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Datasheet for the decision of 22 March 2021

Case Number: T 1964/18 - 3.3.04

Application Number: 05825249.5

Publication Number: 1831258

IPC: C07K16/28, A61K39/395

Language of the proceedings: EN

Title of invention:
Monoclonal antibodies against NKG2A

Patent Proprietors:
Innate Pharma S.A.
Universita di Genova

Opponent:
Merck Sharp & Dohme Corp.

Headword:
Inhibitory anti-NKG2A antibodies/INNATE

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 1964/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 22 March 2021

Appellant: (Patent Proprietor 1)	Innate Pharma S.A. Immeuble Grand Pré 121, Ancien Chemin de Cassis 13009 Marseille (FR)
Appellant: (Patent Proprietor 2)	Universita di Genova Via L.B. Alberti 2 16132 Genova (IT)
Representative:	Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Respondent: (Opponent)	Merck Sharp & Dohme Corp. 126 East Lincoln Avenue Rahway, NJ 07065-0907 (US)
Representative:	Böhles, Elena Merck Sharp & Dohme Corp. 120 Moorgate London, EC2M 6UR (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 30 May 2018 revoking European patent No. 1831258 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	P. de Heij
Members:	O. Lechner
	R. Morawetz

Summary of Facts and Submissions

I. An appeal against the interlocutory decision of the opposition division to revoke European patent No. 1 831 258 ("patent") was filed by the patent proprietors ("appellants"). The patent has the title "*Monoclonal antibodies against NKG2A*".

II. The patent is based on European patent application No. 05 825 249.5, which had been filed as an international application and was published as WO 2006/070286.

III. The notice of opposition invoked lack of novelty (Article 54 EPC) and lack of inventive step (Article 56 EPC) under Article 100(a) EPC, as well as the grounds under Article 100(b) and (c) EPC as grounds for opposition.

IV. In the decision under appeal ("decision"), the opposition division dealt with a set of claims of a main request (corresponding to the claims as granted with the correction of typographical errors in claims 15, 22, 24, 26, 28 and 30), and sets of claims of two auxiliary requests. The opposition division decided that auxiliary request 1a (as filed during oral proceedings) complied with Articles 123(2) and (3), 84, and 54 EPC but did not involve an inventive step under Article 56 EPC.

V. Auxiliary requests 2 to 14 were withdrawn during the oral proceedings before the opposition division.

VI. With their statement of grounds of appeal, the appellants re-filed the main request and filed

auxiliary request 1 (corresponding to auxiliary request 1a of the decision under appeal), auxiliary requests 2 to 14 (corresponding to auxiliary requests 2 to 14 as withdrawn during the opposition oral proceedings with some amendments to auxiliary requests 3, 5, 6, 7 and 14), and new auxiliary requests 15 and 16. Moreover, four documents were filed.

VII. In its reply to the statement of grounds of appeal, the opponent ("respondent") submitted arguments to the effect that, *inter alia*, claim 1 of the main request lacked novelty (Article 54 EPC) and an inventive step (Article 56 EPC) and that claim 1 of auxiliary request 1 lacked inventive step (Article 56 EPC). The respondent also puts forward that "*[t]he same arguments which are presented above would also be relevant for Auxiliary requests 1 - 16*".

VIII. The board issued summons for oral proceedings to be held on 29 June 2020 followed by a communication providing the board's preliminary opinion on the appeal pursuant to Article 15(1) RPBA.

IX. By letter dated 4 June 2020, the appellants requested postponement of the oral proceedings due to the travel restrictions imposed by the SARS-CoV-2 pandemic.

X. The board set a new oral proceedings date for 22 and 23 March 2021 and at a later date ordered that the oral proceedings be held by videoconference.

XI. Subsequently, the respondent announced that it would not attend the oral proceedings.

XII. With a letter of 16 March 2021, the appellants provided arguments concerning the admittance of auxiliary requests 15 and 16 and filed new auxiliary request 17.

