from a patient with B-cell non-Hodgkin's lymphoma. However, objections against granted claims 12 to 14 had already been raised in the opponent's notice of opposition dated 14 July 2022 and these objections were part of all subsequent submissions. Document D40 therefore could have been filed in the course of the first instance proceedings.

Auxiliary request 5 - claims 10 and 12
Disclosure of the invention (Article 83 EPC)

The requirement for sufficiency of disclosure of a therapeutic application was met if the disclosure of the patent and/or the common general knowledge enabled the skilled person to obtain the claimed compound (in the present case engineered immune cells endowed with the claimed anti-CD33 CARs) and to use it in therapy. For the claimed subject-matter, there had to be evidence that made it at least plausible that CD33 expressing tumours could be treated with immune cells endowed with the claimed anti-CD33 CARs.

There was no requirement under Article 83 EPC that *in vivo* data had to be provided, let alone a need for clinical trials to be carried out to establish therapeutic suitability (see, for example, decision T 1273/09, citing decisions T 609/02 and T 1023/02).

The patent showed the activation of T cells with the claimed anti-CD33 CARs by CD33+ cells (see Figures 4 to 6) as well as a cytolytic activity of said T cells against CD33+ cells (see Figure 8). These effects were due to CAR expressed on the T cells. This was clear evidence of a therapeutic activity of such T cells against any cells, including any tumour cells, expressing CD33.

The opponent had failed to provide any evidence demonstrating that targeting CD33 would not have a therapeutic effect on any one of chronic lymphoid leukemia (CLL), non-Hodgkin's lymphoma, Burkitt's lymphoma or follicular lymphoma. Moreover, no evidence had been provided by the opponent that CD33 was not expressed on these cancerous cells.

Even if there were some patients suffering from a specific type of lymphoma, such as non-Hodgkin's lymphoma, who might be CD33 negative, this did not render the therapeutic use as such implausible, since usefulness was clearly established for cases where the tumours were CD33 positive (as evidenced by document D30).

Neither the EPC nor the case law required that the therapeutic effect needed to be demonstrated in each and every patient suffering from a medical condition recited in the claims. A CD33-CAR therapy would only be applied to patients who had been diagnosed to express the CD33 marker – anything else would not make sense and would not be approved by regulatory authorities.

XIII. The opponent's submissions, as far as relevant to the decision, are summarised as follows:

Admission of document D40 (Article 12(4)(6) RPBA)

Admittance of document D40 was justified for the following reasons:
(i) it was *prima facie* relevant for the assessment of sufficiency of disclosure, because it was implausible that a CD33-CAR could target a CD33-negative cancer and document D40 showed that Jeko-1, a CD33-negative comparative cell line used in the patent, was obtained from a patient having a cancer recited in claim 12 (non-Hodgkin's lymphoma)
(ii) taking document D40 into account would not affect procedural efficiency, because it was very short and opponent's argument based on it was straightforward

Auxiliary request 5 - claims 10 and 12
Disclosure of the invention (Article 83 EPC)

The therapeutic efficacy of the immune cells expressing the CD33-specific CARs in the treatment of the above-recited cancers was not credible and, according to established case law of the Boards of Appeal of the EPO, the medical use claims 10 and 12 therefore failed to meet the requirement for sufficiency of disclosure.

The main reasons for this were as follows:

(1) It was not credible that a CD33-specific CAR could be useful in the treatment of cancers which did not express CD33

(2) Expression of CD33 by any of chronic lymphoid leukemia (CLL), non-Hodgkin’s lymphoma, Burkitt’s

lymphoma and follicular lymphoma (small cell and large cell) was neither demonstrated by the opposed patent nor commonly known in the art. Documents D30 and D31 cited by the patent proprietor were not prior art and could not reflect common general knowledge

(3) There were a large variety of different lymphomas and different leukemias, while only a fraction of the patients suffering from these diseases had cancer cells that expressed CD33. This was apparent from the graph on page 2 of document D30 showing that CD33 was found only in about 40% of lymphoma patients. This verifiable evidence substantiated serious doubts that all of the cancers recited in item (2) above expressed CD33

(4) The cancers recited in claims 10 and 12 were not limited to CD33-expressing cancers, and it could not reasonably be expected that all expressed CD33

XIV. Appellant I (patent proprietor) requested that the decision under appeal be set aside and the patent be granted on the basis of the set of claims of auxiliary request 5, filed with the statement of grounds of appeal. The former main request and auxiliary requests 1 to 4 were withdrawn. It further requested that documents D37 to D42 not be admitted into the proceedings.

