Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 13 May 2025

Case Number: T 2552/22 - 3.3.04

Application Number: 15156647.8

Publication Number: 2905030

IPC: A61K39/00, C07K17/00, A61K39/395, A61K51/10, C07K16/28

Language of the proceedings: EN

Title of invention:
Human antibodies that bind lymphocyte activation gene-3 (LAG-3) and uses thereof

Patent Proprietor:
E. R. Squibb & Sons, L.L.C.

Opponent:
Regeneron Pharmaceuticals, Inc.

Headword:
Anti-LAG-3 antibodies

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 12(4), 12(6)

Keyword:
Inventive step - obvious alternative
Amendment to case - amendment within meaning of Art. 12(4) RPBA 2020 (yes) - admitted (yes)

Decisions cited:
G 0001/24, T 0415/11, T 0524/17

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0

Case Number: T 2552/22 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 13 May 2025

Appellant I: (Patent Proprietor)	E. R. Squibb & Sons, L.L.C. Route 206 & Province Line Road Princeton, NJ 08540 (US)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Appellant II: (Opponent)	Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown NY 10591 (US)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 4 October 2022 concerning maintenance of the European Patent No. 2 905 030 in amended form**

Composition of the Board:

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

Summary of Facts and Submissions

I. The patent proprietor (appellant I) and the opponent (appellant II) each filed an appeal against the decision of the opposition division that European patent No. 2 905 030 in amended form based upon auxiliary request 5b met the requirements of the EPC.

II. In the present decision, the parties will be referred to by their respective roles in the opposition proceedings, i.e. patent proprietor and opponent.

III. The patent had been opposed on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and of Article 100(b) and (c) EPC.

IV. With its statement of grounds of appeal, the patent proprietor filed sets of claims of auxiliary requests 1a to 1g, 2, 2a to 2g, 3, 3a to 3f, 4, 4a to 4f.

V. With its statement of grounds of appeal, the opponent filed Annexes 1 to 6, representing submissions made during the opposition proceedings. Annex 1, which was filed as D45 during opposition proceedings, was renumbered as D48 by the board. The opponent also filed documents D45 to D47.

VI. The parties replied to each other's statements of grounds of appeal.

VII. The board issued a summons to oral proceedings and informed the parties of its preliminary opinion on the appeal case in a communication under Article 15(1) RPBA.

VIII. The opponent provided further comments in light of the board's communication.

IX. Oral proceedings before the board were held as scheduled, in the presence of the patent proprietor and the opponent. During oral proceedings, the patent proprietor withdrew all auxiliary requests of the 2, 3 and 4 series and maintained the main request and auxiliary requests 1a to 1g. At the end of the oral proceedings, the Chairman announced the decision of the board.

X. Claim 1 of the main request (patent as granted) and of auxiliary request 1a reads as follows:

"1. An isolated human monoclonal antibody, or an antigen-binding portion thereof, which binds human Lymphocyte-activation gene 3 (LAG-3) and binds an epitope of human LAG-3 comprising the amino acid sequence of SEQ ID NO: 77."

Claim 1 of auxiliary request 1b contains the following addition:
"1. ..., wherein the antibody exhibits at least one of the following properties:
(a) binds monkey LAG-3;
(b) does not bind mouse LAG-3;
(c) inhibits binding of LAG-3 to major histocompatibility (MHC) class II molecules; and
(d) stimulates an immune response."

Claim 1 of auxiliary request 1c contains the following addition:
"1. ..., wherein the antibody binds monkey LAG-3"

Claim 1 of auxiliary request 1d contains the following addition:
"1. ..., wherein the antibody does not bind mouse LAG-3."

Claim 1 of auxiliary request 1e contains the following addition:
"1. ..., wherein the antibody inhibits binding of LAG-3 to major histocompatibility (MHC) class II molecules."

Claim 1 of auxiliary request 1f contains the following addition:
"1. ..., wherein the antibody stimulates an immune response."

Claim 1 of auxiliary request 1g (identical to claim 2 of the main request, patent as granted) reads as follows:

"1. An isolated human monoclonal antibody, or an antigen-binding portion thereof, which binds human Lymphocyte-activation gene 3 (LAG-3) and binds to the same epitope on human LAG-3 as a reference antibody, said reference antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 37 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 43."

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

D1 WO2010/019570, earlier application as filed.

D2 Triebel et al., J Exp Med, 1990, 171:1393-1405.

D3 Huard et al., PNAS, 1997, 94:5744-5749.

D5 Baixeras et al., J Ex Med, 1992, 176:327-337.

D6 Huard et al., Eur J Immunol, 1994, 24:3216-3221.

D7 Huard et al., Eur J Immunol, 1996, 26:1180-1186.

D9 Maçon-Lemaître and Triebel, Immunology, 2005, 115:170-178.

D10 Huang et al., Immunity, 2004, 21:503-513.

D11 Workman et al., Eur J Immunol, 2002, 32:2255-2263.

D12 Workman and Vignali, The J of Immunol, 2005, 174:688-695.

D13 Workman and Vignali, Eur J Immunol, 2003, 33:970-979.

D14 Huard et al., Immunogenetics, 1994, 39:213-217.

D15 Huard et al., Immunology Letters, 1998, 61:109-112.

D16 US 6,197,524

D17 Declaration Jeanette L. Fairhurst, 4 August 2020

D18 Huard et al., Eur J Immunol, 1995, 25:2718-2721.

D45 Declaration Nicolin Bloch, 13 February 2023

D48 Annex 1, experimental results, filed on 13 July 2022

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

Main request
Claim construction - claim 1

The skilled person would understand claim 1 as defining an antibody that is capable of binding to SEQ ID NO: 77, with certain amino acids within this sequence being critical for the antibody's binding. This understanding was supported by the peptide scan experiment conducted in the patent (Example 3C), which demonstrated that monoclonal antibody 25F7 specifically bound to SEQ ID NO: 77.

