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Datasheet for the decision
of 22 July 2021

Case Number: T 2423/18 - 3.3.04

Application Number: 13704064.8

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IPC: A61K39/395, A61P35/00,
                              C07K16/28

Language of the proceedings: EN

Title of invention:
MICA binding agents

Applicant:
Innate Pharma

Headword:
MICA binding agents/INNATE PHARMA

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - main and auxiliary request (no)

Decisions cited:

Catchword:

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Case Number: T 2423/18 - 3.3.04

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

Appellant: (Applicant)	Innate Pharma 117, Avenue de Luminy 13009 Marseille (FR)
Representative:	Gallois, Valérie Cabinet BECKER & ASSOCIES 25, rue Louis Le Grand 75002 Paris (FR)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 13 April 2018 refusing European patent application No. 13704064.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chair	G. Alt
Members:	B. Claes
	L. Bühler

Summary of Facts and Submissions

I.   The appeal is from the applicant (appellant) against the decision of the examining division to refuse European patent application No. 13 704 064.8 ("the application"), published as international patent application WO 2013/117647 with the title "*MICA binding agents*".

II.   In the decision under appeal, the examining division held the subject-matter of the set of claims of a main request and auxiliary requests 1 to 6 to lack an inventive step (Article 56 EPC). It refused the application for this reason.

III. With their statement of grounds of appeal, the appellant re-submitted the sets of claims of the main request and of auxiliary requests 1 to 6. They submitted arguments to the effect that the claimed subject-matter of each request involved an inventive step (Article 56 EPC).

Claim 1 of the main request read:

"1. A monoclonal antibody that binds to a MICA polypeptide comprising an amino acid sequence of SEQ ID NO: 1, to a MICA polypeptide comprising an amino acid sequence of SEQ ID NO: 2, to a MICA polypeptide comprising an amino acid sequence of SEQ ID NO: 3, and to a MICA polypeptide comprising an amino acid sequence of SEQ ID NO: 4 on the surface of cells for use in the treatment of cancer."

Claim 1 of auxiliary request 1 was identical to claim 1 of the main request but for the insertion of the additional wording ",wherein said antibody comprises a human heavy chain constant region that binds a human FyIIIA receptor or wherein said antibody is conjugated or covalently bound to a toxic agent" at the end of the wording of the claim.

IV.   The appellant was summoned to oral proceedings as requested. Subsequently, in a communication pursuant to Article 15(1) RPBA 2020, the board expressed, *inter alia*, the preliminary view that the claimed subject-matter of the main request lacked an inventive step.

V.   In response to the board's communication, the appellant withdrew former auxiliary requests 2 to 6 and filed new auxiliary requests 2 to 4.

VI.   During the oral proceedings the appellant withdrew auxiliary requests 2 to 4. At the end of the oral proceedings the chair announced the decision of the board.

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

D1: WO 2008/036981

D3: Yizhou *et al.* (2002), Human Immunology, vol.63, No.1, pages 30-39.

D5: Duquesnoy *et al.* (2008), Human Immunology, vol.69, No.12, pages 826-832.

D6: Suarez-Alverez et al. (2009), Transplantation, vol.88, No.3, Suppl., pages S68-S77.

D7: Yizhou *et al.* (2008), Immunogenetics, vol.61,
No.2, pages 91-10.

D8: Spreu *et al.* (2006), J. Immunol., vol.177, No.5,
pages 3143-3149.

D9: "Anti-Human MICA/B Monoclonal Antibody BAMO1",
dated 1 January 2004.

Exhibits 1 and 2: filed by the applicant with the
letter dated 24 June 2016.

Exhibit 3: filed by the applicant with the
letter dated 4 January 2017.

VIII.   The appellant's arguments, as far as they are relevant
for the decision, are summarised as follows:

Main request
Inventive step (Article 56 EPC) - claim 1

Document D1, which represented the closest prior art,
admittedly disclosed (e.g. on page 26, lines 8 to 11),
inter alia, anti-MICA antibodies for use in the
treatment of MICA-expressing cancer by mechanisms such
as complement-dependent cellular cytotoxicity (CDC) and
antibody-dependent cellular toxicity (ADCC).

However, document D1 did not disclose a concrete
monoclonal anti-MICA antibody. It did not consider the
polymorphism of MICA either - there are over 50 MICA
alleles existent in the human population. Document D1
thus concerned the concept of a patient-specific
antibody rather than antibodies which bind to multiple
key MICA alleles.

The claimed antibody differed from those disclosed in
document D1 in that a monoclonal anti-MICA antibody
which is capable of binding to MICA alleles *001, *004,
*007 and *008 was used (these alleles are referred to
in the claim by polypeptides comprising the amino acid
sequences of SEQ ID NO: 1 to SEQ ID NO: 4). The
application disclosed nine antibodies with the binding
pattern referred to in the claim (page 116, lines 14 to
16).