Appellant II (the opponent) requested that the decision under appeal be set aside and the patent be revoked. It further requested that documents D37 to D42 be admitted into the proceedings.

Reasons for the Decision

Admission of documents D37 to D39, D41 and D42

1. Documents D37 to D39 relate to the design of Chimeric Immune Receptors (CIR) and CAR-T cells. Documents D41 and D42 relate to the expression of CD33 on cancer cells. They were cited by the opponent in the context of inventive step of auxiliary request 1 which was withdrawn at the oral proceedings (see statement of grounds of appeal, point II.4, pages 8 to 10 and summary on page 50). Since these documents were not required for the decision, the board did not need to decide on their admittance.

Admission of document D40 (Article 12(4)(6) RPBA)

2. The opponent argues that it filed the document in response to the finding of the opposition division in the decision under appeal that the invention to which claims 12 and 14 of auxiliary request 1 related was sufficiently disclosed.

3. Document D40 was not admitted into the proceedings (Article 12(6) RPBA). Document D40 represents a new fact, in the sense of Article 12(2) RPBA, introduced on appeal and as such its admittance is at the discretion of the board (Article 12(4) EPC). The board further notes that the issue of sufficient disclosure of the further medical use claims 12 and 14 of the patent as granted had been part of the opposition proceedings from the beginning (see notice of opposition). In its preliminary opinion in preparation of the oral proceedings, the opposition division had even indicated that it found the invention sufficiently disclosed

(point 10. of the annex to the summons to oral proceedings of 7 April 2021). The board therefore finds that the proprietor had reasons to file document D40 already in the proceedings leading to the decision under appeal. Moreover, there is nothing in the circumstances of the appeal case that justifies its admission, since no new issue was raised in the appealed decision or in the opponent's statement of grounds of appeal.

Auxiliary request 5 - claims 10 and 12
Disclosure of the invention (Article 83 EPC)

4. The sole objection raised by the opponent against this request was under Article 83 to claims 10 and 12. The opponent argued that the application as filed did not contain any *in vivo* data and that the *in vitro* data in Example 3 which provided some support for the therapeutic effect mentioned in the claims were limited to cell lines K562 and U937. The cancers to be treated according to the medical use claims 10 and 12 were not limited to types of cancers related to K562, a cell line derived from a patient with chronic myelogenic leukemia (CML), and U937, a leukemic monocyte lymphoma cell line. Neither of these cell lines was representative for chronic lymphocytic leukemia (CLL), non-Hodgkin’s lymphoma, Burkitt’s lymphoma or follicular lymphoma. A therapeutic effect against these cancers was therefore not plausible from the application as filed. Furthermore, the claims were not limited to cancers known to express CD33. A therapeutic effect against cancers negative for the CD33 marker was equally not plausible and thus not sufficiently disclosed in the application as filed.

5. The opponent was further of the opinion that since there was neither supporting evidence nor a plausible concept for the therapeutic effect on some of the cancers listed in the claims the burden of proof had shifted to the patent proprietor. Any further substantiation by the opponent, such as experimental evidence for a lack of a therapeutic effect, was thus not required.

6. The board is not persuaded by the above arguments. It is established case law that an objection against sufficiency of disclosure needs to be based on serious doubts substantiated by verifiable facts (see T 19/90, OJ 1990, 476, point 3.3 of the Reasons).

7. In the case in hand, experimental evidence has been provided in the application as filed, showing the activation of T cells expressing the claimed anti-CD33 CARs by CD33+ cells (see Figures 4 to 6) as well as a cytolytic activity of said T cells against CD33+ cells (see Figure 8). As the activity is conferred by the CAR expressed in the T cells the data provide evidence of a therapeutic activity of such T cells against tumour cells expressing CD33. This has also been noted by the opposition division (see point 22.2 of the decision under appeal).

8. The experimental results presented in the application as filed are sufficient to create a strong presumption that the therapeutic effect claimed can be achieved. In line with established case law the opponent in such case bears the burden of proving insufficiency of disclosure and rebutting this presumption (see e.g. T 63/06, "headnote"; T 491/08, point 12 of the Reasons).

9. The opponent has provided no evidence showing that the skilled person at the effective date would have had doubts about whether the tumours listed in the claims could be treated with an anti-CD33 CAR. There is also no evidence on file that any of the cancers recited in the claim do not express CD33. Rather, the opponent bases its allegation entirely on the fact that the two cell lines used in the patent were derived only from two cancer types, namely chronic myelogenic leukemia (CML) and leukemic monocyte lymphoma.

10. In view of the known mechanism of activity of CAR T-cells (see e.g. review article D16, Figure 1), the experimental results in the application as filed and the teaching of the application as a whole (see page 1, line 12, to page 2, line 2, and page 2, lines 17 to 19: "*CD33* [...] *is a transmembrane receptor expressed on cells of myeloid lineage. It is usually considered myeloid-specific, but it can also be found on some lymphoid cells*") the board considers that the skilled person at the relevant date would have considered it credible that the therapeutic effect could be achieved for cancer of the myeloid and also of the lymphoid lineage.

11. With regard to the second argument of the opponent that the claims were also directed to therapy of CD33 negative cancers, the board considers that the skilled person when putting a therapy into practice uses their common general knowledge to establish the relevant basic requirements for such therapy. This can be a suitable dosage (i.e. effective, but not toxic), a suitable administration route (e.g. parenteral for biological molecules) or, as in the present case, the appropriate patient group. For CAR T cell therapy it belonged to the common general knowledge of the skilled

person at the relevant date, that the action of CAR T cells against cancer required binding to a target on a cancer cell. They would thus have understood that the cytolytic activity, i.e. the therapeutic effect, could only be achieved in cells expressing CD33 (see e.g. review articles D16, Abstract and Figure 1; D15, Abstract). This is also supported by the disclosure of the application as a whole which states on page 1, lines 7 to 8: "*the present invention provides with* [sic] *CD33 specific CARs, which can be expressed in immune cells to target CD33+ malignant cells with significant clinical advantage*" and on page 3, lines 4 to 6: "*CD33 specific CARs, which can be expressed in immune cells to target CD33+ malignant cells with significant clinical advantage*". It is also in line with established case law that a claim has to be interpreted in a technically sensible way ruling out illogical interpretations (see e.g. decision T 190/99, point 4.2 of the Reasons; decision T 596/96, point 3.2 of the Reasons and Case Law of the Boards of Appeal, 10th edition 2022, II.A.6.1.).

12. In view of the above considerations, the invention of claims 10 and 12 relate to an invention which is disclosed sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

Further patentability requirements

13. "*The power of an Opposition Division or a Board of Appeal to examine and decide on the maintenance of a European patent under Articles 101 and 102 EPC depends upon the extent to which the patent is opposed in the notice of opposition pursuant to Rule 55(c) EPC.*" (see decision G 9/91 Headnote). In the case at hand, novelty

and inventive step of the alternative of "A CD33 specific chimeric antigen receptor (CAR) having the polypeptide structure V1 as illustrated in Figure 2", which is part of the subject-matter of claim 1 of the patent as granted and the only embodiment remaining in claim 1 of this request, has never been objected to during the opposition and appeal proceedings and the board has no objections of its own.

14. Thus, the appeal of the opponent must be dismissed.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent as amended on the basis of the set of claims of auxiliary request 5, submitted with the statement of grounds of appeal, and a description and drawings to be adapted thereto as necessary.

The Registrar: The Chairman:

I. Aperribay A. Chakravarty

Decision electronically authenticated