In the field of antibody technology, it was well established that a monoclonal antibody bound to an epitope on an antigen through specific interactions between the antibody's paratope and the epitope. These specific interactions resulted in a defined degree of binding, which was more than the generalized "any degree of binding" suggested by the opponent. The definition in claim 1 did not permit arbitrary binding, but instead required specific binding.

From the peptide scan and the human versus rhesus experiments in Example 3 it was evident that residue H63 which was the first residue of SEQ ID NO: 77 was not mandatory for binding by antibody 8B7. As also stated in the patent the antibodies 25F7 and 8B7 had different epitopes on LAG-3. Antibody 8B7 was therefore not covered by the scope of the claim.

Admission of document D45 (Article 12(4) and 12(6) RPBA)

Document D45 represented an amendment to the opponent's appeal case. The opponent had had the opportunity to present this data earlier in the proceedings. The relevance of data on antibody 8B7 to the issues under consideration was not subject to change based on the opposition division's perspective on claim construction which had remained consistent throughout the proceedings. It was the amendment in auxiliary request 5b, which had already been filed with the reply to the notice of opposition and added "which epitope comprises" to claim 1, that convinced the opposition division that the claim was to be interpreted in alignment with one of the two claim interpretations suggested in the preliminary opinion (point 10.1 of the communication annexed to the summons to oral proceedings dated 10 May 2021). In the first Lag3-CD3z reporter assay (filed as Annex 1, D48, on 13 July 2022) the opponent sought to compare the functional activity of three antibodies encompassed by the invention: 25F7, 8B7, and 26H10. However, they failed to compare the functional activity of these antibodies with that of the prior art antibody, 17B4.

The tests done in document D45 employed the same Lag3-CD3z reporter assay as Annex 1 (D48), but now included additional data on the prior art antibody 17B4. This late submission of data put the proprietor at a disadvantage because it left only four months to evaluate the data and respond accordingly with the reply to the statement of grounds of appeal. This time-frame was particularly short considering the opponent's decision to use their own assay rather than the one described in the patent.

It was the opponent who initially had claimed that antibody 17B4 represented the closest prior art antibody. According to document D17, antibody 17B4 was procured and tested by the opponent at an early stage in the proceedings, but not included in the data of Annex 1 (D48). The document therefore could and should have been filed during opposition proceedings.

Inventive step - claim 1

The prior art antibody 17B4, described by Prof. Triebel's group in document D5, could serve as a starting point for assessing inventive step, but the context of the document, which was aimed at exploring LAG-3 biology and not therapeutic application, should be taken into account when assessing obviousness.

The key distinction between the antibody claimed in the patent and the prior art antibody 17B4 lay in the epitope to which each antibody bound. While an additional distinction was that the claimed antibody was human and 17B4 was a murine antibody this was would not be further addressed. The results in the patent revealed that antibodies 25F7, 8B7, and 26H10, and to a lesser extent 25E3, successfully stimulated IL-2 production.

The additional data comparing the effectiveness of 25F7 and 17B4 in a 3A9 T-cell peptide stimulation assay showed that 25F7 induced a stronger IL-2 response than 17B4.

While antibody 8B7 might not be as potent as 25F7, it proved more effective in the 3A9 T-cell stimulation assay than 25E3 (see Table 8 of the patent). 25E3,

although binding to the extra loop, targeted a region more towards the N-terminal end of the extra loop, as outlined in Table 5 of the patent. A comparison of T-cell stimulation data for 8B7 and 25E3 reinforced the same trend: binding to the C-terminal part of the extra loop, where the epitope comprising SEQ ID NO: 77 was located, correlated with enhanced IL-2 production in the 3A9 T-cell stimulation assay as compared to anti-LAG-3 antibodies binding towards the N-terminal side of the extra loop, such as 25E3 and prior art 17B4.

The objective technical problem could be defined as providing an improved anti-human LAG-3 antibody.

The problem was solved by the claimed antibodies in a manner that was not obvious.

None of the antibodies characterized by Prof. Triebel's group would have directed a skilled person toward the invention at hand. There was also no reasonable expectation of success in producing anti-human LAG-3 antibodies that bound to the extra loop and still exhibited enhanced functional properties compared to prior art antibodies such as 17B4.

Even if the objective technical problem was formulated as providing an alternative anti-LAG-3 antibody, there was no incentive to create and utilise alternative antibodies, let alone ones directed to the epitope identified by the present invention. The documents published by the scientists at Jude Children’s Research Hospital and Johns Hopkins University School of Medicine (D10 to D13) which bound to the D2 domain of LAG-3 would rather have led the skilled person away from the claimed antibodies.

Auxiliary request 1g

Stay of proceedings in view of referral G 1/24 to the Enlarged Board of Appeal

If the board ignored the teaching of the description in its claim construction, a stay of the proceedings was requested in order to await the decision in case G 1/24 by the Enlarged Board of Appeal.

Claim construction - claim 1

The claim explicitly required that the claimed antibody bound to the same epitope as the reference antibody. Neither the constant regions nor the overall nature of the antibody would have been expected to alter the epitope of an antibody containing the VH/VL regions defined in the claim. Antibody 8B7 was not an embodiment of the claim because, as stated in the patent (paragraph [0241]), it did not bind to the same epitope.

Inventive step - claim 1

The same arguments as for the main request applied.

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

Main request
Claim construction - claim 1

Even if the epitope referred to in the claim was considered to comprise the amino acid sequence of SEQ ID NO: 77, the epitope could be larger than the recited sequence and was otherwise entirely undefined -

with respect to either size or structure, or any limitation to a linear or conformational epitope. Also, the patent did not provide any definition of what was understood by the term "epitope" as used in the claim. In line with the established case law, it had thus to be given its broadest technically sensible meaning. Antibody 8B7 was thus an embodiment of the claimed subject-matter.