XIII. Oral proceedings took place as scheduled in the presence of the appellants.

During the oral proceedings, the appellants withdrew their main claim request. Auxiliary request 1, filed with the statement of grounds of appeal, became the new main request.

Claim 1 of the main request reads as follows:

"1. A monoclonal antibody or a fragment thereof characterized by:

a. specifically binding to NKG2A, wherein the antibody or fragment is characterized by binding the same epitope on NKG2A as the antibody produced by the cell deposited at the CNCM under accession number I-3549;

b. not specifically binding to human NKG2C;

c. not specifically binding to human NKG2E;

d. not binding, via its Fc region, to a human Fc gamma receptor; and

e. when bound to NKG2A on a human NK cell, causing said NK cell to lyse a target human cell bearing HLA-E or Qal^b on the target cell surface, when said target cell comes into contact with said NK cell."

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

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

D19: Guma M. *et al.*, "*Imprint of human cytomegalovirus infection on the NK cell receptor repertoire*", Blood (2004), volume 104, pp. 3664-3671

D20: US 2003/0095965 Al

D25: Exhibit by Dr L. Gauthier dated 13 February 2017

D38: Introduction of Morris, G.E., "Epitope Mapping of Protein Antigens by Competition ELISA"; in Walker, J.M. (eds) "The Protein Protocols Handbook", pp. 595-600; 1996

D39: Tzartos, S.J.,"Epitope Mapping by Antibody Competition"; in Morris G.E. (eds), Methods of Molecular Biology. Epitope Mapping Protocols, vol. 66, pp. 55-66; 1996

XVI. The arguments of the appellants relevant for the present decision, as advanced in the written submissions and at the oral proceedings, may be summarised as follows.

Main request

Inventive step (Article 56 EPC)

Document D20 disclosed that the full-length anti-NKG2A antibody 3S9 caused the inhibition of its target, presumably via cross-linking. According to paragraphs [0010], [0063] and [0066], the bivalent 3S9 antibody specifically bound to the CD94/NKG2A, -C and/or -E

receptors. Based on the data provided in, for example, paragraphs [0211] and [0212], document D20 suggested in paragraphs [0136] ff to use the 3S9 antibody for the treatment of diseases associated with autoimmune disease and transplantation. This was the opposite of the purpose of the claimed invention.

Paragraphs [0070] and [0114] of document D20 speculated that antibody 3S9 in a monovalent Fab format had the opposite effect of its bivalent format and would not result in cross-linking of the CD94/NKG2 receptors but would rather prevent the receptors from binding their physiological ligand Qa1b in mice or HLA-E in humans. This would result in activation of the NK cells and the killing of the target cells. However, document D20 was not enabling since it neither provided the sequences nor the hybridoma deposit number for antibody 3S9. In addition, it failed to provide any evidence for the alleged NKG2 receptor blocking effect of the monovalent 3S9 Fab fragment. Thus, the skilled person could not derive any useful information from the teaching of D20, for lack of "*clear evidence of exactly what the biochemical was*".

The antibody according to claim 1 differed from the 3S9 antibody of document D20 in that it:

- was specific for human NKG2A and did not bind to NKG2C or -E

- had to bind to the same NKG2A epitope as the antibody produced by the cell deposited at the CNCM under accession number I-3549

- did not bind to a human F_c gamma receptor

The technical effect of this difference was an improved targeting of the NKG2A-receptor useful for the modulation of NK-cell activity.

The technical problem was how to obtain an NKG2A binding antibody resulting in optimum modulation, especially activation, of NK cells.

The claimed solution was not obvious since document D20 failed to provide any suggestion to target only the NKG2A receptor to activate NK cells. On the contrary, D20 stated that binding to NKG2C or NKG2E did not impact the function of the antibody as NKG2A was dominant over NKG2C and NKG2E. D20 aimed at inhibiting NK cell-activation, not activating NK cells, and contained no evidence of NK cell-type specific activation by antibody 3S9.

