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Datasheet for the decision of 16 September 2020

Case Number: T 1628/16 - 3.3.04

Application Number: 06748745.4

Publication Number: 1866339

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Language of the proceedings: EN

Title of invention:
GITR binding molecules and uses therefor

Patent Proprietor:
GITR, Inc.

Opponents:
Bristol-Myers Squibb Company
Amgen Inc.
Zwicker, Jörk

Headword:
GITR binding molecules/GITR

Relevant legal provisions:
EPC Art. 123(2), 56

Keyword:
Amendments - added subject-matter (yes)
Inventive step - (no)

Decisions cited:
T 0512/94, T 0735/00

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Case Number: T 1628/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 16 September 2020

Appellant: (Patent Proprietor)	GITR, Inc. 55 Cambridge Parkway, Suite 102 Cambridge, MA 02142 (US)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 9 May 2016 concerning maintenance of the European Patent No. 1866339 in amended form.**

Composition of the Board:

Chairwoman G. Alt
Members: A. Schmitt
R. Romandini

Summary of Facts and Submissions

I. The appeal lodged by the patent proprietor (appellant) lies from the opposition division's interlocutory decision maintaining European patent No. 1 866 339 in amended form. The patent, entitled "*GITR binding molecules and uses therefor*", derives from European patent application No. 06 748 745.4 which was filed as an international application under the PCT with the application number PCT/US2006/11114 and published as WO 2006/105021 ("application as filed" or "application").

II. The patent was opposed by three parties under Article 100(a) EPC on the grounds of lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) and under Article 100(b) and (c) EPC.

The opposition division decided that claim 17 of the patent as granted (and the same claim in auxiliary requests 1 and 2, and the corresponding claims 16, 12 and 2 in auxiliary requests 3, 4 and 5, respectively) extended beyond the content of the application as filed. The subject-matter of claim 1 of auxiliary request 6 (and of the same claim in auxiliary requests 7 and 8) was held not to involve an inventive step. Auxiliary request 9 was considered to meet the requirements of the EPC.

III. With the statement of grounds of appeal, the appellant filed auxiliary requests I to VI. It requested, *inter alia*, that the decision under appeal be set aside and the patent be maintained as granted (main request) or, alternatively, on the basis of the set of claims of any of auxiliary requests I to VI.

Claims 1 and 17 as granted read as follows:

"1. An isolated monoclonal antibody comprising a heavy chain and a light chain, or an antigen-binding fragment thereof, which antibody or antigen-binding fragment specifically binds glucocorticoid-induced TNFR family-related receptor (GITR), wherein said antibody or antigen binding fragment thereof comprises:
(a) the heavy chain complementarity determining region (CDR) amino acid sequences in SEQ ID NO:1 or SEQ ID NO. 66, wherein said heavy chain CDR amino acid sequences comprise amino acid residues 45-56 of SEQ ID NO: 1, amino acid residues 119-127 of SEQ ID NO:1, and one of amino acid residues 71-86 of SEQ ID NO:1 and amino acid residues 71-86 of SEQ ID NO:66; and
(b) the light chain CDR amino acid sequences in SEQ ID NO:2, wherein said light chain CDR amino acid sequences comprise amino acid residues 44-54 of SEQ ID NO:2, amino acid residues 70-76 of SEQ ID NO:2, and amino acid residues 109-117 of SEQ ID NO:2.

17. An isolated monoclonal antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment specifically binds glucocorticoid-induced TNFR family related receptor (GITR) at the same epitope as, and competes for binding to GITR with, the antibody or antigen-binding fragment of claim 1, 2, or 3."

Claim 1 of each of auxiliary requests I, II, III, V and VI is identical to claim 1 of the patent as granted.

Claim 17 of each of auxiliary requests I and II and claims 16 and 14 of auxiliary requests III and IV,

respectively, are identical to claim 17 of the patent as granted.

IV. The opponents did not appeal against the decision under appeal, and are thus respondents in the appeal proceedings (respondents I, II and III). All respondents requested that the appeal be dismissed.

