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Datasheet for the decision of 25 April 2023

Case Number: T 1394/21 - 3.3.04

Application Number: 13834707.5

Publication Number: 2892558

IPC: A61K39/395, A61K48/00, A61P35/00

Language of the proceedings: EN

Title of invention:
VISTA modulators for diagnosis and treatment of cancer

Patent Proprietor:
The Trustees Of Dartmouth College
King's College London

Opponent:
Regimbeau Sarl

Headword:
VISTA and PD-L1-antagonists/DARTMOUTH COLLEGE

Relevant legal provisions:
EPC Art. 83, 111(1)
RPBA 2020 Art. 12(6), 13(2)

Keyword:
Late-filed facts - should have been submitted in first-instance proceedings (yes)
Sufficiency of disclosure - main request (yes)
Appeal decision - remittal to the department of first instance (yes)

Decisions cited:
G 0002/21

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Case Number: T 1394/21 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 25 April 2023

Appellant: (Patent Proprietor 1)	The Trustees Of Dartmouth College 11 Rope Ferry Road Room 6210 Hanover, NH 03755 (US)
Appellant: (Patent Proprietor 2)	King's College London Strand London WC2R 2LS (GB)
Representative:	Stephens, Clare Jean Page White & Farrer Limited Bedford House 21A John Street London WC1N 2BF (GB)
Respondent: (Opponent)	Regimbeau Sarl 20, rue de Chazelles 75017 Paris (FR)
Representative:	Regimbeau 20, rue de Chazelles 75847 Paris Cedex 17 (FR)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 25 June 2021 revoking European patent No. 2892558 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	O. Lechner
	R. Romandini

Summary of Facts and Submissions

I. European patent No. 2 892 558 ("the patent") was granted on European patent application No. 13 834 707.5, filed as an international patent application published as WO 2014/039983 ("the application as filed").

II. The patent proprietors ("appellants") filed an appeal against the opposition division's decision to revoke European patent 2 892 558 under Article 101(3)(b) EPC.

III. The opposition division had decided that the patent application did not disclose the invention according to the set of claims of the main request and auxiliary requests 1 to 4 (all filed with the letter of 7 October 2020) and auxiliary request 5 (filed with the letter of 3 March 2021) in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 83 EPC).

IV. In their statement of grounds of appeal and a further letter, the appellants set out arguments as to why the patent disclosed the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. They also filed new documents D79 to D84 with their statement of grounds of appeal.

V. The opponent ("respondent") replied and filed new documents D85 to D90.

VI. The board issued a communication pursuant to Article 15(1) RPBA providing the board's preliminary assessment of the appeal.

VII. The oral proceedings before the board took place as scheduled on 25 April 2023.

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

VIII. Independent claims 1, 4 and 7 of the main request read:

"1. A VISTA antagonist for use in treating cancer by activating anti-cancer immunity in a subject, wherein the VISTA antagonist comprises an anti-VISTA antibody, and wherein said use comprises administering a PD-1 antagonist to the subject, wherein the PD-1 antagonist is an anti-PD-L1 antibody."

"4. A VISTA antagonist and a PD-1 antagonist for use in combination in treating cancer in a subject having a condition that would benefit from upregulation of an immune response, wherein said VISTA antagonist comprises an anti-VISTA antibody, which when administered is capable of inhibiting the VISTA-mediated suppression of immune responses, and wherein said PD-1 antagonist is an anti-PD-L1 antibody."

"7. A therapeutic composition for use in the treatment of cancer, wherein said therapeutic composition comprises a VISTA antagonist and a PD-1 antagonist; wherein said VISTA antagonist comprises an anti-VISTA antibody; and said PD-1 antagonist is an anti-PD-L1 antibody."

