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Case Number: T 2745/19 - 3.3.08

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Title of invention:
Anti-PD-L1 antibodies and their use to enhance T-cell function

Patent Proprietor:
F. Hoffmann-La Roche AG

Opponent:
Furo Ventures B.V.

Headword:
Anti-PD-L1 antibodies/F.HOFFMANN-LA ROCHE

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
Amendments - extension beyond the content of the application as filed (yes)

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Case Number: T 2745/19 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 20 December 2022

Appellant: (Opponent)	Furo Ventures B.V. Willemsplein 2 5211 AK s'Hertogenbosch (NL)
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Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB P.O. Box 86 07 67 81634 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 25 July 2019 rejecting the opposition filed against European patent No. 2376535 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairman	B. Claes
Members:	R. Morawetz
	M. Blasi

Summary of Facts and Submissions

I. European patent No. 2 376 535 ("the patent"), entitled "*Anti-PD-L1 antibodies and their use to enhance T-cell function*", was granted on European patent application No. 09 764 997.4, filed as an international patent application published as WO 2010/077634 ("the application as filed").

Claim 1 of the patent as granted reads as follows:

"1. An isolated anti-PD-L1 antibody or antigen binding fragment thereof comprising a heavy chain and a light chain variable region sequence, wherein:

(a) the heavy chain comprises an HVR-H1, HVR-H2 and HVR-H3, wherein further:
(i) the HVR-H1 sequence is GFTFSDSWIH (SEQ ID NO:15);
(ii) the HVR-H2 sequence is AWISPYGGSTYYADSVKG (SEQ ID NO:16);
(iii) the HVR-H3 sequence is RHWPGGFDY (SEQ ID NO:3); and
(b) the light chain comprises an HVR-L1, HVR-L2 and HVR-L3, wherein further:
(iv) the HVR-L1 sequence is RASQDVSTAVA (SEQ ID NO:17);
(v) the HVR-L2 sequence is SASFLYS (SEQ ID NO:18);
(vi) the HVR-L3 sequence is QQYLYHPAT (SEQ ID NO:19)."

II. Opposition was filed against the granted patent in its entirety. The opposition proceedings were based on the grounds for opposition in Article 100(a) EPC, in relation to inventive step (Article 56 EPC), and in Article 100(b) and (c) EPC.

III. The appeal of the opponent (appellant) is against the opposition division's decision rejecting the opposition. The patent proprietor is the respondent to this appeal.

IV. In the statement of grounds of appeal, the appellant submitted arguments *inter alia* to the effect that the subject-matter of claim 1 as granted extended beyond the content of the application as filed.

V. With the reply to the statement of grounds of appeal dated 17 April 2020, the respondent maintained the patent as granted as its main request and auxiliary requests 1 to 7 as filed during opposition proceedings, and provided counter-arguments. It also submitted sets of claims of new auxiliary requests 8 to 15.

Claim 1 of auxiliary request 8 differs from claim 1 as granted in that the expression "and wherein said anti-PD-L1 antibody or antigen binding fragment thereof blocks the binding of both human and mouse PD-L1 to PD-1" has been added.

VI. The board scheduled oral proceedings as requested by the appellant, and issued a communication under Article 15(1) RPBA setting out its preliminary opinion with respect to, *inter alia*, the requirements of Article 123(2) EPC as regards the subject-matter of claim 1 of auxiliary request 8.

VII. In response, the respondent filed a set of claims of a new auxiliary request 16. Three further letters comprising substantive submissions were received from the respondent, and one from the appellant.

VIII. In the course of the oral proceedings, the respondent withdrew all claim requests, including the claim request filed at the oral proceedings, except auxiliary request 1, filed as auxiliary request 8 with the reply to the appeal dated 17 April 2020, which became its sole claim request. At the end of the oral proceedings, the Chair announced the board's decision.

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

D12 Declaration of Professor D.A. Ostrov, dated 6 February 2018

D43 J. Maynard and G. Georgiou, Annu. Rev. Biomed. Eng. (2000), Vol. 2, pages 339 to 376

X. The appellant's arguments, in so far as relevant to the decision, are summarised below.

Sole claim request

Admittance (Article 12(4) RPBA 2007)

The request had been filed too late and should not be admitted into the proceedings.

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

The statement on page 130, lines 15 to 30, of the application as filed related to one specific antibody, YW243.55S70, not to antibodies with different framework regions (FRs) covered by the claim. Antibody YW243.55S70 had specific IC_{50} values and a specific structure comprising specific hypervariable regions (HVRs) and FRs (see Figure 11). IC_{50} values were

sensitive to structural changes in the FRs, and binding and blocking ability was difficult to maintain with a different framework, e.g. in the context of humanisation of murine antibodies (see also document D43, pages 354 and 355). FR sequences were important to bring the claimed HVRs into the correct conformation in order to result in effective binding and blocking of the antibody.

There was no suggestion in the application as filed that the disclosure on page 130, lines 15 to 30 could be generalised to other FRs. The fifteen antibodies disclosed in Table 1 all had the same FRs. HVRs on their own, without FRs, did not lead to blocking of the binding of both human and mouse PD-L1 to PD-1.

The disclosure in the application as filed of a general goal did not amount to a direct and unambiguous disclosure that certain disclosed antibodies met that goal.

Page 2, lines 18 to 21, of the application as filed was a general statement, did not refer to PD-1 and did not disclose that antibodies as defined in the claim met the stated goal.

Page 24, lines 26 to 31, of the application as filed provided a general statement, referred to blocking of PD-1, B7.1 or both, and explained a mechanism of action.

Page 42, lines 16 to 26, of the application as filed provided a definition of the term "variable" and was silent about blocking.

Page 49, lines 25 to 27, of the application as filed

related to "certain embodiments" and could not be generalised.

Page 49, lines 29 to 31, of the application as filed provided a general definition of "blocking" and the antibodies mentioned did not have the claimed property of blocking.

Page 49, lines 32 to 33, of the application as filed did not disclose that the antibodies covered by the definition in the claim were blocking and restored the functional response by T-cells.

In sum, the application as filed provided general statements regarding goals, possible blocking of PD-L1 from interaction with PD-1, B7.1 or both, and a mechanism likely to enhance immunity. It also provided a statement relating to a specific antibody on page 130, lines 15 to 18. The application as filed did however not disclose directly and unambiguously that antibodies having the HVRs defined in the claim blocked the binding of both human and mouse PD-L1 to PD-1. The combination of the six HVRs and the feature "blocks the binding of both human and mouse PD-L1 to PD-1" was neither explicitly nor implicitly disclosed in the application as filed.

XI. The respondent's arguments, in so far as relevant to the decision, are summarised below.

Sole claim request

Admittance (Article 12(4) RPBA 2007)

The request was filed with the reply to the statement of grounds of appeal and should be admitted into the

proceedings. The opposition division had rejected the opposition and the respondent had to be given the opportunity to react to the appeal.

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

The claim was based on claim 35 of the application as filed, to which the functional feature had been added. Claim 35, read in the light of claim 48 of the application as filed, disclosed anti-PD-L1 antibodies comprising a heavy chain and a light chain variable region sequence characterised by the six HVRs recited in claim 1.

Basis for the functional feature "blocks the binding of both human and mouse PD-L1 to PD-1" was provided on page 130, lines 15 to 18, of the application as filed, where the antibodies comprising the 6 HVRs of YW243.55S70 as recited in claim 1 were characterised by their common ability to block the binding of both human and mouse PD-L1 to PD-1. Further support for this amendment could be found at least on page 49, lines 25 to 27.

Example 1 disclosed antibody YW243.55S70 and other antibodies having cross-blocking and cross-binding activity (see Table 1). The skilled person would conclude from Table 1 that the binding properties of "YW243.55.S70" were a function of its HVRs and not of its FRs (see also document D12, point 10). The disclosure on page 130, lines 15 to 18, of the application as filed could therefore be generalised to all antibodies having the HVRs recited in claim 1.

The skilled person could make other antibodies maintaining the cross-binding and cross-blocking

function of YW243.55S70 by grafting the HVRs of YW243.55S70 into other FRs (see also document D12, point 11). The statement "*to block binding of both human and mouse PD-L1 to PD-1*" on page 130, lines 15 to 18, of the application as filed was therefore not inextricably linked to antibody YW243.55S70, but could be generalised to all antibodies having the HVRs of YW243.55S70.

Further basis for the feature was found on page 49, lines 25 to 27, of the application as filed, which had to be read with page 2, lines 18 to 21; page 24, lines 26 to 31; page 42, lines 16 to 26; page 49, lines 29 to 33 and Table 1 of the application as filed.

Thus the application as filed disclosed that the invention concerned anti-PD-L1 antibodies (page 2, lines 18 to 21) that could be used to enhance T-cell function by blocking the signalling through PD-1 (page 49, lines 32 to 33). Binding and blocking of the interaction of PD-L1 and PD-1 was disclosed throughout the application as a common denominator or goal (see also page 24, line 26 to 31). Example 1 was designed to identify cross-binding and cross-blocking antibodies, and all the antibodies in Table 1 had been tested for blocking the interaction of PD-L1 and PD-1. The disclosure on page 42, lines 16 to 26 supported the notion that it was the HVRs that determined specificity and binding of an antibody.

In sum, the skilled person reading the application as filed would understand that the goal of the invention was the provision of antibodies binding PD-L1 and blocking its interaction with PD-1. The functional feature did not therefore constitute added subject-

matter.

XII. The appellant requested that the decision under appeal be set aside and the patent be revoked.

The respondent requested that the patent be maintained in amended form on the basis of the sole claim request filed as auxiliary request 8 with the reply to the appeal dated 17 April 2020.

Reasons for the Decision

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

Sole claim request - admittance

2. The appellant submitted that the sole claim request should be held inadmissible pursuant to Article 12(4) RPBA 2007, applicable to the present appeal case pursuant to Articles 24 and 25(2) RPBA in force since 1 January 2020. In view of the board's conclusion on the issue of added subject-matter (see points 3. ff. below), there is no need for the board to give reasons for having decided to take the sole claim request into account under Article 12(4) RPBA 2007 and to consider it in substance.

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

3. The claim is directed to an isolated anti-PD-L1 antibody (or antigen binding fragment thereof) which is characterised structurally as comprising a heavy chain and a light chain variable region sequence with the amino acid sequences of the three heavy and three light chain HVRs indicated in the claim. These HVRs are the

HVRs of antibody YW243.55S70 (it was uncontested that the terms "YW243.55.S70" and "YW243.55S70", both used in the application as filed, designated the same antibody). The antibody (or antigen binding fragment thereof) is furthermore characterised functionally in that it "blocks the binding of both human and mouse PD-L1 to PD-1". This feature is referred to in the following as the "cross-blocking feature".

4. The claim corresponds to claim 1 of the patent as granted (see section I.) to which the cross-blocking feature has been added. While the basis in the application as filed for the structural definition of the antibody has also been disputed by the appellant, the sole issue considered in this decision is whether the combination of the cross-blocking feature with the remaining features of claim 1 results in subject-matter which extends beyond the content of the application as filed within the meaning of Article 123(2) EPC.

5. The respondent alleged that a *verbatim* basis for the cross-blocking feature was provided by the disclosure "*While all fifteen affinity improved Abs* [antibodies] *had acquired significant cross-reactivity to mouse PD-L1, YW243.55S70 was selected as the primary candidate to pursue based on its ability to block binding of both human and mouse PD-L1 to PD-1 (Table 1: IC_{50} values of 49 pM and 22 pM, respectively)*." on page 130, lines 15 to 18, of the application as filed.

6. However, this passage does not characterise the antibodies comprising the six HVRs of YW243.55S70 as recited in claim 1 by "their common ability to block the binding of both human and mouse PD-L1 to PD-1", as asserted by the respondent. Instead, this passage pertains to the characteristics of one particular

antibody, YW243.55S70, and does not disclose that all antibodies characterised structurally solely by comprising the six HVRs of antibody YW243.55S70 block the binding of both human and mouse PD-L1 to PD-1.

7. In the claim, the cross-blocking feature disclosed in the application as filed in the context of antibody YW243.55S70 is generalised to all antibodies characterised structurally as comprising the six HVRs of the YW243.55S70 antibody.

8. In line with the established case law of the Boards of Appeal, such a generalisation is only allowable in the absence of any clearly recognisable functional or structural relationship among the features originally disclosed in combination or if the extracted feature is not inextricably linked with those features (see Case Law of the Boards of Appeal of the European Patent Office, 10th edition 2022 ("CLBA"), II.E.1.9.1).

9. At issue is therefore whether there exists a functional or structural relationship between the cross-blocking feature and the heavy chain and light chain variable region sequences of the YW243.55S70 antibody, these being the features disclosed in combination (see page 130, lines 15 to 18, of the application as filed).

10. The variable domain of an antibody mediates antigen binding and consists of a heavy chain and a light chain variable region. Within the variable regions of both heavy and light chains, some short polypeptide segments show exceptional variability. These are the HVRs, sometimes also referred to as complementary determining regions (CDRs). The intervening peptide segments are the FRs. In both heavy and light chain variable regions there are three HVRs (HVR1 to HVR3) and four FRs (FR1

to FR4). While the antigen binding site is formed from the six HVRs, these are held together in close proximity by the eight FRs (see also application as filed, page 42, lines 16 to 26). Indeed, the FRs are necessary to maintain the HVRs in the correct conformation. It is further part of common general knowledge that changes in the FRs affect the binding properties of antibodies (see e.g. document D43, pages 354 and 355).

11. The technical information conveyed to the skilled person on page 130, lines 15 to 18, of the application as filed is therefore that an antibody having the structure of YW243.55S70, which, as regards the heavy chain and light chain variable regions, consists of specific HVRs held together by specific FRs (see Figure 11A and 11B of the application as filed for the heavy and light chain variable region amino acid sequences), has the function of blocking the binding of both human and mouse PD-L1 to PD-1. Accordingly, the skilled person is aware that there exists a relationship between the structural features of the antibody YW243.55S70 and its cross-blocking function.

12. In a first line of argument, the respondent submitted that the skilled person would have concluded from Table 1 of the application as filed that the binding properties of YW243.55S70 were a function of its HVRs and not of its FRs. The cross-blocking feature disclosed on page 130, lines 15 to 18, of the application as filed could therefore be generalised to all antibodies having the six HVR sequences of antibody YW243.55S70.

13. This line of argument is not found persuasive for several reasons. First, Table 1 (see lower part,

bridging pages 130 and 131 of the application as filed) lists fifteen antibodies including antibody "YW243.55.S70". Each antibody was derived from antibody YW243.55 by affinity maturation (see page 126, lines 20 to 22, of the application as filed) in which the FRs were kept constant and random variations were made in the HVRs (see page 126, line 28 to page 130, line 3 of the application as filed). After reformatting to full length IgG1, the antibodies were tested for their ability to block the binding of human PD-1 to 293 cells expressing either human PD-1 or mouse PD-1 (see page 130, lines 10 to 15 and Table 1, Format 1 and Format 3, of the application as filed).

14. Accordingly, Table 1 of the application as filed provides a comparison of the cross-blocking properties of fifteen antibodies having identical FRs but different HVRs (see Figures 11A and 11B for the light and heavy chain variable region amino acid sequences of these antibodies). The skilled person will therefore understand from Table 1 that the unique blocking properties of YW243.55S70 (see page 130, lines 15 to 18, and Table 1) are determined by its unique HVR sequences in the context of its FR sequences, these FR sequences being the same as in the other fourteen antibodies tested.

15. Second, Table 1 of the application as filed does not provide a comparison of the blocking properties of antibodies comprising the six HVRs of antibody YW243.55S70 in the context of different FRs.
No conclusions can therefore be drawn from this table about the blocking properties of an antibody comprising the six HVRs of antibody YW243.55S70 in the context of different FRs. Accordingly, this table does not provide evidence that there is no functional or structural

relationship among the features of antibody YW243.55S70. In particular, contrary to the respondent's allegation, it cannot be derived from Table 1 that the binding properties of YW243.55S70 are solely a function of its unique HVRs and not its FRs. The board's conclusion is also acknowledged in document D12 by the statement that the functionality of an antibody might be altered by using a different framework and might require "*modifying frameworks to recover function*" (see document D12, point 11).

16. In a further line of argument, the respondent submitted that the skilled person could construct other antibodies that maintain the cross-blocking function by grafting the six HVRs of antibody YW243.55S70 into different FRs. Therefore the cross-blocking feature disclosed on page 130, lines 15 to 18, of the application as filed was not inextricably linked to antibody YW243.55S70, and could be separated from YW243.55S70 and generalised to all antibodies having the HVRs recited in claim 1.

17. This line of argument is not found persuasive either. Example 1 in general and page 130, lines 15 to 18, of the application as filed in particular are silent about the possibility of grafting the HVRs of antibody YW243.55S70 into different FRs while maintaining its cross-binding and cross-blocking function. In these circumstances, the skilled person would need to reflect on how the teaching of Example 1 and page 130, lines 15 to 18, of the application as filed could be applied or changed in order to arrive at the claimed subject-matter. However, what the skilled person might do upon reflection is not part of the content of the application as filed, but concerns matters related to obviousness (see also CLBA, II.E.1.9.3). The

respondent's submissions with respect to the possibility of HVR grafting can therefore not persuade the board that the cross-blocking feature is not inextricably linked to antibody YW243.55S70.

18. In an additional line of argument, the respondent submitted that the passage on page 49, lines 25 to 27, of the application as filed - when read in the light of page 2, lines 18 to 21; page 24, lines 26 to 31; page 42, lines 16 to 26; page 49, lines 29 to 33 and Table 1 - also provided a basis for the cross-blocking feature because the skilled person would understand that the goal of the invention was the provision of antibodies binding PD-L1 and blocking its interaction with PD-1. For this reason too, it submitted, the combination of the cross-blocking feature with the other features of the claim did not extend beyond the content of the application as filed.

19. The passages of the application as filed relied on by the respondent in this context are as follows:

"In certain embodiments, an antibody specifically binds to an epitope on a protein that is conserved among the protein from different species." (page 49, lines 25 to 27)

"The present invention provides for anti-PD-L1 antibodies, including nucleic acid encoding and compositions containing such antibodies, and for their use to enhance T-cell function to upregulate cell-mediated immune responses and for the treatment of T cell dysfunctional disorders, including infection (e.g., acute and chronic) and tumor immunity." (page 2, lines 18 to 21)

"As a result, the antagonism of signaling through PD-L1, including blocking PD-L1 from interacting with either PD-1, B7.1 or both, thereby preventing PD-L1 from sending a negative costimulatory signal to T-cells and other antigen presenting cells is likely to enhance immunity in response to infection (e.g., acute and chronic) and tumor immunity. In addition, the anti-PD-L1 antibodies of the present invention, may be combined with antagonists of other components of PD-1:PD-L1 signaling, for example, antagonist anti-PD-1 and anti-PD-L2 antibodies." (page 24, lines 26 to 31)

"A 'blocking' antibody or an 'antagonist' antibody is one that inhibits or reduces a biological activity of the antigen it binds. In some embodiments, blocking antibodies or antagonist antibodies substantially or completely inhibit the biological activity of the antigen. The anti-PD-L1 antibodies of the invention block the signaling through PD-1 so as to restore a functional response by T-cells from a dysfunctional state to antigen stimulation." (page 49, lines 29 to 33)

"The term 'variable' refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies. The V domain mediates antigen binding and defines the specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the entire span of the variable domains. Instead, it is concentrated in three segments called hypervariable regions (HVRs) both in the light-chain and the heavy chain variable domains. The more highly conserved portions of variable domains are called the framework regions (FR). The variable domains of native heavy and light chains each comprise four FR regions,

largely adopting a beta-sheet configuration, connected by three HVRs, which form loops connecting, and in some cases forming part of, the beta-sheet structure. The HVRs in each chain are held together in close proximity by the FR regions and, with the HVRs from the other chain, contribute to the formation of the antigen binding site of antibodies." (page 42, lines 16 to 26)

As regards the disclosure of Table 1, reference is made to points 5. and 13. above.

20. Evidently, the passage on page 49, lines 25 to 27, mentions binding to the same epitope on a protein that is conserved among the proteins from different species, i.e. cross-binding, in a generic manner. The passage is silent about cross-blocking, PD-L1 and any specific antibody. Indeed, none of the generic passages in the application as filed relied on by the respondent disclose blocking the binding of both human and mouse PD-L1 to PD-1, i.e. cross-blocking (see page 24, lines 26 to 31 and page 49, lines 29 to 33). Even if, for the sake of argument, the passage on page 2, lines 18 to 21 is read together with the disclosure on page 49, lines 29 to 33 to establish the goal of the invention, this goal does not encompass cross-blocking. Furthermore, the disclosure of a general goal of the invention is not a direct and unambiguous disclosure that the cross-blocking feature can without further ado be combined with an antibody characterised only by the HVRs recited in the claim.

21. The fact that all the antibodies in Table 1 were tested for their cross-blocking properties does not support the respondent's case either. As set out above (see points 5. and 13.), these antibodies have HVRs which differ from the HVRs of antibody YW243.55S70 recited in

the claim. Accordingly, already for this reason, disclosure of the functional property of cross-blocking in the context of these antibodies provides no basis for combining the cross-blocking feature with an antibody having different HVRs as recited in the claim.

22. Finally, contrary to the respondent's submission that HVRs determine antibody binding in the first place, it can be derived from the passage on page 42, lines 16 to 26 of the application as filed that FRs are equally important, as they bring the HVRs together in close proximity to result in effective binding and hence blocking (see also point 10. above). Therefore the respondent's additional line of argument based on page 49, lines 25 to 27, of the application as filed is not found persuasive either.

23. The board concludes that by isolating the cross-blocking feature from the context of antibody YW243.55S70 and combining it with antibodies characterised structurally solely by the six HVRs of antibody YW243.55S70, new technical information is generated that the skilled person cannot directly and unambiguously derive from the application as filed. The claim encompasses antibodies having FRs that maintain the six HVRs of antibody YW243.55S70 in the correct conformation such that the claimed antibodies meet the functional requirement *"blocks the binding of both human and mouse PD-L1 to PD-1*", which FRs need not be the FRs of antibody YW243.55S70. Such antibodies are disclosed neither explicitly nor implicitly in the application as filed.

24. The claimed subject-matter therefore extends beyond the content of the application as filed, contrary to

Article 123(2) EPC.

Conclusion

25. The sole claim request on file is not allowable. Therefore the patent cannot be maintained in amended form on the basis of this claim request and 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 Chair:

L. Malécot-Grob B. Claes

Decision electronically authenticated