V. The board scheduled oral proceedings as requested by all parties and subsequently issued a communication pursuant to Article 15(1) RPBA setting out its preliminary opinion.

VI. The oral proceedings were scheduled to take place on 31 March 2020. By a communication of the board's registry dated 23 March 2020, they were rescheduled to take place on 16 September 2020 in view of the communication of the President of the Boards of Appeal dated 20 March 2020 that oral proceedings would not be held at the premises of the boards of appeal until 17 April 2020 in view of the spread of the novel coronavirus (COVID-19).

VII. The appellant and respondents I and III were represented at the oral proceedings which took place on 16 September 2020. Respondent II did not attend the oral proceedings as previously announced in writing. At the end of the oral proceedings, the chair announced the board's decision.

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

D19 "Anti-human GITR/TNFRSF18 Monoclonal Antibody" R&D Systems catalogue excerpt, 21 September 2004

D37 Declaration of José F. Ponte, Ph.D., including Appendix A

IX. The appellant's arguments, submitted in writing and during the oral proceedings, as far as relevant to the present decision, are summarised as follows.

Articles 100(c) and 123(2) EPC

Claim 17 as granted and corresponding claims in auxiliary requests I, II, III and IV

The application as filed disclosed (page 40, lines 17 to 33) generating antibodies and screening them for binding to a specific region or fragment of GITR. A further passage on page 11, lines 25 to 27 described methods for finding antibodies that bound to the same epitope as another antibody.

The skilled person would combine these passages with disclosures that the antibody 6C8 lay "*at the core of the invention*", as evident from the disclosure of the application as a whole, e.g. page 3, lines 3 to 6; page 5, lines 32 to 34; page 23, line 18 et seq. (submitted at the oral proceedings); and, in particular (submitted both at the oral proceedings and in writing), page 22, lines 30 to 31, the latter disclosing that the invention pertained to 6C8 binding molecules "*and other binding molecules with equivalent properties to 6C8*".

Combining these passages resulted in the disclosure of the subject-matter of claim 17.

Inventive step (Article 56 EPC)

Claim 1 of auxiliary requests V and VI

The closest prior art was the anti-human GITR antibody clone 110416 from the company R&D Systems ("the R&D antibody") disclosed in several prior-art documents, including document D19. The subject-matter of claim 1 differed from this antibody on account of the amino acid sequences of the six complementarity determining regions (CDRs).

The technical effect of this difference was an approximately ten-times higher binding affinity. This was demonstrated in Figure 16 of the patent, which showed a comparison between the binding affinity of the patent's antibody 6C8, comprising the six CDRs, and that of the R&D antibody. Since it was the CDRs that determined an antibody's binding specificity and affinity, not the framework regions, antibodies sharing the CDRs of the antibody 6C8 would also share its binding properties.

According to paragraph [0206] of the patent, changing the framework regions might reduce the affinity by a factor of 2 to 5, so even if that were the case the antibodies as claimed would still retain at least twice the affinity of the R&D antibody. As shown in document D37, an antibody comprising the six 6C8 CDRs in a human framework region even had a higher affinity than the 6C8 antibody, which supported the teaching of paragraph [0206].

Neither the opposition division nor the opponents had substantiated their assertion that changing the framework regions would affect the affinity to a

greater degree, and it was disputed that common general knowledge to this effect existed.

Moreover, the subject-matter of claim 1 involved an inventive step even if it was considered to be a mere alternative to the R&D antibody. It was established case law that recognising an inventive step did not require a better solution; an equal solution could also be inventive, as evident e.g. from decision T 1791/08 (Case Law of the Boards of Appeal, 8th edition, 2016, page 181). The R&D antibody had a high affinity in the nanomolar range. Routine antibody production methods would not be expected to lead to an antibody "*of even a comparable affinity to the R&D antibody without undue burden*".

X. The respondents' arguments, submitted in writing and during the oral proceedings, as far as relevant to the present decision, are summarised as follows.