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

D4: S. L. Topalian et al., Curr. Opin. Immunol. (2012); 24(2), 207–212

D13: L. Wang et al., J. Exp. Med. (2011); 208(3), 577-592

D17: J. R. Brahmer et al., N. Engl. J. Med. (2012); 366(26), 2455-2465

D19: M. A. Curran et al., PNAS (2010); 107(9), 4275-4280

D29: Experimental Report (submitted by the opponent on 10 January 2020), 3 pages

D41: Y. Zhang et al., Crit. Care (2010); 14: R220, 1-9

D46: R. J. Greenwald et al., Annu. Rev. Immunol. (2005); 23, 515–548

D47: WO2008/083174 A2

D48: US2010/0040614 A1

D49: US2010/0151492 A1

D50: US2007/0122378 A1

D54: S. A. Newland et al., Eur. J. Immunol. (2011); 41(10), 2966-2976

D65: T. Nomi et al., Clin. Cancer Res. (2007); 13(7), 2151-2157

D70: J. Liu et al., Proc. Natl. Acad. Sci. (2015); 112(21), 6682-6687

D79: Y. Kitazawa et al., Transplantation (2007); 83(6), 774-782

D80: J. J. A. Coenen et al., J. Immunol., (2006); 176, 5240-5246

D81: V. A. L. Huurman et al., Clin. Exp. Immunol. (2007); 150, 487-493

D82: M. S. Sabel et al., Cancer Immunol. Immunother. (2005); 54, 944-952

D83: Journal of Experimental Medicine, Editorial Policies, https://rupress.org/jem/pages/editorial-policies#data-sharing, retrieved on: 16 October 2021

D84: Declaration by Randolph J. Noelle, 21 October 2021, 2 pages

D85: I. Le Mercier et al., Cancer Res. (2014); 74(7), 1933-1944 and Supplemental Material and Methods, 5 pages

D86: Declaration by Alex Slater (Crown Biosciences), 8 March 2022, 1 page

D87: CV of Mingxuan Du

D87a: Training record of Mingxuan Du

D88: CV of Xiang Wang

D88a: Training record of Xiang Wang

D89: CV of Xiaotong Xing

D89a: Training record of Xiaotong Xing

D90: CV of Haochen Wu

X. The appellants' arguments, in so far as relevant to the decision, can be summarised as follows:

(a) Admittance of documents D83 to D87, D87a, D88, D88a, D89, D89a and D90

D83 and D84
Documents D83 and D84 were filed in support of the public availability of the antagonistic anti-VISTA antibody 13F3 in response to the opposition division's new reasoning raised at the oral proceedings and the subsequent decision that possession of antibody 13F3 was essential for carrying out the invention.

D85
Post-published document D85 did not undermine the teaching of the application as filed. The section referred to by the opponent discussed the immunogenicity of the 13F3 antibody, yet the subsequent paragraph indicated that "*despite the apparent immunogenicity and short half-life of the 13F3 in vivo, 13F3 treatment significantly suppressed tumor growth in the B16OVA model (Fig. 1A)*" (see page 1934, right-hand column, first full paragraph). Furthermore, it could be seen in Figure 1A of document D85 that the suppression of tumour growth was observed over the course of the experiment up to day 18.

D86 to D87, D87a, D88, D88a, D89, D89a and D90
Documents D86 to D90 were late-filed and did not address all the reasons why the opposition division did not find document D29 persuasive.

(b) Admittance of arguments made for the first time during oral proceedings in the context of document D70

The arguments put forward by the respondent during oral proceedings in the context of document D70 were completely new since they relied on new passages and represented an inadmissible amendment to the case. They could and should already have been provided in the respondent's reply letter.

(c) Disclosure of the invention - main request

Anti-VISTA antibody 13F3

The antagonistic anti-VISTA antibody 13F3 was an example and was not required in order for a skilled person to be in possession of the invention, so the availability of the 13F3 antibody was not essential.

This notwithstanding, antibody 13F3 had been placed in public possession due to its disclosure in prior art document D13 as of 11 March 2011. It was incorrect that only the sequence of the 13F3 antibody or a hybridoma would make this antibody publicly available. Document D13 disclosed that antibody 13F3 was a hamster anti-rodent VISTA antagonist antibody. It was evident when reading document D13 that the 13F3 antibody was the same as the 13F3 antibody referenced in the patent. The

application as filed also cited document D13 in several places (see paragraphs [0305], [0615] and [0675]).