Admission of document D45 (Article 12(4) and 12(6) RPBA)

The document was filed in reaction to a change of claim interpretation by the opposition division which became apparent only during the oral proceedings. In its preliminary opinion, the opposition division did not consider it necessary to address inventive step because it considered that the claimed subject-matter was not novel (see point 13.6.1 of the opposition division's preliminary opinion). Only from the written decision did the opponent learn that the opposition division had not taken the comparison with antibody 8B7 into account for assessing whether the alleged effect was achieved over the whole scope of the claim. The data in Annex 1 (D48) indicated (in supplementation to the data provided by the patent proprietor), that antibody 8B7 did not share the properties of antibody 25F7, and showed no improvement over prior art antibody 17B4. Document D45 brought together the data provided by the patent proprietor (comparing 25F7 and 17B4) and the data provided by the opponent (comparing 25F7 and 8B7) in one assay. The additional experimental evidence was therefore submitted at the earliest possible time and was a legitimate reaction to a development, which could not be predicted. It was also relevant to the appeal proceedings.

Inventive step - claim 1

Document D5 disclosing antibody 17B4, could serve as a starting point for assessing inventive step. Antibody 17B4 was raised against the extra loop (see page 329, end of right column) and inhibited binding of LAG-3 to MHC class II (see Figure 5). It was also known from document D9 that antibody 17B4 activated T cells and increased IL-2 production (see Figures 3 and 6). Following *arguendo* the patent proprietor' s own data, 17B4 bound to the N-terminal part of the "extra loop". 25F7 bound to a region adjacent thereto. Since the epitope could extend beyond SEQ ID NO: 77, in view of the "comprising" language, the difference between antibody 17B4 and the antibodies claimed in claim 1 was that the claimed antibodies bound to an adjacent or partially overlapping epitope.

The patent proprietor carried the burden of proof to demonstrate that a surprising technical effect had its origin in the distinguishing feature and was achieved over the whole claim scope. The patent proprietor had only shown an effect for the exemplified antibody, but not for all antibodies falling under the claim.

The the patent (see e.g. Table 8) and the experimental evidence provided by the opponent (documents D48 and D45) showed that an antibody disclosed in the patent and falling under the claim (antibody 87B) did not possess the improved effects alleged for antibody 25F7. This effect was thus not achieved over the whole scope of the claim.

The objective technical problem was thus the provision of alternative anti-human LAG-3 antibodies.

The extra loop that consisted of 30 amino acids was known in the art to be a good antigenic region that provided anti-human LAG-3 antibodies that blocked the binding between LAG-3 and MHC class II and led to T cell activation measurable by increased IL-2 production. The amino acid sequence of the small extra loop was known and the epitope comprising SEQ ID NO: 77 was simply one of the accessible epitopes in said extra loop. The epitope comprising SEQ ID NO: 77 was an arbitrary selection from this known binding region because no surprising technical effect was associated therewith. Moreover, the claimed antibodies were generated using standard technology. They thus lacked an inventive step.

Auxiliary request 1g

Request for stay of proceedings in view of referral G 1/24 to the Enlarged Board of Appeal

There was no reason to stay the proceedings because the claim could only be interpreted in a way that included antibody 8B7 in its scope, even after consulting the description. This was independent from a decision by the Enlarged Board of Appeal in case G 1/24

Claim construction - claim 1

The claim required antibody binding to an epitope. The epitope, however, was not defined by any sequence, but merely by the binding of a group of reference antibodies (that shared the recited the VL and VH sequences). The antibody variable regions only needed to comprise the recited sequences, thus the variable regions could have more amino acids. The size or

sequence of the constant regions was also not defined. The term "reference antibody" thus referred to a genus of antibodies with potentially unlimited structural attributes, e.g. having various isotypes and/or accessory sequences attached. The resulting epitope was thus not defined. The method used to determine the binding was also not defined. While a method such as e.g. peptide scan rather defined a binding region, more accurate methods such as X ray crystallography would determine which individual amino acids interacted with the antibody. Thus, by choosing how to determine the epitope of the reference antibodies, the skilled person might identify different epitopes. While two antibodies might bind the same epitope in the sense of binding region, the two antibodies might not bind the same amino acids within this region. The binding itself was also not defined. It was thus not required that the claimed antibodies bound the same epitope with equal strength as the reference antibody, nor was it required that the claimed antibody bound all of the amino acids of the "same epitope". Since antibodies 8B7 and 25F7 bound the same peptides in the peptide mapping experiments, they both were covered by the claim.

Inventive step - claim 1

The same arguments as for the main request applied.

XIV. The patent proprietor (appellant I) requests

- that the decision under appeal be set aside and the opposition be rejected, i.e. the patent be maintained as granted
- alternatively, the patent be maintained based on one of the sets of claims of auxiliary requests 1a to 1g

- the decision by the opposition division not to admit documents D41 to D43 be upheld
- documents D45 and D46 be not admitted into the appeal proceedings

XV. The opponent (appellant II) requests that
- the decision under appeal be set aside and the patent be revoked
- none of the auxiliary requests be admitted into the appeal proceedings
- documents D41 to D43 and D45 to D47 be admitted into the proceedings

Reasons for the Decision

Main request - claim 1
Claim construction

1. The parties did not agree on the claim construction for a number of different reasons. Only those reasons relevant to the present decision are addressed below.

"binds an epitope of human LAG-3 comprising the amino acid sequence of SEQ ID NO: 77"

2. The opponent was of the view that this feature referred to any epitope on human LAG-3 because the amino acid sequence of SEQ ID NO: 77 could be read as relating only to the human LAG-3 protein.

3. The board disagrees because the skilled person would not consider it technically meaningful to refer to an epitope as comprising a short sequence of eight amino acids on a protein, if this sequence was not the one contained in the epitope to which the claimed antibody binds. The board therefore considers the expression

"epitope of human LAG-3 comprising the amino acid sequence of SEQ ID NO: 77" to refer to an epitope which comprises the amino acid sequence of SEQ ID NO: 77.

