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Datasheet for the decision of 24 September 2020

Case Number: T 0957/18 - 3.3.04

Application Number: 10817793.2

Publication Number: 2477648

IPC: A61K39/00, C12P21/08, C07K16/28

Language of the proceedings: EN

Title of invention:
Synergistic anti-CD47 therapy for hematologic cancers

Applicant:
The Board of Trustees of the Leland Stanford Junior University

Headword:
Synergistic anti-CD47 therapy/LELAND STANFORD JUNIOR UNIVERSITY

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes)

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Case Number: T 0957/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 24 September 2020

Appellant: (Applicant)	The Board of Trustees of the Leland Stanford Junior University Office of the General Counsel Building 170, Third Floor, Main Quad P.O. Box 20386 Stanford, CA 94305-2038 (US)
Representatives:	Chapman, Desmond Mark M and Goodman, Daniel Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 11 October 2017 refusing European patent application No. 10817793.2 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Chakravarty
Members:	A. Schmitt
	P. de Heij

Summary of Facts and Submissions

I. The appeal of the applicant ("the appellant") lies from the decision of the examining division refusing European patent application No. 10 817 793.2 ("the application"), filed under the PCT as an international patent application published as WO 2011/034969. The title of the application is "*Synergistic anti-CD47 therapy for hematologic cancers*".

II. The examining division held that claims 1 to 10 of a main request and claims 1 to 9 of auxiliary request 1 did not meet the requirements of Article 56 EPC. No decisions regarding Articles 123(2), 54, 83 and 84 EPC were taken. The examining division further stated that auxiliary requests 2 and 3 were not discussed during the oral proceedings before the examining division but "*would appear to suffer from the same deficiencies as the main request and AR1*".

III. With the statement of grounds of appeal, the appellant re-submitted the sets of claims of the main request and auxiliary requests 1 to 3 as filed in the proceedings before the examining division and submitted a set of claims of a new auxiliary request 4.

IV. The board issued a summons to oral proceedings and subsequently a communication pursuant to Article 15(1) RPBA, in which the board, *inter alia*, raised objections under Articles 54 and 84 EPC, pursuant to Article 111(1) EPC as clarified in decision G 10/93 (OJ EPO 1995, 172, Reasons, point 3).

V. In response to the board's communication, the appellant submitted auxiliary requests 5 and 6. The appellant

further confirmed that they did not request a remittal to the examining division for further prosecution of auxiliary requests 2 and 3 because of possible procedural violations.

VI. In a further letter, the appellant requested that the oral proceedings be conducted by videoconference.

VII. Oral proceedings were held on 24 September 2020 by videoconference. During the oral proceedings, the appellant submitted a set of claims of a new main request comprising only a single claim which replaced all former claim requests.

VIII. The claim of the sole request reads:

"1. A synergistic combination of agents for use in the treatment of a hematologic cancer in a patient, wherein the hematologic cancer is non-Hodgkin's lymphoma (NHL) and wherein the NHL is a diffuse large B cell lymphoma, wherein the combination of agents comprises a first agent that selectively blocks CD47 and a second agent that binds to CD20, wherein the first and second agents are comprised in a bispecific FcR-engaging antibody selective for CD47 and for CD20."

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

D1: Chao M. P. et al. (2009), Experimental Hematology 37(9) Suppl. 1, S8-S9

D2: WO 2009/091547

D9: Piccione E. C. *et al*. (2015), MABS, 7(5), 946-956

D10: Baeuerle P. *et al.* (2009), Cancer Research, 69(12), 4941-4944

D11: Müller D and Kontermann R E (2008), Chapter 2 "Bispecific Antibodies" in "Handbook of Therapeutic antibodies Volume I" edited by Dübel S., 352-378

D13: Dheill E. *et al.* (2017), Molecular Therapy, 25(2), 523-533

X. The appellant's arguments in relation to the claim of the main request are summarised as follows:

Article 123(2) EPC

Support for the claim was provided in claims 1, 8, 9, 10 and 13 and paragraphs [0054], [0083], [0087], [0200], [0209] of the application as filed. As the molecule CD20 did not have any known ligands, "inhibits or blocks" in the context of CD20 could only mean "binding to", a wording used in paragraph [0209]. The specific combination of anti-CD47 and anti-CD20 antibodies to treat diffuse large B cell lymphoma was further singled out in the examples of the application using a diffuse large B-cell lymphoma-engrafted mouse model and an *in vitro* assay using diffuse large B-cell lymphoma-derived cells to dissect the Fc dependency. The claim thus complied with the requirements of Article 123(2) EPC.