But also, even if there had been a suggestion in document D20 to target only the NKG2A receptor to activate NK cells, there would have been no reasonable expectation of successfully arriving at the claimed antibody. The skilled person knew that NKG2A, -C and -E all interacted with HLA-E and also antibody 3S9. This implied that they have conserved interaction sites.

Contrary to the evidence provided in document D20, Examples 5 and 6 in the patent showed an NKG2A-specific-neutralising effect that was Fc-gamma-receptor independent for the anti-NKG2A Z270 antibody, both as a full-length antibody and as a F(ab')2 fragment, resulting in enhanced target cell lysis.

The 3S9 antibody of document D20 and, as a consequence, fragments of it, were raised against murine NKG2A and, thus, were unlikely to bind to human NKG2A since NKG2A,

-C and -E were significantly different between mice and humans.

Contrary to the reasoning in the opposition division's decision, the skilled person also had no motivation to combine the closest prior art's teaching with that of document D19. It was not clear how a study on viral-infection modulated expression of NKG2 receptors could be related to functional NK-cell activation as discussed in document D20. Furthermore, contrary to the statement in document D19 on page 3665, left column, "*Antibodies and reagents*", antibody Z199 was not specific for NKG2A. As shown in the respondent's notice of opposition in Figure 1B, antibody Z199 also bound to NKG2C (see page 11). The fact that inhibitory NKG2A antibodies also bound to NKG2C and/or -E might have been considered an inevitable fact because the only NKG2A-blocking antibodies available at the time of the invention, Z199, 20D5 and 3S9, all lacked specificity over NKG2C and NKG2E.

XVII. The arguments of the respondent, submitted in writing, relevant for the present decision, may be summarised as follows.

Main request

Novelty

The same arguments regarding novelty of the subject-matter of the main request also applied to auxiliary request 1. Accordingly, the claimed subject-matter was anticipated by the Z199 antibody. "Binding the same epitope on NKG2A" had to be construed as "competing with the Z270 antibody". Z199 competed with the Z270 antibody and, thus, satisfied feature a) of claim 1.

Thus, documents D11 to D19 anticipated the claimed subject-matter.

Inventive step (Article 56 EPC)

Document D20 could be selected as the closest prior art. Document D20 was enabling. Based on the information provided in paragraphs [0070] and [0114] of document D20, stating that monovalent 3S9 antibody Fab fragments resulted in the killing of target cells, a person skilled in the art was able to produce such NK-cell activating antibody fragments. Document D20 provided sufficient information to allow the person skilled in the art, using their common general knowledge, to perform the invention without undue burden and without needing inventive skill. Therefore, it was irrelevant whether document D20 had tested antibody 3S9 for its ability to block NKG2 receptors as a monovalent Fab fragment.

Reference was made to the differences as described in point 23.3.1 of the opposition division's decision, i.e. "*D20 discloses an antibody differing from the antibody of claim 1 in that*
- 1) it is not known if the antibody or fragment is characterized by binding the same epitope on NKG2A as the antibody produced by the cell deposited at the CNCM under accession number 1-3549;
- 2) it is binding specifically to NKG2C;
- 3) it is binding specifically to NKG2E"

The technical problem was, as defined by the opposition division, "*the provision of an antibody specifically binding to NKG2A having an improved ability for enhancing the lysis activity of NK cells*".

It would be obvious to the skilled person to try modifying the specificity of the mAb disclosed in D20 for more effective use in humans. Seeking to solve the problem of the invention, a skilled person would have been motivated to combine the teachings of documents D20 and D19. Both documents were in a very similar technical field, thus, the skilled person would have been aware of both.

Contrary to the appellant's allegation, paragraph [0114] of document D20 did not provide a disincentive to modify the specificity of the antibodies. It merely indicated that the antibodies provided were adequate for use in mice. Document D19, on the other hand, provided an incentive to modify the specificity of the antibodies described in D20 to solve the problem of the invention at issue because it clearly showed that the situation in humans was different to the one in mice.

Document D20 provided in paragraph [0003] (first line) the statement "*Natural Killer cells are capable of lysing tumor and viral-infected cells...*". Thus, it was clear that the intention of document D20 was to manipulate NK cells to both upregulate and downregulate their activity and not only to downregulate it as suggested by the appellants.

There was no evidence of any particular difficulties to isolate antibodies specifically binding to NKG2A only using standard screening selection procedures. Even the patent did not suggest any difficulties in finding the antibodies of the invention.

The appellants' argument that the skilled person would assume the ligand binding regions of NKG2-receptors needed for inhibition to be highly conserved was

incorrect. The skilled person understood from the art at the time, specifically document D19, that the NKG2A/C/E receptors had different effects. Thus, the ligand binding sites could not be conserved to the point that the same ligand would bind all three receptors in nature.

Requests of the parties as far as relevant to this decision

XVIII. The appellants' initial and final requests at the oral proceedings were that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the set of claims of auxiliary request 1, filed with the statement of grounds of appeal (new main request).

XIX. The respondent requested in their written submissions that the appeal be dismissed and that the opposition division's decision to revoke the patent be upheld.

Reasons for the Decision

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

2. As it previously announced in writing, the respondent did not attend the oral proceedings. The proceedings were continued in its absence, and the respondent was treated as relying on its written case in accordance with Rule 115(2) EPC and Article 15(3) RPBA.

Main request

Novelty (Article 54 EPC)

3. The opposition division had considered the prior art antibody Z199 not to anticipate the subject-matter of claim 1 of the main request (auxiliary request 1a in the decision under appeal) because Z199 specifically bound not only to NKG2A but also NKG2C.

4. The board understands that the respondent considers this decision to be incorrect, but it has not provided any arguments as to why this is the case. The objection is therefore not substantiated. Since the board considers that it is not self-evident that the opposition division's decision is incorrect on this point, the objection need not be considered further by the board (Articles 12(2) and (4) RPBA 2007).

Inventive step (Article 56 EPC)

Closest prior art

5. The board considers document D20 to represent a suitable starting point for determining the inventive step of NKG2A-specific antibodies as claimed.

6. Document D20 relates to, among others, monoclonal antibodies (mAb) which specifically bind to the CD94/NKG2A, -C and/or -E receptors and/or fragments of these receptors on human and mouse NK-cells (see paragraph [0010]). The CD94/NKG2 heterodimer containing NKG2A is reported to be inhibiting, whereas the two other heterodimers (i.e. CD94/NKG2C and -E) are described as being activating (see paragraph [0063]). Heterodimers with NKG2A represent ~95% of the total number of NKG2

receptors in NK cells, and the signal generated by inhibitory receptors (i.e. NKG2A) is dominant compared to the one generated by activating receptors. Cross-linking of all CD94/NKG2 receptors with, for instance, the mAb 3S9 (which binds to NKG2A, -C and/or -E) "*will*" result in an overall inhibition of NK cells and cells expressing CD94/NKG2 receptors (see paragraph [0066]). It is reported that "[o]*pposite to the effect of bivalent 3S9 antibody, monovalent Fab fragments of the 3S9 mAb will not result in cross-linking of the CD94/ NKG2 receptors, but will prevent the receptors from binding their physiological ligand Qa1b (mouse) or HLA-E (human). This will result in the absence of inhibitory signals, in activation of the NK cells, and in killing of the target cells*" (see paragraphs [0070] and [0114]).

The difference, its technical effect and the problem to be solved

7. The mAb according to claim 1 differs from the anti-NKG2 antibody disclosed in the closest prior art at least in that the claimed mAb:
   (a) is specific for NKG2A, i.e. does not bind to NKG2C and -E
   (b) does not bind, via its Fc region, to a human Fc gamma receptor

8. Based on the evidence provided in Examples 5 and 6 of the patent, the technical effect due to the identified differences is that the claimed antibody results in NKG2A-specific inhibition and consequently improved activation of the lytic capability of NK cells.

9. The board does not agree with the technical problem as formulated by the opposition division in the appealed

decision and by the respondent in its reply given that it comprises a pointer to the claimed solution, i.e. an antibody specifically binding to NKG2A.

10. In light of the data provided in the patent (see point 8.), the board concurs with the appellants that the technical problem is how to obtain an NKG2A binding antibody resulting in optimum modulation, especially activation, of NK cells.

Obviousness

11. The question to be answered in assessing the obviousness of the claimed subject-matter is whether the skilled person, when faced with the problem above, would have modified the antibody disclosed in the closest prior-art document D20 to render it specific for NKG2A.

12. The board concurs with the respondent that document D20 provides sufficient information to allow the person skilled in the art, using their common general knowledge, to provide further antibodies binding to NKG2A, -C, and/or -E. The necessary information is provided in paragraph [0156] of document D20. Furthermore, it appears to be undisputed that only NKG2A is inhibiting, whereas NKG2C and -E are activating receptors.

13. However, as put forward by the appellants, document D20 teaches that the NKG2A inhibitory signal is dominant over the activating signals of NKG2C and -E, resulting in overall inhibition of NK cells. Document D20 does not suggest that the difference between the signals of these NKG2 receptors can be used to improve the NK-cell activation. On the contrary, document D20 holds that

cross-linking of all CD94/NKG2 receptors will result in overall inhibition of NK-cell activity and proposes using monovalent Fab fragments of the S39 antibody for the activation of NK cells (see paragraph [0114] and point 6. above). Therefore, the board concurs with the appellants that document D20 does not provide any incentive - nor the necessary information on how - to produce antibodies specific for NKG2A only and capable of inhibiting the interaction of this inhibitory receptor with its counter-receptor.

14. Moreover, the board concurs with the appellants that, based on the reported prevalence of heterodimers with the NGK2A receptor, which are described to account for 95% of the total number of NKG2 receptors in NK cells (see document D20, paragraph [0063], last sentence; paragraph [0066], line 9; and paragraph [0114], third sentence), neither these passages nor any other of document D20 indicate that the population of receptors might differ from the stated 95% NKG2A proportion of the total number of NKG2 receptors. Thus, from document D20, a skilled person would understand that it is satisfactory to have binding to all NKG2 receptors because of the indicated proportion of NKG2A receptors.

15. It remains to be answered whether the skilled person would have combined the teaching of the closest prior art with that of document D19.

16. The board concurs with the respondent that a skilled person in the art of NK-cell immunology would have been aware of document D19. This scientific article analyses the expression of the activating CD94/NKG2C and the inhibitory CD94/NKG2A receptors as well as other receptors in human peripheral blood lymphocytes.

17. However, document D19 is concerned with viral-infection modulated expression of NKG2 receptors and not with NK-cell activation or the problem of finding better means for activating these cells.

18. The board concurs with the appellants that the skilled person had no incentive to combine the teaching of document D19 with respect to NKG2C expression on NK cells with the teaching in document D20. In fact, the board considers that this combination involves hindsight. Accordingly, the board finds that the opposition division was not correct in holding that the skilled person would have realised from document D19 that an improvement of the 3S9 Fab of document D20 can be obtained with antibodies that inhibit the binding of HLA-E to NKG2A without inhibiting the binding to NKG2C and NKG2E.

19. The board concludes from the above considerations that starting from the teaching of document D20, a skilled person would not have arrived at the claimed invention in an obvious way. Consequently, an inventive step can be acknowledged.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent with the following claims and a description to be adapted thereto: claims 1 to 34 of the new main request, filed as auxiliary request 1 with the statement of grounds of appeal.

The Registrar: The Chair:

I. Aperribay P. de Heij

Decision electronically authenticated