4. The board recalls that the term "epitope", as understood by the skilled person at the relevant date of the patent, does not refer to an exact amino acid sequence or a specific number of amino acids in a protein target which together form the epitope. Rather the determination of an "epitope" of a particular antibody depends on the assay method used and the parameters with which the assay is carried out. Different assays can, as also pointed out by the opponent, measure different properties of an epitope, e.g. functional or structural ones, and thus result in different amino acids being included or not included as part of an epitope for a given antibody on a given target. Examples of functional assays are e.g. peptide mapping (see patent, Example 3) or alanine scanning, examples of structural assays as provided by the opponent during oral proceedings are e.g. cryo-electron microscopy, X-ray crystallography or hydrogen deuterium exchange (HDX) combined with mass spectrometry (MS).

5. Furthermore, the parties at oral proceedings were in agreement that the phrase "binds an epitope" used in the claim, would not be understood as requiring that the antibody binds to all amino acids within the epitope. Rather the skilled person would have known that some amino acids in an epitope might be required only for the appropriate spacing or orientation of other residues which are in direct contact with residues of the antibody. It was also common general knowledge that epitopes are limited in size, because an antibody can only engage with a limited number of amino acids, e.g. between six and ten amino acids (see

epitope mapping in Example 3C and Table 5 in the patent). The epitope "comprising the amino acid sequence of SEQ ID NO: 77" can therefore be understood as slightly extending to either side of the eight amino acids represented by SEQ ID NO: 77 or as possibly including a few additional amino acids from other regions of the protein which are in spatial proximity due to the 3D-structure of the LAG-3 protein, but it would have been clear that the epitope cannot include, for example, the whole extra loop of 30 amino acids. This was not disputed by the parties.

6. Since neither the method of determining the epitope nor the extent of binding are defined in the claim, the broadest technically sensible interpretation of the term "epitope" has to be adopted (see Case Law of the Boards of Appeal of the EPO, 10th edition 2022, II.A.6.1). In view of the above considerations and for the purpose of this decision, the board considers an epitope to be the region in a protein that is necessary and sufficient to permit specific binding of an antibody.

Antibody 8B7 as an embodiment of the claim

7. During the oral proceedings, the patent proprietor stated that it was of the view that antibody 8B7 was not an embodiment of the claimed subject-matter because this antibody did not bind an epitope "comprising the amino acid sequence of SEQ ID NO: 77", as required by the claim. The antibody 8B7 might bind to an overlapping region, but as the patent stated in paragraph [0241] "*the 25E3, 25F7 and 8B7 antibodies bind to different although closely located epitopes within human LAG-3*". This argument was raised for the first time in appeal at the oral proceedings and there

is no record of it having been raised in the opposition proceedings.

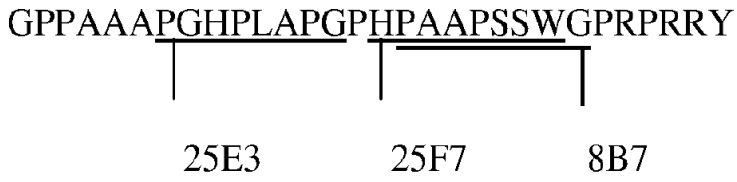
8. The opponent did not object to the admission of this new argument in appeal and the board decided to admit this submission from the patent proprietor. Moreover, in view of the claim construction adopted (see below) the board deems it not necessary to provide reasons for its admission.

9. The patent proprietor's claim construction is in apparent contradiction to the submission made in its reply to the appeal in point 211 where, when discussing the presence of an improved effect linked to all antibodies binding SEQ ID NO:77 in the context of inventive step (see point 210), it argued that "*If the opponent intended to prove that 8B7 does not perform better than 17B4 in their T cell activation assay, which differs from the one used in the patent, they should have compared the two antibodies as part of their first series of experiments. The opponent's indirect comparison of 8B7 and 17B4 via 25F7 data cannot undermine the robust evidence we have provided through the direct comparison of 25F7 and 17B4*". By asking for comparative data on antibody 8B7 with the prior art antibody 17B4, the patent proprietor can be understood to have taken the view that antibody 8B7 falls under the claim. The new claim construction also appears to contradict point 214 of the patent proprietor's reply to the appeal where it is stated that "*Notably, while 8B7 may not be as potent as 25F7, it proved more effective in the 3A9 T-cell stimulation assay than 25E3.* [...] *A comparison of T-cell stimulation data for 8B7 and 25E3 reinforces the same trend: binding to the C-terminal part of the extra loop, where the epitope comprising SEQ ID NO: 77 is*

located, correlates with enhanced IL-2 production in the 3A9 T-cell stimulation assay as compared to anti-LAG-3 antibodies binding towards the N-terminal side of the extra loop, such as 25E3 and 17B4."

10. The apparent change in claim construction adopted by the patent proprietor enforces the view that the skilled person would have considered antibody 8B7 as an embodiment of the claim.

11. According to the patent "*the 25F7 antibody recognized a region within the extra loop comprising the amino acid sequence HPAAPSSW (SEQ ID NO: 77) and 8B7 appeared to recognize a region within the extracellular loop comprising the amino acid sequence PAAPSSWG (SEQ ID NO: 78)*" (paragraph [0240]). This conclusion was based on a peptide scan experiment wherein both antibodies, 25F7 and 8B7, bound equally well (++) to immobilised peptides PGP**HPAAPSSW**G (SEQ ID NO: 86), P**HPAAPSSW**GPR (SEQ ID NO: 87; highlighting of residues corresponding to SEQ ID NO: 77 by the board). Peptide **PAAPSSW**GPRPR (SEQ ID NO: 88) which lacks the N-terminal histidine of SEQ ID NO: 77 was bound less strongly by antibody 25F7 (+). The patent further states in paragraph [0241] that "[t]*he regions identified in this study are underlined in the full-length extra loop sequence*" and depicts this with the regions for 25F7 and 8B7 shifted by one amino acid:



12. While recognising a slightly stronger dependence on the N-terminal histidine in SEQ ID NO: 77 (**H**PAAPSSW) by

antibody 25F7 compared to antibody 8B7, the board cannot see how these results could lead the skilled person to the conclusion that antibody 8B7 does not bind an epitope comprising the amino acid sequence of SEQ ID NO: 77. On the contrary, as the data in Table 5 in the patent shows, antibody 8B7 binds strongly (++) to both peptides (SEQ ID NO: 86, 87) which contain SEQ ID NO: 77 in its entirety, i.e. in the peptide scan assay antibody 8B7 binds to an epitope "comprising the amino acid sequence of SEQ ID NO: 77".