Antagonistic anti-VISTA antibodies

The application as filed and the prior art taught the skilled person how to make anti-VISTA antibodies and demonstrated that these methods reliably produced antibodies specific for VISTA. Such methods were routine in the art at the effective filing date and could be used to generate a panel or array of different anti-VISTA antibodies. Suitable mixed-lymphocyte reaction (MLR) assays for identifying antagonistic anti-VISTA antibodies were described in the prior art document D13 (see Figure 10 and page 590, paragraph "*In vitro plate-bound T cell activation assay*"), the content of which was repeated almost exactly in Example 20 of the application as filed. Further suitable assays were described in paragraphs [0624], [0712], [0713] and [0736] of the application as filed. Document D13 and the application as filed further disclosed an *in vivo* experimental autoimmune encephalitis (EAE) model which could be used to confirm an antagonist's activity. The application as filed also taught mouse tumour models which could be used for confirming that a candidate anti-VISTA antibody was a VISTA antagonist.

MLR assays were well known in the art and had already been used, e.g. in documents D79 to D81, to evaluate the functional activities of antagonistic antibodies to programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).

Antagonistic anti-PD-L1 antibodies

The opposition division itself had indicated in point 14.3.3.1 of its decision that the appellants had shown that anti-PD-L1 antibodies antagonistic to PD-1 had been known and available from documents D4, D17, D47 to D50 and D65. Moreover, as evidenced by document D41 (see Material and Methods section), antagonistic anti-PD-L1 antibodies were also commercially available from eBioscience.

Suitability of the claimed antibodies for the claimed therapeutic effect

The patent as a whole contained sufficient information and data for a skilled person to reasonably conclude that the claimed medical use of the invention was plausible, and furthermore this was clearly demonstrated by the application as filed/patent.

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

(a) Admittance of documents D83 to D87, D87a, D88, D88a, D89, D89a and D90

D83 and D84
The objection as to the enablement of the 13F3 antibody had already been raised in the notice of opposition (see page 38, paragraph 1.1.2) and reiterated in the letter of 4 March 2021 (see pages 16 and 17) filed during the opposition proceedings. The appellants did not contest the lack of enablement until their statement of grounds of appeal. Thus, documents D83 and D84 could and should already have been filed during the

opposition proceedings. These late-filed documents should not be admitted.

D85
Document D85 was filed in response to new comments made by the appellants in the statement of grounds of appeal in relation to the *in vivo* anti-tumour activity of antibody 13F3. Post-published document D85 showed that antibody 13F3 has a very narrow window of therapeutic efficacy.

D86 to D87, D87a, D88, D88a, D89, D89a and D90
Documents D86 to D90 had been filed in response to the comments made on pages 20 and 21 of the statement of grounds of appeal concerning the identity, skills and expertise of the person(s) performing the experiments described in document D29.

(b) Admittance of arguments made for the first time during oral proceedings in the context of document D70

The data provided in document D70 (see page 6685, right-hand column, legend to Figure 5; page 6686, Figure 6A and right-hand column, last paragraph before the "*Discussion*") supported the results in document D29. This was not a new line of argument, and the appellants could have expected such an argument since they had cited document D70. Moreover, in its communication under Article 15(1) RPBA, the board had invited the parties to discuss document D70.

(c) Disclosure of the invention - main request

Anti-VISTA antibody 13F3

The application as filed/patent did not provide any sequences of antibody 13F3, nor did it contain any reference to a hybridoma deposited in accordance with Rule 31(1) EPC.
The mere mention of an antibody 13F3 in document D13 was thus not enough to prove that this antibody was available to the public at the effective date.

Antagonistic anti-VISTA antibodies

The application as filed disclosed several methods for isolating monoclonal anti-VISTA antibodies which could be either agonistic or antagonistic (see e.g. paragraph [0103]).