The effect of this technical difference was that the
antibody defined in the claim was pan-allelic by virtue
of sequence similarity to other alleles and permitted
coverage of substantially all known MICA alleles. This
permitted treatment of numerous types of tumours in a
large patient population. The antibody thus obviated
the need to analyse which MICA allele(s) (homozygous or
heterozygous) is/are expressed by a patient in need of
treatment. It also obviated the need for the
development of a particular antibody for each allele.
This reduced the cost of the marketed drug.

The technical problem to be solved was thus to provide
an improved treatment for cancer.

The skilled person could have selected, among the
antibodies disclosed in document D1, any of those
suggested as suitable for therapeutic use. The claimed
antibody, however, was not suggested.

Equally, none of the other cited documents suggested
using a monoclonal antibody capable of binding to
multiple alleles of MICA, especially to MICA alleles
*001, *004, *007 and *008, for the treatment of cancer.
Each of documents D2, D8 and D9 disclosed anti-MICA

monoclonal antibodies for use as research/detection agents. Each of documents D3 and documents D5 to D7 related to allograft rejection and not to cancer therapy.

Document D3 disclosed two antibodies that only bound to MICA *008, two antibodies that bound only to group 2 alleles and two antibodies that bound to both group 1 and group 2 alleles (i.e. *001, *002, *004, *008 and *009.).

Document D5 (pages 830 and 831), document D6 (Table 2 on page S71) and document D7 (Table 3) each disclosed observations in which organ-transplanted patients became immunised against MICA and presented anti-MICA auto-antibodies. They illustrated that sera isolated from human donors never contained antibodies for each of MICA *001, *004, *007 and *008 alleles. Immuno-dominant epitopes on MICA were thus not present on each of these alleles.

The skilled person was thus dissuaded from developing a single antibody directed against several alleles of MICA for a therapeutic purpose as claimed. If anything, the skilled person would deduce from the aforementioned disclosures that an antibody directed against several alleles of MICA could not be used for a therapeutic purpose.

Document D9 was a product sheet disclosing information on the mouse monoclonal antibody BAMO1, a monoclonal antibody binding to the MICA alleles *001, *004, *007 and *008 and to the MICB allele *02. The product sheet, however, only indicated applications for *in vitro* use, i.e. flow cytometry, ELISA and immunoblot. It further stated the conditions that the mAB was for research use

only and not for use in diagnostic or therapeutic procedures.

The skilled person had no motivation to choose the reagent of document D9 as a solution to the technical problem, because the antibody of document D9 was not disclosed for the same purpose as the antibodies that were disclosed in document D1 or claimed. In fact, the combining of the disclosures of document Dl with the disclosure of document D9 was the result of an *ex post facto* analysis. Once the solution as claimed was known, it could be perceived as obvious to look for a document disclosing an antibody capable of binding to multiple alleles of MICA. However, in the absence of that knowledge, the skilled person had no reason or motivation to combine the disclosures of documents D1 and D9.

The BAMO1 antibody itself was not suitable for human cancer therapy as it was a mouse antibody and its Fc part was not bound by the human Fc receptor.

Exhibits 1 to 3 provided data obtained with BAMO1 and a chimeric derivative thereof. The data illustrated that, even if the skilled person had combined the disclosures of documents D1 and D9, the results with the chimeric derivative would have discouraged or even dissuaded the skilled person from using such an antibody for the treatment of cancer.

Exhibit 1 demonstrated that BAM01 bound to MICA*007 allele with a very high EC50. Thus, while BAMO1 might bind to MICA *007 and other MICA alleles sufficiently for detection in research uses, it was not effective for inducing ADCC as an *in vivo* therapeutic agent.

Exhibit 2 demonstrated that a chimeric derivative of BAMO1, which was indeed usable in humans, did not induce ADCC at concentrations consistent with its use as a therapeutic agent with MICA *007 target cells.

Exhibit 3 further demonstrated that, in order to achieve receptor saturation in a MICA *007 individual, BAM01 would need to be dosed, for intravenous administration, in the range of 100 mg/kg (i.e. around 6 000 mg for an average human) at least every week. Such a dose and regimen did not provide a treatment of cancer compatible with a therapeutic use.

The results presented in Exhibits 1 to 3 represent experiments that the skilled person would conduct when undertaking to implement a BAM01 derivative for human cancer therapy. In view of those results, the skilled person would not expect any BAM01-derived antibody to ever bind with an affinity and specificity to each of cell-surface MICA *001, *004, *007 and *008 alleles for it to be useful in therapy.