Articles 100(c) and 123(2) EPC

Claim 17 as granted and corresponding claims in auxiliary requests I, II, III and IV

The application disclosed two different monoclonal anti-GITR antibodies, 6C8 and 2F8, and variants thereof. The scope of claim 17 extended the subject-matter beyond the two specific antibodies to those not disclosed in the application, on a functional basis.

The passages cited by the appellant in the application on pages 11 and 40 belonged to parts of the description concerning definitions and the production of binding molecules in general. They did not disclose an isolated monoclonal antibody or antigen-binding fragment thereof

that bound to a particular epitope, including the epitope of said antibody. Therefore, passages from these parts could only be introduced into a claim to explain an expression or term, but could not be used as a reservoir for new embodiments.

The passage on page 11 discussed using a competitive binding assay to identify binding molecules that recognised the same epitope, i.e. unidentified antibodies.

The passage on page 40 described two general methods for determining epitopes, including determining epitope specificity in a competition assay. These passages were not linked to a specific epitope or to a reference antibody, let alone the antibody of claims 1 to 3.

Inventive step (Article 56 EPC)

Claim 1 of auxiliary requests V and VI

The R&D antibody constituted the closest prior art, from which the subject-matter of claim 1 differed on account of the six specific CDR sequences.

However, the alleged technical effect of improved binding affinity was not shown over the whole scope of claim 1 because the claimed antibodies could contain any framework region. On page 32, lines 9 to 12, the patent application discussed the need for "back-mutations" in the human framework regions to preserve the binding affinity, thereby recognising the problem.

Moreover, it was common general knowledge that loss of binding affinity due to changes in the framework region of an antibody was not limited to a fivefold degree.

The problem to be solved could thus only be considered to be the provision of an alternative monoclonal anti-GITR antibody.

It was established case law of the boards of appeal (see for example T 906/91, T 512/94 and T 735/00) that an antibody obtained by routine methods was only inventive if it had surprising properties. Providing an alternative monoclonal anti-GITR antibody with no surprising properties, as was the case with that claimed in claim 1, was an arbitrary solution to the problem which did not involve an inventive step.

Reasons for the Decision

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

Articles 100(c) and 123(2) EPC

Claim 17 as granted and corresponding claims in auxiliary requests I, II, III and IV

2. In the decision under appeal the opposition division held that claim 17 as granted related to subject-matter extending beyond the content of the application as filed because there was no direct and unambiguous disclosure of an antibody or antigen-binding fragment thereof that specifically bound to GITR "*at the same epitope as, and compete[d] for binding to GITR with, the antibody or antigen-binding fragment of claim 1, 2, or 3*".

3. The appellant did not dispute that the application did not explicitly disclose an antibody that bound to GITR at the same epitope as, and competed for binding to GITR with, the antibody of claim 1, 2 or 3. It also agreed that the application did not disclose to which epitope the antibody of claim 1, 2 or 3 bound.

However, the appellant asserted that the passages on page 11, lines 25 to 27 and page 40, lines 27 to 31 of the application would have been "*implicitly understood to be relevant*" for the antibody 6C8, an embodiment of claim 1 which was "*at the core of the invention*". The disclosure on pages 11 and 40 in combination with the disclosure of this antibody, in particular on page 22, lines 30 to 31, thus resulted in the disclosure of the subject-matter of claim 17.

4. The board is not persuaded by this argument. The passage cited by the appellant on page 11, lines 25 to 27 is part of the chapter "I. *Definitions*" of the application. This chapter starts on page 10, line 22 with the definition of the terms "*GITR*" and "*binding molecule*". The sentence cited by the appellant (page 11, lines 25 to 27) follows the definition of the term "*epitope*" and reads "*Binding molecules that recognize the same epitope can be identified in a simple immunoassay showing the ability of one antibody to block the binding of another antibody to a target antigen, i.e., a competitive binding assay*".

This passage thus describes, in general terms, an assay for identifying binding molecules by screening candidate molecules for a particular property in relation to a reference binding molecule. Neither the candidate molecules nor the reference molecule are specified any further. This general description of a

screening assay does not constitute a direct and unambiguous disclosure of specific binding molecules resulting from the screening assay, let alone molecules that bind to the same epitope as and compete with the antibody defined in claim 1.