Several *in vitro* methods for screening antibodies for antagonists were described in Example 26 of the application as filed. Anti-VISTA antibodies generated by immunisation might first be tested for efficacy in blocking T cell responses in an MLR assay. Four types of MLR assays were described in Example 20. Lastly, the VISTA-inhibitory antibodies identified in these assays were tested *in vivo* for promoting anti-tumour responses in animal models of cancer (see paragraph [0780]).

However, this was just an invitation to carry on a research program. Providing an assay was a first step in identifying an antagonistic anti-VISTA antibody, yet the skilled person did not have any pointer regarding the number of antibodies which had to be screened in order to successfully identify an antagonist. The only positive control described, i.e. the only guide which

might help the skilled person perform this screening successfully, was antibody 13F3, which was not enabled.

Antagonistic anti-PD-L1 antibodies

The application as filed failed to disclose how to obtain antagonistic anti-PD-L1 antibodies. The anti-PD-L1 antibody allegedly used in Example 26 was only described by reference to the arbitrary designation MIH5. It was mentioned once in Figure 37 without any further details. The application as filed did not contain any other information whatsoever regarding this antibody. There was no citation of a publication, no mention of structural features such as CDR sequences, no reference to a deposit of a hybridoma pursuant to the Budapest Treaty, no indication of commercial availability, etc. There was also no reference to document D54, which the opposition division had regarded as enabling said antibody. However, even if document D54 did disclose the same MIH5 antibody as that in Example 26, there was still no indication that MIH5 was an antagonist of PD-1. The skilled person therefore had absolutely no way of identifying antibody MIH5, which meant that the results of Example 26 could not be reproduced.

Suitability of the claimed antibodies for the claimed therapeutic effect

Even if the description gave enough information for obtaining antagonistic anti-VISTA antibodies and antagonistic anti-PD-L1 antibodies, the medical use of claim 1 was still not sufficiently disclosed.

The experimental conditions of Example 26 were not described: no information was given on the number of

tumour cells implanted in the recipient mice, the amounts of antibodies administered or the administration regimen. Thus, the skilled person had to try every combination of these parameters without any certainty of success. Notably, the skilled person was unable to assign a negative result to the absence of therapeutic activity or to the experimental conditions. Therefore, the application as filed did not comprise any enabling data demonstrating that the combination of the two antibodies had any anti-tumour activity.

Neither antibody 13F3 nor antibody MIH5 possessed any anti-tumour activity in the B16F10 mouse model, as also demonstrated by the examples of the application as filed. Figure 40A stated that the antibody 13F3 had no effect on tumour growth in a B16F10 model when administered therapeutically. This was confirmed by Example 13 and Figure 21 in which, once again, no anti-tumour effect could be detected in the B16F10 model when antibody 13F3 was administered four days after transplantation of the tumour cells (day +4). In line with the explanations provided in paragraphs [0180], [0774] and [0775] of the application as filed, Figure 40B only showed synergy of VISTA-Ig and PD-L1-Ig in suppressing T cell responses.

The same was true for antibody MIH5; there was no indication on file that this antibody might have any anti-tumour effect.
Document D19, referred to in the opposition division's decision, did not disclose the MIH5 antibody.
Document D54 was concerned with preventing diabetes resulting from *Salmonella typhimurium* infection, not with cancer treatment.
The application as filed showed that MIH5 actually had no anti-cancer activity, at least in the B16F10 model

used in Example 26. This was apparent from Figure 40A, for the same reasons as for antibody 13F3, and confirmed by Example 24 and Figure 37 (see [0177]).