It was implicit in the wording of the claim that the claimed antibody was also useful in the treatment of cancer expressing the MICA alleles mentioned in the claim. The skilled person would thus be dissuaded from continuing to develop the antibody as referred to in the claim, because it was not useful for treating cancer expressing the MICA *007 allele.

Figure 11 of the application, showing results of testing in a mouse long-term RAJI-MICA*01 tumour model in example 11, demonstrated that the claimed antibodies were superior to antibodies only recognising two MICA alleles.

The claimed subject-matter thus involved an inventive step.

Auxiliary request 1 – claim 1
Inventive step (Article 56 EPC)

Essentially the same arguments as submitted for claim 1 of the main request applied to this claim.

IX.   The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims of the main request, or, alternatively, of auxiliary request 1, both filed with the statement of grounds of appeal.

Reasons for the Decision

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

Main request and auxiliary request 1 – claim 1

Claim construction

2.   What is claimed is a monoclonal antibody that binds to four MICA polypeptides comprising sequences of the *001, *004, *007 and *008 alleles (these alleles are referred to in the claim by polypeptides comprising the amino acid sequences of SEQ ID NO: 1 to SEQ ID NO: 4) on the surface of cells for use in the treatment of cancer. In auxiliary request 1, the antibody is further specified to comprise a human heavy chain constant region that binds a human FyIIIA receptor (see section III).

3.   xcdIt is specified in the claim that the antibody *binds*
        to the four alleles comprising the indicated sequences
        on the surface of cells. The claim does not require,
        however, that this antibody should also be suitable for
        the treatment of all cancers expressing each particular
        one of these alleles.

4.   The board cannot, therefore, concur with the appellant
        that it is implicit in the wording of the claim that
        the defined antibodies are useful also in the treatment
        of each and every cancer expressing one of the
        particular MICA alleles mentioned in the claim.

Inventive step (Article 56 EPC)

5.   The board agrees with the appellant that the anti-MICA
        antibodies for use in the treatment of MICA-expressing
        cancer by complement-dependent cellular cytotoxicity
        (CDC) or antibody-dependent cellular toxicity (ADCC),
        as disclosed in document D1 (see e.g. page 25, line 29,
        to page 26, line 11), represent the closest prior art
        for the assessment of inventive step of the claimed
        subject-matter.

6.   The board also agrees with the appellant that the
        difference between the antibodies and use disclosed in
        document D1 and the claimed antibody and use is that
        the latter antibody is capable of binding to MICA
        alleles *001, *004, *007 and *008 (but see point 4).

7.   However, the board has not seen evidence that the
        antibody in the claim, as alleged by the appellant, is
        pan-allelic in MICA binding to such an extent that it
        permits coverage of substantially *all known alleles*,
        thus permits treatment of numerous types of tumours in
        a large patient population and thus obviates the need

to analyse which MICA allele is expressed by a given patient in need of treatment. Equally, in fact, the board has not seen evidence that the claimed antibody is capable of treating tumours expressing each of the particular MICA alleles mentioned in the claim.

8.   Nevertheless, the board can accept that, as was argued by the appellant, the "multi-allelic" binding character of the claimed antibody (here "tetra-allelic") allows the coverage of more than one MICA allele and thus treatment of different MICA allele-expressing types of cancer.

9.   Accordingly, the board accepts this technical effect to justify that the objective technical problem, as submitted by the appellant, can be formulated as the provision of an improved treatment for cancer.

10.   Accordingly, when assessing obviousness, it needs to be established whether or not the skilled person, aiming to improve cancer treatment in the sense that cancers expressing different MICA alleles can be treated using a single antibody, would have provided the antibody referred to in the claim.

11.   Document D1 itself, as submitted by the appellant, does not consider or refer to the polymorphism of MICA - there are over 50 MICA alleles present in the human population (see application, page 3, lines 19 to 30). However, this polymorphism undoubtedly formed part of the common general knowledge of the person skilled in the art and the appellant has not argued differently.

12.   The board notes further that a number of antibodies were known to the person skilled in the art which recognise more than one allele of MICA (see, *inter*

alia, document D3, "DISCUSSION", first paragraph, and
document D9, disclosure of BAMO1). This fact was not
contested by the appellant either. In fact, the
appellant argued that such antibodies had merely not
been disclosed for the treatment of cancer.

13.   The board considers, therefore, that the skilled
        person, having knowledge of the existence in the art of
        anti-MICA antibodies which are reactive to different
        allelic forms of MICA, would also consider using anti-
        MICA antibodies with a broad binding spectrum to
        allelic forms of MICA for treating cancers. In fact, it
        is the binding character of the antibody to the very
        allele expressed by a given cancer in need of treatment
        that determines the therapeutic success of the cancer
        treatment and not the antibody's multi-allelic binding
        character. This conclusion is plainly based on the
        knowledge of the skilled person and, therefore, does
        not constitute the result of an *ex post facto* analysis.
        The board, accordingly, judges that the multi-allelic
        binding characteristic of the antibody referred to in
        the claim, as such, does not attribute inventive
        character to the claimed subject-matter. Therefore, the
        provision of a MICA multi-allele-recognising antibody
        for improving cancer treatment was obvious to the
        skilled person.

14.   As to the four particular alleles to which the claimed
        antibody is said to bind, document D9 discloses the
        mouse IgG1 monoclonal antibody BAMO1 having a binding
        specificity for the very same four MICA alleles *001,
        *004, *007 and *008 as referred to in the claim. The
        board is satisfied that, accordingly, document D9
        teaches that modelling suitable antibodies for cancer
        therapy on the tetra-allelic binding characteristics of
        BAMO1 provides an antibody that can reasonably be

expected to allow treatment of cancers expressing one or more of the alleles *001, *004, *007 and *008. The skilled person, when formulating a solution to the objective technical problem, would thus in an obvious manner consider using an antibody suitable for the envisaged therapeutic use which is capable of binding to these four MICA alleles.

15.   The appellant argued that the skilled person had no motivation to choose the reagent of document D9 as a solution to the technical problem. It argued that the document D9 - a product sheet disclosing information on the mouse monoclonal antibody BAMO1 - did not disclose BAMO1 for the same purpose as the antibodies disclosed in document D1 or referred to in the claim. Instead, it merely indicated applications for *in vitro* use, i.e. flow cytometry, ELISA and immunoblot. Document D1 further stated that the mAB was for research use only and not for use in diagnostic or therapeutic procedures.

16.   However, the fact that document D9 does not disclose the antibody for cancer therapy but merely for *in vitro* applications is fully comprehensible for the skilled person. In fact, it is part of common general knowledge that the administration of a <u>murine</u> antibody to humans carries huge immunological health risks. In fact, the conclusion reached by the board in point 12, above, takes into account such known risks of antibodies which are not suitable for administration to human patients.

17.   The appellant's further argument was that the binding characteristics of BAMO1 are such that the antibody as well as a chimeric derivative of BAMO1, which was usable in humans, were not effective for inducing ADCC

as an *in vivo* therapeutic agent for the treatment of
MICA*007-expressing cancer (which was argued with
reference to Exhibits 1 to 3). Reference is made in
this connection to point 3, above, in which the board
concluded that the claim does not require the claimed
antibody to be suitable for the treatment of all
cancers expressing a particular one of the alleles
indicated in the claim. Accordingly, the board is not
persuaded by the argument that these binding
characteristics would have discouraged or dissuaded the
skilled person from formulating antibodies capable of
binding to the four MICA alleles indicated in the claim
for use in the treatment of cancer, at least such
cancer expressing the other indicated MICA alleles.

18.   The same applies to the appellant's argument, based on
      the disclosures in document D3, document D5 (pages 830
      and 831), document D6 (Table 2 on page 71) and document
      D7 (Table 3), that the skilled person was aware that
      immuno-dominant epitopes were not present on each of
      the MICA *001, *004, *007 and *008 alleles and that
      this dissuaded the skilled person from developing a
      single antibody directed against several alleles of
      MICA for a therapeutic purpose as claimed. As noted
      above in points 3 and 16, the claim in fact does not
      require the suitability of the antibody for the
      treatment of cancer expressing at least one of the
      indicated MICA alleles. Furthermore, document D9
      discloses a murine antibody which the board considers
      to be appropriate for modelling suitable antibodies for
      cancer therapy as claimed (see point 13). The argument
      accordingly fails to support the inventive character of
      the claimed subject-matter.

19.   Finally, the appellant also submitted that figure 11 of
      the application, showing results of testing in a mouse

long-term RAJI-MICA*01 tumour model in example 11,
demonstrated that the antibodies referred to in the
claim were superior to antibodies only recognising two
MICA alleles. The board refers anew to the conclusion
in point 3, above: the claim does not require that the
claimed antibody, although binding to the MICA *001
allele, is necessarily *required* to be effective in
treating cancers expressing this particular allele. In
fact, in this context therefore, the board is not
persuaded that the appellant's argument, namely that
particular antibodies recognising the four MICA alleles
indicated in the claim are superior to other antibodies
only recognising two MICA alleles in the context of the
treatment of MICA*001-expressing cancer, is relevant
for supporting the inventive character of the claimed
subject-matter.

20.   In view of the above considerations, the board
        considers that the subject-matter of claim 1 of both
        the main request and auxiliary request 1 does not
        involve an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chair:

I. Aperribay   G. Alt

Decision electronically authenticated