5. The second passage cited by the appellant in the application – page 40, lines 27 to 31 – is part of the general chapter "III. *Production of Binding Molecules*" starting on page 39. The paragraph on page 40 that includes the cited passage (lines 17 to 33) describes producing monoclonal binding molecules and screening them for binding to a specific region or fragment of GITR. The cited passage starting in line 27 discloses that "*[a]lternatively, epitope specificity can be determined by a competition assay in which a test and reference binding molecule compete for binding to GITR. If the test and reference binding molecule compete, then they bind to the same epitope (or epitopes sufficiently proximal) such that binding of one binding molecule interferes with binding of the other*".

This passage thus likewise describes, in a general manner, a screening assay to determine epitope specificity using undefined test and reference molecules. Therefore, as with the passage on page 11 discussed in point 4., the passage on page 40 does not directly and unambiguously disclose binding molecules resulting from this screening assay, let alone molecules that bind to the same epitope as and compete with the antibody defined in claim 1.

6. The appellant then argued that the skilled person would combine the cited passages on pages 11 and 40 with the antibody 6C8 because it lay "*at the core of the invention*". In particular, page 22, lines 30 to 31

disclosed that the invention pertained to 6C8 binding molecules "*and other binding molecules with equivalent properties to 6C8*".

7. However, there is no indication in the application that the "*equivalent properties to 6C8*" mentioned on page 22 include binding to the same epitope, as apparent from the properties subsequently listed as examples, which merely include binding affinity and GITR effector functions (page 22, lines 31 to 38). Therefore, contrary to the appellant's argument, the board does not believe that the skilled person would construe this disclosure to mean that this passage related to, and thus should be read in conjunction with, the general screening methods described on pages 11 and 40 of the application.

8. Consequently, the application as filed does not directly and unambiguously disclose an antibody or antigen-binding fragment thereof that specifically binds to GITR "*at the same epitope as, and competes for binding to GITR with, the antibody or antigen-binding fragment of claim 1, 2, or 3*".

9. Therefore, the subject-matter of claim 17 as granted extends beyond the content of the application as filed (Article 100(c) EPC and 123(2) EPC).

10. Claim 17 of each of auxiliary requests I and II and claims 16 and 14 of auxiliary requests III and IV, respectively, are identical to claim 17 of the patent as granted, so they do not meet the requirements of Article 123(2) EPC either.

Inventive step (Article 56 EPC)

Claim 1 of auxiliary requests V and VI

Closest prior art, technical effect and problem to be solved

11. The parties agreed that the "R&D antibody" disclosed, for example, in document D19 constituted the closest prior art and that the subject-matter of claim 1 differed from this antibody on account of the amino acid sequences of the six CDRs. The board has no reason to diverge from this assessment.

12. The parties, however, disagreed on the technical effect of this difference: the appellant considered it to be an increased binding affinity, as demonstrated for the patent's antibody 6C8 comprising the six CDRs, but the respondents argued that this effect was not achieved by all embodiments of the claim.

13. The appellant in particular disputed that it was common general knowledge that framework regions influenced an antibody's binding affinity, further arguing that a more than fivefold loss of affinity was not to be expected with antibody 6C8 for every framework encompassed by the scope of claim 1.

14. However, in its general disclosure, i.e the disclosure summarising the prior art, the patent corroborates the disputed common general knowledge that framework regions influence an antibody's binding affinity. This is evident from the section that describes binding molecules comprising framework-region and/or constant-region amino acid sequences derived from another species, such as human amino acid sequences (paragraph [0138] to paragraph [0206]).

This section discusses prior-art methods for selecting appropriate human variable-domain framework regions on the basis of different criteria such as CDR homology (paragraphs [0144] to [0144]), retention of the correct spatial orientation of the mouse variable-domain framework (paragraphs [0177] to [0178]) and homology to framework regions of the 6C8 binding molecule (paragraph [0179]). This section thus acknowledges that the framework regions influence the binding properties of the resulting antibodies to such an extent that "*appropriate human acceptor sequences*" (paragraph [0179]) must be selected according to specific criteria in order to maintain the desired binding properties.