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

The appellants requested that:

- the decision under appeal be set aside and the patent be held to comply with what is set out in Article 83 EPC on the basis of a set of claims of the main request or one of auxiliary requests 1 to 5 as filed during opposition proceedings
- the case be remitted back to the opposition division for consideration of the grounds of opposition under Article 100(a) EPC and for consideration by the opposition division of the admissibility of documents D72 to D78
- documents D79 to 84 (as filed with the statement of grounds of appeal) be admitted into the proceedings
- documents D85 to D87, D87a, D88, D88a, D89, D89a and D90 not be admitted
- the new arguments against the reproducibility of the invention made by the respondent during oral proceedings and based on document D70 not be admitted

The respondent requested that:

- the appeal be dismissed and the patent be revoked
- documents D83 and D84 not be admitted
- documents D85 to D87, D87a, D88, D88a, D89, D89a and D90 (filed with the respondent's reply to the statement of grounds of appeal) be admitted

Reasons for the Decision

1. Admittance of documents D83 to D87, D87a, D88, D88a, D89, D89a and D90

1.1 Documents D83 and D84

The argument that antibody 13F3 was not sufficiently disclosed had already been raised in point 1.1.2. of the notice of opposition, so documents D83 and D84 could and should already have been submitted in the opposition proceedings.
Thus, documents D83 and D84 were not admitted into the proceedings (Article 12(6) RPBA).

1.2 Document D85

The board did not consider it necessary to decide on the admittance of document D85 and the submissions based on it, the reason being that the limited therapeutic window or effect mentioned in document D85 would still fall within the scope of claim 1 of the main request. Therefore, neither the data nor the arguments based on them could have changed or influenced the board's assessment of sufficiency.

1.3 Documents D86 to D87, D87a, D88, D88a, D89, D89a and D90

Apart from the fact that documents D86 to D87, D87a, D88, D88a, D89, D89a and D90 do not address the central issue of the lack of positive controls in the D29 experimental report, these documents, which are intended to provide information as to who carried out the experiments of document D29, could and should

already have been filed during the opposition proceedings and were therefore not admitted into the proceedings (Article 12(6) RPBA).

2. Admittance of lines of argument made for the first time during oral proceedings in the context of document D70

The objection as to sufficiency of disclosure regarding the claimed medical use had already been raised with the notice of opposition. Document D70 had already been cited in the appellants' reply to the notice of opposition. Furthermore, the arguments under discussion relating to documents D70 and D29 had already been put forward by the appellants during the opposition proceedings (see point 14.2.5 of the decision under appeal). They were reiterated in the statement of grounds of appeal.

During the oral proceedings before the board, the respondent presented a new line of argument based on previously uncited passages of document D70.

Although the board had stated, in its communication under Article 15(1) RPBA, that the data in document D70 confirmed the effect of targeting VISTA and PD-L1, this cannot be construed as an invitation to provide a new line of argument based on document D70. Thus, no exceptional circumstances existed.

Consequently, the board decided that newly cited passages in document D70 and the corresponding arguments made in the context of document D29 were not to be taken into account (Article 13(2) RPBA).

3. Disclosure of the invention - main request

3.1 Anti-VISTA antibody 13F3 and anti-PD-L1 antibody MIH5

3.1.1 The opposition division held that antibody 13F3 was not disclosed in an enabling manner.

The opposition division decided on the other hand that the specific antagonistic anti-PD-L1 antibody MIH5 used in Example 26 had been known from document D54 and, thus, was enabled.

3.1.2 The application as filed does not disclose the specific antagonistic anti-VISTA antibody 13F3 in an enabling way. The board agrees with the opposition division and the respondent that document D13, relied on by the appellants, also fails to provide further details on the 13F3 antibody such as its amino acid sequence, a deposit number of the corresponding hybridoma made according to the Budapest Treaty (see Rule 31 EPC) or proof/a source of commercial availability.
The putative in-house designation 13F3 may be used for different antibodies and does not allow an antibody to be clearly identified.

3.1.3 Similarly, the application as filed does not disclose the specific antagonistic anti-PD-L1 antibody MIH5 in an enabling way. No specific sequence, hybridoma deposit accession number pursuant to Rule 31 EPC, commercial source or any prior art document disclosing the MIH5 antibody has been provided. The application as filed does not cite document D54.
There is no evidence whatsoever that the MIH5 of the application as filed could be the same as the MIH5 of document D54.