Inventive step (Article 56 EPC)

Document D1 represented the closest prior art. Document D1 disclosed the treatment of Non-Hodgkin

lymphoma-engrafted mice with an anti-CD47 antibody in combination with the anti-CD20 antibody rituximab.

The claimed subject-matter differed from the treatment disclosed in document D1 in the type of Non-Hodgkin lymphoma, namely diffuse large B-cell lymphoma, and in that a bispecific FcR-engaging antibody selective for CD47 and for CD20 was used instead of two separate antibodies specific for CD20 and CD47, respectively.

The technical effect of the latter difference was reduced antibody toxicity. This antibody toxicity was caused by the binding of antibodies to CD47 expressed on non-cancerous cells. However, this off-target binding was reduced by the preferential binding of the bispecific antibody to dual-positive cells expressing both CD47 and CD20. This effect was plausible and would seem "logical" to the skilled person, once informed about it in paragraph [0209] of the application and in view of the data in Figure 17D, showing that anti-CD47 antibodies can cause cell-lysis of CD47-expressing cells, i.e. they are potentially toxic for normal cells. Documents D9 and D13 published after the application's filing date confirmed selective binding of a bispecific FcR-engaging antibody specific for CD47 and CD20 to tumour cells and reduced binding to normal cells.

The skilled person would also consider the statement in paragraph [0209], that the bispecific antibody retained the synergistic effect relative to treatment with either anti-CD20 or anti-CD47 antibodies alone, credible, and thus, evidence showing that the bispecific antibody retained the claimed synergistic effect could be taken into account, although it was published after the filing date (documents D9 and D13).

The expression "*could reduce potential antibody toxicity*" used in paragraph [0209] reflected the fact that neither antibody toxicity, nor a reduction thereof, necessarily took place in every treated patient under every treatment regimen, due to individual differences in drug response. It did not reflect a general doubt regarding the occurrence of antibody toxicity by off-target binding and the reduction thereof by the bispecific antibody.

The objective technical problem solved by the claimed invention was thus the provision of an improved synergistic antibody therapy for hematologic cancer with reduced side effect due to off-target binding.

The solution provided in claim 1 was not obvious to the skilled person in view of the disclosure in document D1 alone or in conjunction with any other cited prior art. Although bispecific antibodies were part of the skilled person's common general knowledge, the use of bispecific antibodies for reducing off-target binding and antibody toxicity was neither known nor obvious. The generation of a bispecific antibody retaining the synergistic effect was not known or obvious either.

Document D10 was cited by the examining division as evidence that the use of bispecific antibodies to target cancer was common general knowledge at the time of filing of the application. However, document D10 related only to the use of antibodies to connect T-cells and cancer cells.

Document D11, a text book from 2007, represented the skilled person's common general knowledge with respect to therapeutic antibodies. Document D11 contained a

chapter "Bispecific Antibodies" (pages 345 to 378) disclosing a variety of bispecific antibody forms, only some of which comprised Fc regions. Although document D11 disclosed possible uses for bispecific therapeutic antibodies, these did not include the reduction of off-target binding. This illustrated that therapeutic bispecific antibodies had not been used in the prior art for this purpose prior to the filing date of the application.

Document D2 was a patent application that related to a different disease and to different marker combinations and would not have been consulted by the skilled person. In relation to the sentence in paragraph [0122] of document D2, it was was not clear which antibodies were meant nor to which antigens of the listed immune cells the risk of toxicity referred.