13. The patent proprietor cited the comparative experiment performed with human and rhesus LAG-3 (Table 6 in the patent) as further evidence. In this experiment antibody 25F7 bound poorly to the rhesus LAG-3 extra loop while antibody 8B7 maintained binding. Since rhesus LAG-3 differed in the region corresponding to SEQ ID NO: 77 this was evidence that antibodies 25F7 and 8B7 bound different epitopes.

14. This line of argument does not convince the board. The rhesus extra loop has the following sequence (SEQ ID NO: 90 in paragraph [0242] of the patent): GPPAPAPGHPPAPGHRPAAPYSWGPRPRRY, i.e. the region corresponding to SEQ ID NO: 77 in human is H**R**PAAP**Y**SW or **R**PAAP**Y**SW depending on the alignment (differences to SEQ ID NO: 77 highlighted). While this might show that antibodies 25F7 and 8B7 have slightly different binding specificities, it does not resolve whether the presence of the divergent "R" or "Y" in the epitope made a difference or whether other sequences outside of the epitope influenced the conformational structure of the epitope (see definition in point 6. above). In any case, the experiment leading to the results in Table 6 does not show that antibody 8B7 does not bind "an epitope of human LAG-3 comprising the amino acid

sequence of SEQ ID NO: 77", i.e. the functional requirement set out in claim 1, because antibody 8B7 binds the human LAG-3 extra loop comprising SEQ ID NO: 77 with high affinity (see Table 6) and also binds the two peptides comprising the entire amino acid sequence of SEQ ID NO: 77 as shown in Table 5 for SEQ ID NOs: 86 and 87.

15. The board thus concludes that antibody 87B binds to an epitope comprising the amino acid sequence of SEQ ID NO: 77 and is thus an embodiment of the claimed subject-matter.

Admittance of document D45 (Article 12(4) and 12(6) RPBA)

16. Document D45 was filed for the first time by the opponent with its statement of grounds of appeal. According to Article 12(4) RPBA it thus represents an amendment of the opponent's appeal case which may be admitted only at the discretion of the board. According to Article 12(6) RPBA, the board shall not admit evidence which should have been submitted in the proceedings leading to the decision under appeal, unless the circumstances of the appeal case justify their admittance.

17. During oral proceedings, the board exercised its discretion and admitted document D45 into the appeal proceedings for the following reasons.

18. The evidence in document D45 serves to support the point made by the opponent that the effect alleged by the patent proprietor for the claimed antibodies was not achieved over the whole scope claimed. This argument was already presented by the opponent in its notice of opposition (see pages 47 to 51 under the

heading: "*The alleged effect is not supported by the data in the patent: 8B7 vs 25F7*"). At that stage of the proceedings the opponent relied on the data in the patent to support its argument (e.g. comparing IL-2 induction of antibodies 25F7, 8B7 and 25E3 in Table 8 of the patent) and on document D17, filed with the notice of opposition, in which the opponent had compared the functional activity of antibody 25F7 encompassed by the invention with the prior art antibody 17B4.

19. In its communication sent in preparation of the oral proceedings, the opposition division indicated "*that a discussion on inventive step is superfluous as long as the claims are not proven to be novel*" (point 13.6.1 therein) and since it was of the view that the claimed subject-matter was not novel, gave no indication about its view on the technical effect achieved by any difference between the claimed subject-matter and the prior art. It also stated that document D17 would have to be discussed, so that it cannot be said that the opposition division's communication triggered a need for the opponent to provide further evidence. At this stage, the opponent therefore could have, but actually had no reason to produce a direct comparison of antibodies 8B7 with prior art antibody 17B4.

20. Nevertheless, the opponent filed comparative data in Annex 1 (document D48) on 13 July 2022, i.e. before the final date set by the opposition division under Rule 116(1) EPC. In this document antibodies 25F7, 87B and 26H10 are compared to each other. The opponent concluded from these experiments that "*8B7, although reported to bind the same peptides as 25F7 (see table 5 of the patent) shows substantially different functional properties as 25F7. Also these additional data*

demonstrate that no particular benefit can be linked to the target region of SEQ ID NO:77" (see page 44 to 47 of the opponent's submission accompanying the comparative data in D48). In the decision under appeal the argument of the opponent with regard to the effect not being achieved over the whole scope was addressed in point 19.3.2 by stating "*It is conceded that antibody 8B7 falls within the scope in view of the resolution in Table 5, but this antibody too still shows a respectable IL-2 production. Moreover, the Proprietor has provided comparative data (Fig. 4 in the submission of 04-03-2021) showing conclusively that 25F7 outperforms 17B4 in this assay in a head-to-head comparison.*".

21. The board considers that only with the decision under appeal did it become apparent that the opposition division did not consider the evidence so far provided for antibody 8B7 sufficient to question that the effect was achieved over the whole scope ("*still shows a respectable IL-2 production*"). The new comparative data in document D45 therefore represents a legitimate and timely reaction to the findings in the decision under appeal. Its admittance is also allowable for reasons of fairness, since, after the issue of the decision, the burden was shifted to the opponent to show that the patent did not contain sufficient information that the effect was achieved over the whole scope.