Yet even if the application as filed did refer to document D54, said document would not be enabling on its own either since it does not further characterise the antibody designated MIH5.

3.1.4 Although neither antibody 13F3 nor MIH5 is sufficiently disclosed in the application as filed, the board agrees with the appellants that a skilled person would absolutely understand that the two specific antibodies are example antagonistic antibodies to VISTA and PD-L1, respectively, and that other antagonistic anti-VISTA and anti-PD-L1 antibodies may be used in combination in order to perform the invention, provided that the skilled person knew how to generate such antibodies.

3.2 Antagonistic anti-VISTA and anti-PD-L1 antibodies

3.2.1 The opposition division did not deny that the skilled person could generate anti-VISTA antibodies *per se* without undue burden on the basis of general, commonly known antibody production methods which had been exemplified in paragraphs [0414] to [0419] of the patent (see [0498] to [0505] of the application as filed).

The opposition division, however, was of the opinion that none of the examples in the application as filed/ patent provided the detailed technical information and criteria for convincingly identifying antagonistic anti-VISTA antibodies.
Figure 40B showed that only certain types of T cells could be affected and, if they had been affected at all, it had not been in a convincing manner. The tumour size reduction experiments with murine tumour models were difficult and unreliable to work with and

certainly did not constitute a meaningful way of screening and selecting/identifying antibodies.

Document D13, to which the application as filed refers, did not provide the technical details and criteria for identifying antagonistic anti-VISTA antibodies either.

Therefore, identifying antagonistic anti-VISTA antibodies constituted an undue burden.

3.2.2 The board cannot agree. It is undisputed that paragraphs [0498] to [0505], [0621], [0706] and [0722] of the application as filed provide the information needed for producing anti-VISTA antibodies in general, i.e. comprising agonistic and antagonistic antibodies.

Example 26 of the application as filed (see paragraphs [0777] and [0778]) refers to the use of MLR assays for identifying antagonistic anti-VISTA antibodies. Paragraphs [0165], [0713] and [0736], and Figures 25A to D of the application as filed describe how to perform such MLR *in vitro* assays and the effect to be expected for antagonistic anti-VISTA antibodies.

According to the description in paragraph [0180] of the application as filed, Figure 40B provides the effects of immobilised VISTA-Ig and PD-L1-Ig, i.e. the soluble receptors and not the antibodies as (erroneously) indicated in the figure caption for the X-axis, together with anti-CD3/CD28 on the proliferation of CD4+ and CD8+ T cells (see Example 26, paragraph [0774]). Thus, contrary to the opposition division's assessment, this figure cannot show that the assay is unsuitable for identifying antagonistic antibodies.

MLR assays measuring T cell activation were well known in the art and already used for identifying antagonistic antibodies targeting immune checkpoint proteins such as PD-L1 (see documents D4, D17, D47 to D50, D65 or D79) or CTLA-4 (see documents D80 to D82). The application as filed also identifies VISTA as a putative immune checkpoint protein ligand (see e.g. paragraphs [0002], [0013] and [0014]), thus providing a link to the known methods for identifying antagonists to well-known and characterised checkpoint proteins (such as CTLA-4 and PD-L1).

Example 26 of the application as filed also states that VISTA-inhibitory antibodies identified in *in vitro* assays are further tested *in vivo* for promoting anti-tumour responses in animal models of cancer (see paragraph [0780]) "*e.g. as further described in the preceding examples*", i.e. the tumour models of Examples 7 and 8 (see also Figures 20A to D).

The opposition division argued (see point 14.3.2, paragraph 7 of the decision under appeal) that the appellants had indicated in their letter of 6 October 2020 (see page 68, penultimate paragraph) that the B16F10 tumour model was complex and unpredictable. Example 26 (see page 218, fifth and sixth penultimate lines) of the application as filed also states that "[d]*ue to its poor immunogenicity, B16F10 also represents a very challenging murine tumour system for immune-interventions against cancer*".