Thus, the prior art did not suggest the use of a bispecific antibody for reducing antibody toxicity. This only became "logical" to the skilled person after reading the patent application. Moreover, even if the skilled person had contemplated the use of bispecific antibodies for the treatment of diffuse large B cell lymphoma, there was no teaching in the prior art that the Fc portion had to be retained in the bispecific antibody for its therapeutic activity. The claimed subject-matter thus was not obvious to the skilled person and involved an inventive step (Article 56 EPC).

XI. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 99 EPC and is admissible.

Fundamental deficiencies

2. From the minutes of the hearing of the opposition division and from the grounds for the decision it can be concluded that appellant's auxiliary requests 2 and 3 were neither discussed during the oral proceedings nor properly considered by the opposition division. The grounds for the decision only state that the claim requests "*would appear*" to suffer from the same deficiencies as the main request and auxiliary request 1. The wording "*would appear*" indicates that the opposition division did not come to a definitive conclusion as regards the allowability of these claim requests. Nonetheless, the appellant's application was refused. Appellant's right to be heard has therefore been violated. For this reason alone, the decision under appeal needs to be set aside.

3. Fundamental deficiencies in the procedure before the opposition division as a rule constitute reasons to remit the case to the opposition division (Article 11 RPBA). However, since the appellant explicitly stated that they did not request remittal of the case for this reason, the board decided not to do so.

Admittance of the main request
(Article 13(2) RPBA 2020)

4. The board decided to admit the claim request into the proceedings. As further examination of the appeal was

required and the claim request was clearly allowable, exceptional circumstances as referred to in Article 13(2) RPBA justified its admittance.

Amendments (Article 123(2) EPC)

5. The claimed subject-matter finds a basis in paragraphs [0083], [0087] and [0209] of the application as filed.

6. Paragraph [0083] discloses that the invention provides methods for reducing the growth of hematologic cancer cells using a CD47 blocking agent in combination with a second agent that blocks a second cancer cell marker. The cancer can be diffuse large B cell lymphoma and the second marker can be *inter alia* CD20 and CD22. Paragraph [0087] then discusses an embodiment that uses a bi-specific antibody directed against CD47 on the one hand and directed on the other hand against a cancer cell marker such as CD20, CD22, CD33, CD44, CD52, CD123, CD96, CD97, CD99, PTHR2 and HAVCR2.

7. These passages thus disclose that diffuse large B cell lymphoma can be treated using a bi-specific antibody targeting CD47 and a second cancer cell marker. They hence provide general information pertaining to the invention, but do not disclose the specific combination of cancer cell markers CD47 and CD20.

8. However, paragraph [0209] describes a bispecific FcR-engaging antibody with one arm binding and blocking CD47 and the other arm binding to CD20, having a synergistic effect, for use in a combination therapy of Non Hodgkin lymphoma, which, as is disclosed in paragraph [0083], can be diffuse large B cell lymphoma. The single selection of diffuse large B cell lymphoma

as the disease to be treated does not disclose any new technical information to the skilled person.

9. The sole claim of the request thus meets the requirements of Article 123(2) EPC.

Clarity (Article 84 EPC)

10. The board considers that the claim is clear and thus complies with the requirements of Article 84 EPC for clarity.

Novelty (Article 54 EPC)

11. The claimed subject-matter relates to a bispecific FcR-engaging antibody selective for CD47 and for CD20 for use in the treatment of diffuse large B cell lymphoma in a patient. The use of a bispecific FcR-engaging antibody selective for CD47 and for CD20 for treating diffuse large B-cell lymphoma was not disclosed in the cited prior art. The requirements of Article 54 EPC are met.

Inventive step (Article 56 EPC)

Closest prior art

12. Both the appellant and the examining division considered that document D1 could be taken to represent the closest prior art for the claimed invention. The board sees no reason to differ.