22. In relation to the patent proprietor's submission that the time limit for replying to the appeal by the opponent was not sufficient to provide its own comparative data, it is noted that neither in the opposition proceedings nor in appeal did the patent proprietor attempt to counter the opponent's argument that the alleged effect was not achieved over the whole

scope claimed, by filing its own comparative data involving antibody 8B7. It rather chose to present for the first time at the oral proceedings before the board of appeal, a new argument that antibody 8B7 was not an embodiment of claim 1 (see point 7. above). Thus the argument of the patent proprietor that the time limit for replying to the appeal by the opponent was not sufficient to provide its own comparative data is not persuasive. Furthermore, the patent proprietor could have but did not request an extension of the time limit to provide a reply to the appeal by the opponents.

23. Document D45 is also considered relevant to the appeal proceedings and in view of its similarity to the earlier filed document D48 cannot be seen to present the patent proprietor or the board with complex new issues.

Inventive step
Starting point and differences

24. The parties agreed that the mouse monoclonal antibody 17B4 disclosed in document D5 was a suitable starting point for assessing inventive step.

25. The opponent maintained that document D17 showed that antibody 17B4 bound an epitope that comprised the amino acid sequence of SEQ ID NO: 77. The board finds the evidence presented by the patent proprietor convincing that this is not the case (see document D3, Table 1) and thus also agrees with the opposition division on this point (see point 19.3.1 in the decision under appeal). During the oral proceedings, the opponent albeit *arguendo* conceded to this point.

26. The relevant difference between antibody 17B4 and the claimed antibody is thus the binding site in the extra loop of LAG-3. While antibody 17B4 binds on the N-terminal side of the extra loop (see Table 1 in document D3), the claimed antibody binds to an epitope comprising the amino acid sequence of SEQ ID NO: 77 which is more C-terminal. The further difference of the claimed monoclonal antibody being human in contrast to the mouse monoclonal antibody 17B4 in document D5 was considered by both parties as not relevant for assessing inventive step.

Effect and objective technical problem

27. The effect arising from this difference was in dispute between the parties. The patent proprietor considered the epitope defined in the claim to result in antibodies which had improved properties compared to monoclonal antibody 17B4, as evidenced by increased IL-2 production (see Example 3c and Table 8 in the patent). The patent proprietor supported its view with post-published data directly comparing antibody 25F7 to prior art antibody 17B4 (see point 96 and Figure 4 of its statement of grounds of appeal). The opponent in contrast was of the opinion that such improved effect had only been shown for the specific antibody 25F7, but not for all antibodies binding to an epitope comprising the amino acid sequence of SEQ ID NO: 77 and relied on data for antibody 8B7 in this regard (documents D48 and D45).

28. It is established case law that for taking into account an effect for the formulation of the objective technical problem this effect has to be shown to be credibly achieved over the whole scope of the claim (see Case Law of the Boards of Appeal of the EPO, 10th

edition 2022, I.D.4.3.1). The burden to credibly demonstrate that the alleged technical effect could be achieved across the whole scope of the claim lies first with the patent proprietor (see e.g. Case Law of the Boards of Appeal of the EPO, 10th edition 2022 I.D. 4.3.1 and decision T 524/17 cited therein). In this regard decision T 415/11 is of relevance which found in Reasons 46.1: "*when the credibility that a technical effect is achieved by substantially all claimed compounds is at issue and in a situation where, it is prima facie unlikely that this is credible, it is not the opponent, but the patentee who has the burden of proving that the effect is achieved.*"

29. The alleged improved effect of increased IL-2 induction and improved stimulation of antigen-specific T cell response (see Table 8 in the patent) compared to the prior art antibody 17B4 thus should be achieved by substantially all antibodies "binding to an epitope comprising the amino acid sequence of SEQ ID NO: 77", including antibody 8B7, which is designated as a preferred antibody in the earlier application as filed (see document D1, page 20, lines 8 to 11) and is an embodiment of the claimed subject-matter (see claim construction in points 7. to 15. above)

30. The experiments in Table 8 of the patent, show that the IC_{50} range of IL-2 induction, a measure of stimulation of antigen-specific T cell response, by antibody 8B7 is substantially higher than that for antibody 25F7 (3.25-13.90 nM compared to 0.14-1.94 nM, respectively), i.e. less antibody 25F7 is required to block the interaction efficiently and thus increase IL-2 induction more strongly. The IC_{50} range of antibody 8B7, however, overlaps with that of 25E3 (3.88-70.78 nM), an antibody that binds to the N-

terminal part of the extra loop in a region overlapping with the binding region of prior art antibody 17B4 (compare mapping in the patent proprietor's statement of grounds of appeal, point 84 to 86, with paragraph [0241] in the patent, reproduced in point 11. above). From the data in the patent it can therefore be concluded that not all antibodies binding to an epitope comprising SEQ ID NO: 77 have an equally improved effect on IL-2 induction as antibody 25F7 compared to the antibody 17B4 of the prior art.

31. The experimental data submitted by the opponent during the opposition proceedings (D48) shows the scale of this difference, i.e. about ten-fold for antibody 25F7 compared to antibody 8B7 in a LAG-3 MHC class II binding assay (see Table 1 and Figure 1 in D48). The further experimental data submitted with the opponent's statement of grounds of appeal (D45) directly compares antibodies 25F7, 8B7 and 17B4 in the same assay and reveals that antibody 25F7 shows improved activity compared to prior art antibody 17B4, while antibody 8B7 does not show such improved activity (see Table 1 and Figure 2 in D45). The patent proprietor has not provided any evidence beyond that for antibody 25F7 to establish a link between the epitope defined in the claim and the alleged improved activity. In summary, there is data for two antibodies binding to an epitope comprising the amino acid sequence of SEQ ID NO: 77 on file: 25F7 with better activity and 87B with worse activity than the prior art antibody 17B4 disclosed in document D3. The board thus concludes that the effect of increased IL-2 induction or improved T cell activation has not been proven to be achieved over the whole scope of the claim, i.e. for all antibodies or antibody fragments binding to an epitope comprising the amino acid sequence of SEQ ID NO: 77.

32. This effect is therefore not to be taken into account in formulating the objective technical problem, which can thus be formulated as the provision of alternative human monoclonal antibodies binding to human LAG-3 protein.

Obviousness

33. Starting from the disclosure of document D5 and aiming to provide alternative antibodies specifically binding to human LAG-3 protein, the skilled person would have chosen the extra loop as an antigen for raising antibodies because document D5 discloses that "[a] *unique feature of the LAG-3 molecule is the presence of a 30-aa extra loop sequence in the first NH2 terminus Ig-like domain between B strands C and C'. Such a long extra loop structure has not been described in IgSF molecules*". Cross-reactivity with other IgSF molecules, e.g. CD4, which is not desirable could thus be avoided by targeting the extra loop. D5 furthermore discloses that antibodies (including 17B4) were "*generated by immunizing animals with a 30-aa peptide corresponding to the extra loop aa sequence*" (page 328, left column, first complete paragraph) and thus provides a straightforward method for generating antibodies against epitopes in the extra loop. The loop is not large (30 amino acids), so that the skilled person could have either chosen the whole loop for immunisation (as was done in document D5) or generated a limited number of 5 to 10 peptides covering the loop to use as immunogens as was routine in the art at the relevant date of the patent. Following this routine path of antibody generation, the skilled person would have arrived at the claimed subject-matter.

34. Document D5 also provided a motive for doing so by disclosing that an antibody binding to the extra loop was active in inhibiting LAG-3/HLA (human leukocyte antigen, the human version of the MHC) class II interaction: "[r]*osettes between LAG-3-positive COS cells and Raji* [expressing HLA class II] *were specifically inhibited in a dose-dependent manner by the LAG-3-specific 17B4 mAb (Fig. 9 A)*" (page 333, right-hand column, second paragraph and Figure 9) and *"the formation of rosettes between LAG-3-transfected COS-7 cells and HLA class II bearing B lymphocytes, which is specifically dependent on LAG-3/class II interaction as shown in blocking experiments using 17B4 and anti-class II mAbs*" (page 334, right-hand column).

35. The opposition division reasoned that "[a]*ttainement of the same effect by binding to a different epitope could already have been surprising and sufficient for the claimed antibodies to qualify as a non-obvious alternative*" (point 19.3.2 of the decision under appeal). The board does not agree with this reasoning because at the relevant date it was straightforward and routine to generate antibodies binding to the extra loop (see above). In view of the statement in document D5 that "*this extra loop does not disrupt the core of the IgSF fold that consists of β strands A, B, E and G, F, C, and therefore may be exposed to the solvent outside the hydrophobic Ig fold (1)*" (page 328, left column, first complete paragraph) together with the proposed 2D-structure of domain 1 of LAG-3 in document D2 (see Figure 1), the skilled person also had a reasonable expectation of success to obtain such alternative antibodies.

36. The patent proprietor further argued that the disclosure in a number of prior art documents would have steered a skilled person away from the claimed invention. In documents from Prof. Triebel's group (e.g. documents D3, D5, D6, D7, D9, D14, D15, D16, D18), traditional anti-LAG-3 antibodies, including 17B4, were frequently used for investigating the role of this molecule in the immune response. In these documents there was no incentive to contemplate creating and utilising alternative antibodies, let alone ones directed to the epitope identified in the patent. In contrast, the documents originating from scientists at St. Jude Children's Research Hospital and Johns Hopkins University School of Medicine, i.e. a different research group, disclosed a different antibody, C9B7W (rat IgG1), which bound within the D2 domain and not in the D1 domain containing the extra loop (see e.g. documents D10 to D13). This antibody would have been more of interest to the skilled person because it was an anti-murine LAG-3 antibody which was useful in mouse cancer models and thus would have led the skilled person away from the claimed invention.

37. The board does not agree. In view of the objective technical problem being the provision of alternative antibodies binding to the human LAG-3 protein (see point 32.), the skilled person did not need additional motivation to look for such antibodies. It is also established case law that the skilled person would take into account any alternative known in the underlying technical field (unless the closest prior art teaches away from it). In such cases it might not be required to justify the selection of a particular solution, because it was assumed that an invention based on incorporating known features for the sole purpose of establishing novelty must be rendered obvious by a

corresponding step of selecting any alternative known in the art (see Case Law of the Boards of Appeal of the EPO, 10th edition 2022 I.D.4.5). The board is furthermore of the view that documents disclosing alternative approaches to that of the closest prior art cannot "undo" the teaching of the closest prior art unless the disclosure in these documents amounts to a prejudice generally known and recognised in the field (see Case Law of the Boards of Appeal of the EPO, 10th edition 2022, I.D.10.2). In other words, the fact that another research group targeted a different epitope in mouse LAG-3 would not have dissuaded the skilled person from seeking alternative antibodies targeting the extra loop in human LAG-3, the functional importance of which had already been shown in document D5 (see point 34. above). As the antibodies in documents D10 to D13 were targeted against mouse LAG-3 which has a low degree of homology (about 36%) in the extra loop to human LAG-3, (see opponent's reply to the appeal), the skilled person would, in any case, not have adopted the teaching of those documents when starting from the disclosure of document D5 and aiming at alternative antibodies against human LAG-3.

38. Furthermore, claim 1 is directed to a product, i.e. not limited to any particular use. The alternative antibody sought by the skilled person could therefore also have any possible use, including in research, diagnostic or therapy and did not need to be suitable for e.g. a therapeutic use.

39. During oral proceedings before the board, the patent proprietor argued that it would not have been obvious for the skilled person to generate the claimed antibodies, even if the objective technical problem was formulated as the provision of alternative antibodies

binding to human LAG-3 because the method to generate antibodies used in the patent relied on immunisation with Fc-fusion proteins comprising the entire extracellular region (domains 1-4) or extracellular domains 1 and 2 of human LAG-3 (see Example 1 in the patent). This was different from the method used in document D5 which employed only the extra loop peptide coupled to tetanus toxoid. The method of document D5 had yielded antibody 17B4 and a competing antibody 4F4, but no antibody against the more C-terminal part of the extra loop.

40. Apart from this argument having been raised very late in the appeal proceedings (i.e. during oral proceedings in appeal) the board has not been presented with any evidence or conclusive argument that the method disclosed in document D5 was inherently not suitable to provide antibodies to the C-terminal part of the extra loop. The available evidence (e.g. D5, D9, D16) rather indicates that the extra loop is solvent accessible and immunogenic. The skilled person would therefore not have encountered any hurdle to generate antibodies also to the C-terminal part of the 30 amino acid long extra loop which only contains 3 to 5 overlapping epitopes (see depiction in paragraph [0241] of the patent).

41. The patent proprietor further argued that document D5 taught away from antibodies binding in the extra loop because it could not detect inhibition of HLA class II-dependent cellular responses (see document D5, page 335, left-hand column, last paragraph). The board does not find this argument convincing because in the following sentence the authors explain that "[t]*he absence of inhibition of HLA class II-dependent cellular responses by 17B4 may relate to the complexity of cellular interactions known to involve other*

molecules expressed on activated lymphocytes (e.g., CD4/HLA class II, LFA-1/ICAM-1, or CD2/LEA-3). In addition, these initial experiments designed to assess primary in vitro stimulation might be inappropriate to detect inhibitory effects of anti-LAG-3 mAb because cells are already committed to proliferate when the LAG-3 protein is expressed at the cell surface." The skilled person therefore had no reason to assume that antibody 17B4 was ineffective in inhibiting HLA class II-dependent cellular responses given the positive results on inhibition of HLA class II interaction (see Figure 9 in document D5). The inhibitory activity of antibody 17B4 was also confirmed by later published documents which the skilled person would have consulted to obtain more information about antibody 17B4 and the relevance of the extra loop. Document D9, for example, shows in Figure 6 increased production of IL-2 (a Th1 cytokine) by inhibiting the LAG-3/MHC class II interaction with antibody 17B4.

42. In conclusion, and taking all of the above considerations into account, the subject-matter of claim 1 lacks an inventive step (Article 56 EPC).

Auxiliary requests 1a to 1g
Admittance (Article 12(4) RPBA)

43. The board exercised its discretion to admit the requests into the appeal proceedings. In view of the finding on inventive step (see below) the board does not consider it necessary to provide reasons for admitting them.

Auxiliary requests 1a to 1f
Inventive step (Article 56 EPC) - claim 1

44. Claim 1 of these requests include antibody 8B7 as an embodiment because this antibody also (a) binds monkey LAG-3; (b) does not bind mouse LAG-3; (c) inhibits binding of LAG-3 to major histocompatibility (MHC) class II molecules; and (d) stimulates an immune response (see examples in the patent). The patent proprietor has also not provided arguments to the contrary. The claimed subject-matter therefore lacks an inventive step for the same reasons as outlined for the main request (see points 24. to 42. above).

Auxiliary request 1g
Claim construction - claim 1

Stay of proceedings in view of referral G 1/24 to the Enlarged Board of Appeal

45. During oral proceedings, the patent proprietor requested that the proceedings be stayed in case the board was considering not taking the disclosure in the description into account to interpret claim 1 of auxiliary request 1g. The board notes that for claims referring to sequences (e.g. with SEQ ID NOs) it is in most cases not possible not to refer to at least the sequence listings, which are a part of the description, and which are often the only part of the patent or patent application where the full sequence information can be found. This is also the case here. The board thus consulted the description in order to know to which sequences SEQ ID NOs: 37 and 43 refer. In the present case, the board also took the description and the figures into account to identify the epitope to which a "reference antibody comprising a heavy chain

variable region comprising the amino acid sequence of SEQ ID NO: 37 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 43" binds (see paragraph [0221]; Figures 1A, 1B, 7 and 8 and description thereto). This information cannot be deduced from the claims alone and is also not common general knowledge. As is evident from the claim interpretation above (see points 7. to 15.) the board also consulted paragraph [0241] of the description and the experimental results in Table 6 as relied upon by the patent proprietor.

46. Since the board had to consult the description for claim construction, the condition for which the patent proprietor requested a stay of proceedings did not arise.

"*binds to the same epitope on human LAG-3 as a reference antibody*"

47. The variable heavy and light chains of an antibody in combination are the main determinants of its binding specificity. The epitope bound by a reference antibody having SEQ ID NOs: 37 and 43 as heavy and light chains, respectively, is therefore considered to be at least very similar to the epitope bound by antibody 25F7 which comprises these sequences (see paragraph [0221] and Fig. 1a of the patent).

48. The patent proprietor referred to paragraph [0241] in the patent which states that "*the peptide scan results indicate that the 25E3, 25F7 and 8B7 antibodies bind to different although closely located epitopes within human LAG-3*". This meant that antibody 8B7 was not an embodiment of claim 1 because it did not bind to the same epitope as the reference antibody 25F7 which had

SEQ ID NOs: 37 and 43 as heavy and light chains, respectively. The objective technical problem in view of the disclosure of document D5 was therefore the provision of an improved human monoclonal antibody binding human LAG-3.

49. The board does not agree with this argument because the claim does not exclude reference antibodies of different isotypes or with additional accessory sequences ("comprising") compared to the antibody 25F7 tested in the patent. The expression "binds to the same epitope" thus leaves the epitope defined only by reference to a binding entity which is itself not exactly defined. The claim also does not define the method or parameters to be used when determining the epitope of the reference antibody nor what "binding" means. The board therefore adopts the broadest technically sensible interpretation of the feature "binds to the same epitope on human LAG-3 as a reference antibody" in the claim which is that the epitope bound by the reference antibody comprises the sequence with SEQ ID NO: 77. As outlined with regard to claim construction of claim 1 of the main request this includes antibody 8B7 (see points 7. to 15. above).

Inventive step (Article 56 EPC) - claim 1

50. Since the claimed subject-matter includes antibody 8B7, it lacks an inventive step for the same reasons as outlined for the main request (see points 24. to 42. above).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

A. Vottner A. Chakravarty

Decision electronically authenticated