It is, however, not clear on which basis the opposition division concluded that "*[a]s regards the tumor size reduction experiments, the murine tumor models are difficult and unreliable to work with and certainly do not constitute a meaningful way to screen and select/*

identify antibodies", i.e. has evidently extrapolated this statement to all *in vivo* tumour models used in the application as filed, such as Example 8.

The board agrees with the appellants that no evidence or specific technical reason has been provided as to why the skilled person could not repeat the tests of Examples 7 and 8 with another anti-VISTA antibody that has been preselected *in vitro* to have efficacy in blocking T cell responses induced by VISTA.

As an alternative, the skilled person could use the EAE model used in Example 20 (see paragraphs [0717] and [0737] of the application as filed) and in prior art document D13 for the *in vivo* evaluation of candidate antagonistic anti-VISTA antibodies.

In the board's view, screening a pool of anti-VISTA antibodies for antagonistic properties using the MLR assays described in the application as filed and further selecting therapeutically interesting clones on the basis of the described *in vivo* models can be considered routine and does not involve an undue burden for a person skilled in the art in the field of immunology.

Thus, on the basis of the teaching in the application as filed and in line with what is taught in the relevant prior art, such as document D13, a skilled person in the field of immunology would understand that an anti-VISTA antibody that is a "VISTA antagonist" is an antibody that blocks (inhibits or neutralises) the suppressive effects of VISTA on T cell responses. An antagonistic anti-VISTA antibody can accordingly be identified on that basis using the methods described in the application as filed.

The board does not agree with the respondent's assertion that the skilled person needed information on the number of antibodies to be tested before identifying a single antagonistic antibody, since this is an issue inherent to all screening methods.

As argued by the appellants, the skilled person would know that blocking antagonistic anti-PD-L1 antibodies would be suitable positive controls for selecting antagonistic anti-VISTA antibodies which act by deblocking the VISTA-mediated suppression of T cell proliferation (see also [0777] of the application as filed).

3.2.3 As argued by the opposition division, antagonistic anti-PD-L1 antibodies in general and their antagonistic properties, i.e. the properties to be screened for when trying to identify such PD-L1 antagonists, were known in the art, see e.g. documents D4, D17, D47 to D50, D54, D65 or D79. Thus, providing such antagonistic anti-PD-L1 antibodies was not an undue burden and was within the skilled person's capabilities.

3.2.4 Therefore, in the board's opinion, a person skilled in the art was able to provide antagonistic anti-VISTA antibodies on the basis of the teaching in the application as filed and anti-PD-L1 antibodies on the basis of what was known to the skilled person from the relevant prior art.

3.3 Suitability of the claimed antibodies for the claimed therapeutic effect

3.3.1 The independent claims have been drawn up as purpose-related product claims in accordance with

Article 54(5) EPC. The subject-matter is directed to an antagonistic anti-VISTA antibody and an antagonistic anti-PD-L1 antibody for use in treating cancer.

According to established case law of the boards of appeal of the EPO, attaining the claimed therapeutic effect is a functional technical feature of claims directed to medical uses.
Thus, under Article 83 EPC, the application as filed must render it credible that the claimed antagonistic anti-VISTA antibody and antagonistic anti-PD-L1 antibody are suitable for treating cancer unless this is already known to the skilled person at the filing date (see G 2/21, especially Reasons 74 and 77).

3.3.2 The appellants argued that the skilled person was able to repeat Example 26 on the basis of their knowledge and the teaching of the application as filed, such as Example 8, which described the effect of an example antagonistic anti-VISTA antibody on the regression of different tumours.

3.3.3 The respondent pointed to the data in the application as filed and to document D29 – an attempt by the respondent to rework Example 26 of the application as filed – as showing that neither an antagonistic anti-VISTA antibody or antagonistic anti-PD-L1 antibody alone nor a combination of them had any therapeutic effect on the growth of B16F10 tumour cells *in vivo*.

3.3.4 The board agrees with the opposition division that the validity of the negative results for the experiments performed in document D29 cannot be assessed as there are no controls to show that the anti-VISTA and anti-PD-L1 antibodies used in them were functional at all.