15. Moreover, the subsequent section of the patent discloses that substituting residues in both the murine CDRs and the human framework regions may be necessary "*to optimize the properties of the resulting humanized binding molecule*" (first sentence of paragraph [0180]). Changing or substituting residues in the selected human framework regions, i.e. "*backmutations*", may be required "*so as to preserve the binding affinity of the humanized antibody*" (paragraph [0181]). In particular, framework residues in close proximity to the CDRs "*may distort the donor CDRs and reduce affinity*" (paragraph [0185]), and other framework residues may also interact with the CDRs and affect the affinity, as discussed in paragraphs [0186] to [0190]. This section of the patent therefore discloses that the selection of appropriate human acceptor sequences alone may still not be sufficient to maintain a desired binding affinity, thus further emphasising the influence of the framework regions on an antibody's binding affinity.

16. The board therefore concludes that the influence of the framework regions on an antibody's binding affinity was known to the skilled person, as acknowledged in and thus evident from the patent alone. No further evidence is required to substantiate this conclusion.

17. Secondly, the patent does not present any information or evidence that would suggest that a more than fivefold loss of affinity was not to be expected with antibody 6C8 for every framework encompassed by the scope of claim 1.

The appellant argued that paragraph [0206] of the patent provided such evidence. However, the board does not agree. Firstly, this passage discusses humanised binding molecules and the subject-matter of claim 1 is not restricted to these.

Secondly, this passage does not specifically relate to antibodies comprising the CDRs of the 6C8 antibody.

Thirdly, the upper and lower limits of the binding affinity of the humanised binding molecule compared with the donor immunoglobulin are merely indicated to be "*[u]sually*" and "*[o]ften*" within the indicated limit. The use of the term "often" in relation to the lower limit shows that the loss of affinity is not restricted to this particular lower limit. The patent thus does not contemplate any absolute limit as regards the loss of binding affinity.

Therefore, the disclosure of the patent does not support the appellant's assertion that a more than fivefold loss of affinity is not to be expected with antibody 6C8 irrespective of the selected framework regions.

18. The board thus holds that, contrary to the appellant's argument, not all embodiments of the claim achieve the technical effect of an increased binding affinity.

This being the case, the problem has to be formulated as the provision of an alternative monoclonal anti-GITR antibody.

Obviousness

19. The question to be answered when assessing the obviousness of the claimed subject-matter is whether or not the skilled person, faced with the technical problem as formulated above, would have provided an isolated monoclonal antibody as defined in claim 1 of the patent without inventive effort.

20. The respondents referred to established case law of the boards of appeal under which generating further monoclonal antibodies directed to a known target was a routine task for the skilled person and thus devoid of inventive merit unless the antibody exhibited unexpected properties or providing it was associated with unexpected difficulties. The board adheres to this case law (see e.g. the board of appeal decisions T 512/94, point 28 of the Reasons, and T 735/00, point 26 of the Reasons).

21. According to the appellant it was not a routine task to prepare further anti-GITR antibodies with a comparable affinity, i.e. in the nanomolar range, to the prior-art "R&D antibody".

22. However, the subject-matter of claim 1 is not restricted to antibodies having a binding affinity in

the nanomolar range. Furthermore, the appellant's assertion that it was not possible to prepare a further anti-GITR antibody with an affinity in the nanomolar range by routine methods is not supported by any evidence. The patent does not support this notion either because the 6C8 antibody was prepared by a routine method (see paragraph [0210] of the patent) and the patent did not report any apparent difficulties in this regard.

23. In light of this, the generation of the antibodies as defined in claim 1 was not associated with any unexpected difficulties. Furthermore, those antibodies do not possess unexpected properties (see point 18. above). This being the case, and in accordance with the established case law of the boards of appeal (see point 20. above), providing the antibodies as defined in claim 1 was a routine task for the skilled person devoid of inventive merit.

24. Consequently, the subject-matter of claim 1 of auxiliary requests V and VI does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

L. Malécot-Grob G. Alt

Decision electronically authenticated