13. Document D1 is a meeting abstract reporting on scientific experiments to elucidate the therapeutic potential of an anti-CD47 antibody alone and in combination with an anti-CD20 antibody for the

treatment of Non-Hodgkin lymphoma. It discloses that a combination therapy of an anti-CD47 antibody and the CD20-specific monoclonal antibody rituximab "*led to prolonged survival and to cure in a fraction of NHL engrafted mice compared to either antibody treatment as a single agent*" (see the penultimate sentence of abstract 16 on page S9), i.e. it reports a synergistic effect of the two separate antibodies in the treatment of NHL in a mouse model. It is concluded in document D1 that "*this data provides the rationale for utilizing an anti-CD47 antibody either alone or in combination with rituximab in treating human NHL*" (see the last sentence of abstract 16 on page S9).

Objective technical problem

14. The subject-matter of claim 1 differs from the disclosure of document D1 in that the first agent that selectively blocks CD47 and the second agent that binds to CD20 are combined in a bispecific FcR-engaging antibody selective for CD47 and for CD20. A further difference is that the Non-Hodgkin lymphoma is diffuse large B cell lymphoma.

15. The application discloses that treatment with CD47-specific antibodies can cause cell-lysis of CD47-expressing cells (Figure 17D of the application). The appellant argued that the claimed bispecific antibody had reduced antibody toxicity when used in the treatment as claimed as compared to treatment using two separate antibodies. This was said to be due to decreased binding of the claimed bispecific antibodies to normal CD47-expressing tissue compared to a conventional CD47-specific antibody.

16. In the board's view the skilled person would consider the above mentioned reduced off-target toxicity plausible although the application does not contain an example demonstrating it. This is because they would have known that a bispecific antibody having a single binding site for a target would have a lower binding avidity to a cell expressing this target than a bivalent antibody with two binding sites for this target. Furthermore, they would have understood that if both binding sites of the bispecific antibody are engaged when binding to cells expressing both targets, the antibody would bind with higher avidity than when only a single binding site is engaged, resulting in a preferential binding to dual-positive cells. They would also consider it plausible that off-target binding to normal cells expressing only CD47 and the related toxicity resulting from blocking CD47 signalling on such normal cells would be reduced. For the reasons set out in point 28., retention of synergistic effect is to be expected as well. Consequently, the reduction of potential antibody toxicity, while retaining the synergy effect, especially as CD47 is expressed in multiple normal tissue (see paragraph [0209] of the application), will be taken into account in formulating the technical problem.

17. In view of the differences between the closest prior art and the claimed subject-matter and the technical effect thereof, the problem to be solved can be formulated as the provision of a treatment for diffuse large B cell lymphoma having reduced antibody toxicity.

Obviousness

18. The question to be answered in assessing obviousness is therefore whether or not the skilled person, starting

from document D1 and seeking a solution to the problem formulated above, would have arrived at the claimed solution.

19. As set out in point 12. above, document D1 suggests using an anti-CD47 antibody as therapeutic agent "*alone or in combination with rituximab*" but does not mention the problem of a potential antibody toxicity due to ubiquitous CD47 expression. Thus, the skilled person, starting from the disclosure in document D1 and taking no other documents into account would not have considered constructing the claimed bispecific antibody.

20. The use of bispecific antibodies to target cancer cells was known at the filing date of the application. Documents D10 and D11 provide examples of this. However, neither of these documents discloses the use of bispecific antibodies to decrease off-target binding. Document D10 is only concerned with the use of bispecific antibodies to bring together two different cell types, cytotoxic T-cells and cancer cells, which is a different purpose to that of the claimed antibody. According to document D11, the therapeutic applications of bispecific antibodies relate to "*redirecting effector systems to diseased areas*" (page 345, chapter 2.1, first paragraph), i.e. the same purpose described in document D10, and to "*increasing neutralizing or stimulating activities of antibodies*" (ibid.). This second purpose is further specified in chapter 2.5, pages 364 to 366, describing bispecific antibodies binding to two different epitopes on the same or different antigens. However, this is disclosed in the context of targeting and blocking two different receptors on the same cell simultaneously or increasing the neutralizing effect of a bispecific antibody

targeting two surface antigens of a virus. There is no disclosure of reducing antibody toxicity by reducing off-site target binding.

21. Thus, neither document D10 nor document D11 and the common general knowledge which it represents, suggest the use of bispecific antibodies to reduce antibody toxicity due to off-target binding. The combination of the teaching of document D1 with the teaching of any of documents D10 and D11 hence does not lead the skilled person to the subject-matter of claim 1 in an obvious manner.

22. Document D2 discloses the identification of markers of acute myeloid leukemia stem cells (AMLSC), including CD47, and their use as targets of therapeutic monoclonal antibodies. It also discloses therapies using combinations of monoclonal antibodies targeting CD47 and further AMLSC marker(s) (paragraphs [0012] to [0014], Example 1, Table 1), which may be in the form of bispecific or multispecific antibodies (paragraphs [00119] to [00127]). However, document D2 neither discloses a specific effect or purpose associated with such a bispecific or multispecific antibody nor the requirement that the bispecific antibody is FcR-engaging (see paragraph [0121]). In paragraph [0122], it is mentioned that *"the antibodies of the present invention may have low risk of toxicity against granulocyte (neutrophil), NK cells, and $CD4^+$ cells as bystander cells*.". However, this sentence does not disclose whether the possible low risk of toxicity is due to the use of bispecific antibodies nor why there was thought to be a risk of toxicity for the specific cells of the immune system listed. Absent a clear indication of which antibodies this sentence relates to and what the reason for the possible low toxicity

against the listed cells of the immune system may be, the board can see no disclosure in document D2 that would have suggested, when taken alone or in combination with the disclosure of document D1, the provision of a bispecific FcR-engaging antibody selective for CD47 and CD20.

23. In the reasons given for holding the claimed subject-matter to lack an inventive step, the examining division stated that the skilled person was "*always motivated to provide a single medicament as opposed to two separate ones*" requiring separate formulating and testing (see point 5.2 of the decision under appeal). Combining "*the essential features of rituximab (anti-CD20 with Fc functionality) with a blocking anti-CD47 domain into a bispecific format including the Fc domain of Rituximab*" (*ibid*) was thus considered obvious.

24. The board notes however, that the examining division did not provide any support for the above cited assertion, and the board has not seen any evidence that the combination of separate therapeutic agents into a single one as opposed to e.g. providing them in a composition was part of the skilled person's common general knowledge.

25. In view of the above considerations on the evidence before it, the board concludes that the subject-matter of the claim of the sole request was not obvious and involves an inventive step (Article 56 EPC).

Sufficiency of disclosure (Article 83 EPC)

26. Although the decision under appeal does not deal with sufficiency of the disclosure of the invention, the

board has the following considerations (Article 111(1) EPC).

27. A purpose-limited product as provided for by Article 54(5) EPC meets the requirements of Article 83 EPC if, at the relevant date of the application, the skilled person is able to prepare the claimed product, here a bispecific FcR-engaging antibody selective for CD47 and for CD20, and if the application discloses that the claimed product is suitable for the claimed therapeutic application, unless this is already known to the skilled person at the priority date (see Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019, II.C. 7.2.).

28. The application discloses the suitability and synergy of a combination of an anti-CD47 antibody and the anti-CD20 antibody rituximab for the treatment of diffuse large B-cell lymphoma (paragraph [0200]). The board sees no reason why the skilled person would doubt that a bispecific FcR-engaging antibody selective for CD47 and for CD20 could be produced, for example by following the procedures disclosed in e.g. document D11. Moreover, given that the separate antibodies are suitable for the treatment of diffuse large B-cell lymphoma, it considered that it the skilled person would find it plausible that the claimed bispecific antibody would also be suitable for the claimed use and also retain the synergistic effect shown in the application for the composition comprising the separate antibodies.

29. Therefore, the claimed invention meets the requirements of Article 83 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division with the order to grant a patent with the claim of the main request, filed during the oral proceedings of 24 September 2020, and a description to be adapted thereto.

The Registrar: The Chair:

I. Aperribay A. Chakravarty

Decision electronically authenticated