3.3.5 Moreover, the board has doubts about the reproducibility of the data provided in Example 26 of the application as filed. Apart from the lack of enablement of the antibodies 13F3 and MIH5 used (as discussed in points 3.1.2 and 3.1.3 above), essential parameters such as the amount of anti-VISTA and anti-PD-L1 antibodies applied, the drug administration route or the number of B16F10 tumour cells inoculated are missing in Example 26, nor is there any relevant reference to other examples in the document.

3.3.6 However, none of the claims requires a synergistic effect of the claimed treatment with an antagonistic anti-VISTA antibody and an antagonistic anti-PD-L1 antibody.
What matters is whether the skilled person would have reasonably expected, on the basis of the application as filed, the common general knowledge and the prior art, that an antagonistic anti-VISTA antibody together with an antagonistic anti-PD-L1 antibody would be suitable for treating cancer.

The application as filed shows that VISTA can suppress T cell-mediated responses (Example 3) and that an antagonistic VISTA-specific antibody enhances cell-mediated immune responses (Example 7).
Example 8 (see also Figures 20A to D) shows that treatment with an antagonistic anti-VISTA antibody reduced tumour growth in four different tumour models in which mice were inoculated subcutaneously with (A) MB49 (bladder carcinoma), (B) MCA105 (fibrosarcoma) or (C) EG7 (thymoma) tumour cells, or (D) intraperitoneally with ID8 (ovarian cancer) tumour cells, and treated with 300 µg antibody every other day beginning one day after inoculating B6 mice with the respective tumour cells, i.e. day +1. Thus, the

application as filed/patent credibly shows that an antagonistic anti-VISTA antibody has an anti-cancer therapeutic effect *in vivo*.

This is consistent with the teaching of prior art document D13, which discloses that VISTA negatively regulates T cell responses and shows that an anti-VISTA antagonistic antibody interferes with VISTA-induced suppression of T cell responses by VISTA-expressing antigen-presenting cells *in vitro* (see abstract, Figure 10).

As argued by both parties, the anti-cancer effects of anti-PD-L1 antibodies were part of the common general knowledge represented by e.g. document D46 (as also cited in the application as filed in paragraph [0018]) and discussed in document D4 or D17.

Thus, on the basis of the evidence in the application as filed, and having regard to the common general knowledge and the prior art, it was credible and predictable for the skilled person at the filing date that an antagonistic anti-VISTA antibody in combination with an antagonistic anti-PD-L1 antibody was suitable for treating cancer by activating anti-cancer immunity in a subject.

3.4 Document D85 discloses that mice developed strong immune responses against the antagonistic anti-VISTA 13F3 antibody, presumably leading to fast clearance of 13F3. In fact, after a week of continuous treatment no 13F3 antibody could be detected any longer in the serum 24 hours after injection of the antibody (see page 1934, right-hand column, second half of first full paragraph).

The respondent cited this document in support of its argument that there was insufficient disclosure for the claimed medical use. However, the scientific report D85 goes on to explicitly state that "*[d]espite the apparent immunogenicity and short half-life of 13F3 in vivo, 13F3 treatment significantly suppressed tumor growth in the B16OVA model*" (see page 1934, right-hand column, second full paragraph). Thus, this document does not support the respondent's objection.

3.5 In view of the above considerations, the board is of the view that the application as filed discloses the claimed invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art as per Article 83 EPC.

4. Remittal to the department of first instance - Article 111(1) EPC

The appellants requested that the case be remitted back to the opposition division for consideration of the grounds of opposition under Article 100(a) EPC. The decision under appeal did not deal with objections under novelty (Article 54 EPC) and inventive step (Article 56 EPC). Thus, there are special reasons to remit the case to the opposition division for further prosecution, as requested by the appellants (Article 11 RPBA).

Order

For these reasons it is decided that:

- The decision is set aside.
- The case is remitted to the opposition division for further prosecution.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated