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Datasheet for the decision of 24 November 2017

Case Number: T 0991/13 - 3.3.04

Application Number: 07012282.5

Publication Number: 2006304

IPC: C07K16/34

Language of the proceedings: EN

Title of invention:
Anti-HPA-5b monoclonal antibody

Applicant:
Stiftung für Diagnostische Forschung

Headword:
Anti-HPA-5b monoclonal antibody/DIAGNOSTISCHE FORSCHUNG

Relevant legal provisions:
EPC Art. 53(c), 56

Keyword:
Main and first auxiliary request - Exceptions to patentability - method for treatment by therapy (yes)
Second auxiliary request - Inventive step (no)

Decisions cited:

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It can be changed at any time and without notice.

Catchword:

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Case Number: T 0991/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 24 November 2017

Appellant: (Applicant)	Stiftung für Diagnostische Forschung Praz-Rond 1785 Cressier sur Morat (CH)
Representative:	Müller-Boré & Partner Patentanwälte PartG mbB Friedenheimer Brücke 21 80639 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 26 November 2012 refusing European patent application No. 07012282.5 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman	G. Alt
Members:	A. Chakravarty
	L. Bühler

Summary of Facts and Submissions

I. An appeal was filed by the patent applicant (appellant) against the decision of the examining division to refuse the European application No. 07 012 282.5, entitled "*Anti-HPA-5b monoclonal antibody*".

II. The examining division considered a main request and an auxiliary request. It held that the main request did not meet the requirements of Articles 56 or 83 EPC. It did not admit the first auxiliary request into the proceedings because it considered it to suffer from the same deficiencies as the main request.

III. With the statement of grounds of appeal, a main request and two auxiliary requests were filed. The main and first auxiliary request were identical to the main and first auxiliary request considered by the examining division. The second auxiliary request was filed for the first time in the appeal proceedings.

IV. Claim 1 of the main and second auxiliary request reads:

"1. A monoclonal antibody or a fragment thereof selectively recognizing human platelet alloantigen 5b (HPA-5b)".

Claim 8 of the main request reads:

"8. Use of the pharmaceutical composition according to claim 7 for the prevention and/or treatment of an alloimmunisation".

Claims 1 and 10 of the first auxiliary request read:

"1. A monoclonal antibody or a fragment thereof selectively recognizing human platelet alloantigen 5b (HPA-5b) for use in the prevention and/or treatment of an anti-HPA-5b alloimmunisation.

10. Use of the pharmaceutical composition according to claim 9 for the prevention and/or treatment of an alloimmunisation."

V. The following documents are mentioned in this decision:

D2: Griffin H.M. and Ouwehand W.H., Blood, 1995, 86(12), 430-4436.

D5: Kiefel V. *et al.*, Blood, 1989, 72(8), 2219-2223.

D8: Santoso S. *et al.*, J. Clin. Invest., 1993, 92, 2427-2432.

VI. The board appointed oral proceedings and subsequently issued a communication pursuant to Article 15(1) RPBA and supplied the appellant with the document D8. In that communication, the board noted that claim 8 of the main request was for a method for treatment of the human or animal body by therapy and that its subject-matter was thus excepted from patentability according to Article 53(c) EPC. Moreover, even if redrafted along the lines provided in Article 54(5) EPC, the board was in preliminary agreement with the examining division's finding of lack of sufficient disclosure of the invention in relation to antibodies having an Fc domain.

In connection with the assessment of the inventive step of the subject-matter of claim 1 of the main request, the board asked whether or not the platelet specific polyclonal alloantibodies, mentioned in paragraph [0004] of the application as having been used in the phenotyping of human platelet antigen 5b (HPA-5b) and disclosed in document D8 (see page 2427, left column, "*Methods*"), might be a more suitable starting point for assessing inventive step than the monoclonal anti-HPA-1a antibodies disclosed in document D2.

It further posed the question of why the skilled person, starting from the disclosure of document D8, would not have considered the claimed monoclonal anti-HPA-5b antibodies to be an obvious solution to the technical problem of "*provision of an improved means for detecting HPA-5b*" in view of the fact that they (the skilled person) knew from document D2 how to generate "*a human monoclonal antibody specific for the leucine-33 (P1^{a1}, HPA-1a) form of platelet glycoprotein IIIa from a V gene phage display library*" (see document D2, title).

VII. Oral proceedings before the board were held on 24 November 2017. At the end of the oral proceedings, the chairman announced the decision of the board.

VIII. The appellant's arguments presented at the oral proceedings can be summarised as follows:

Main request - claim 1
Auxiliary request 1 - claim 10

Exceptions to patentability - Article 53(c) EPC

The appellant made no submissions in writing or at the oral proceedings with respect to the patentability of the claimed subject-matter according to Article 53(c) EPC.

Auxiliary request 2 - claim 1

Inventive step - Article 56 EPC

Prior to the invention "*the phenotyping for HPA-5b has been dependent on the availability of rare polyclonal human sera containing platelet specific alloantibodies. Most of these sera, however, are impaired by the presence of alloantibodies especially against HLA class I antigens and have to be submitted to extensive absorption and purification protocols. Furthermore, the quality of these antisera is subject to high batch-to-batch variation due to the fluctuations of antibody titers in donor sera*" (see paragraph [0004] of the application). The aim of the invention was the provision of an improved means for detecting the human platelet alloantigen HPA-5b, as well as uses thereof (see application, paragraph [0007]).

Although the skilled person would have realised that an anti-HPA-5b monoclonal antibody (mAb) was a desirable solution to the technical problem, they would have realised that the approach disclosed in document D2 for

the production of an anti-HPA-1a mAb could not be applied to the production of HPA-5b specific mAbs due to the low expression of GPIa/IIa with the HPA-5, expressed at 800 to 2800 copies per platelet, compared to GPIIb/IIIa with HPA-1, expressed at 50 000 to 80 000 copies per platelet. In view of this low expression, the skilled person would have considered that it would be extremely difficult to purify enough GPIa/IIa to use in the selection of anti-HPA-5b specific Fab-phages, as was done by the authors of document D2 in producing HPA-1a (see document D2, page 4430 to 4431, "*Materials and Methods*").

The inventors solved the problem of scarcity of HPA-5 antigen by using a MAIPA (monoclonal antibody specific immobilisation of platelet antigen) assay. The identified positive oligo-clonal cell lines were then expanded to produce supernatants for further analysis and cloned (see paragraph [0051] of the application). This approach and the resulting mAbs were not obvious from any cited document.

In fact, the cited documents taught away from the invention. Document D2 concerned the production of a human monoclonal antibody specific for the related HPA-1a alloantigen. In contrast to the inventors, the authors of document D2 had access to purified GPIIb/IIIa. This situation was reported in the application: "*The [GP]IIb/IIIa containing the HPA-1 is expressed at 50 000 to 80 000 copies per platelet, whereas expression of GPIa/IIa with the HPA-5 is 100 fold lower (800 to 2800 copies per platelet). Due to this low expression it was extremely difficult to purify enough GPIa/IIa which could then be used for the selection of anti-HPA-5b specific Fab-phages. It is why this*

technology is inefficient to produce anti HPA-5b monoclonal antibody" (see paragraph [0005]).

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request, or, alternatively, on the basis of the first or second auxiliary request, all 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 therefore admissible.

Background to the invention

2. Antibodies against platelet alloantigens play an important role in immune-mediated disorders. Human platelet antigens 1 and 5 (HPA-1 and HPA-5) are the most important platelet alloantigens related to pathological situations. The alloantigen containing the differences between the two allelic forms of HPA-5 (HPA-5a and HPA-5b) is located on the glycoprotein Ia (GPIa) which is non-covalently associated with glycoprotein IIa (GPIIa). The HPA-5b allele contains an adenine instead of guanine at base 1648, which results in a glutamic acid to lysine amino acid substitution responsible for immunological distinction of the two alleles (see paragraph [0002] of the application).

Main request - claim 1
Auxiliary request 1 - claim 10

Exceptions to patentability - Article 53(c) EPC

3. The claims are for the use of the pharmaceutical composition for the prevention and/or treatment of an alloimmunisation. As such they are directed to a method for treatment of the human or animal body by therapy. Such methods are excepted from patentability by Article 53(c) EPC.

4. The main and first auxiliary request are therefore not allowable.

Auxiliary request 2 - claim 1

Inventive step - Article 56 EPC

5. The claim is for a monoclonal antibody or a fragment thereof selectively recognizing HPA-5b. According to the application, it is intended for use, *inter alia*, in phenotyping for HPA-5b, see paragraph [0004].

Closest prior art

6. The appellant agreed with the board's assessment that the polyclonal human sera containing platelet specific alloantibodies disclosed for instance in document D8 and used for the phenotyping for HPA-5b (see page 2427, right column, "*Antibodies*") could represent the closest prior art for the assessment of inventive step of the claimed subject-matter.

7. The purpose of both the claimed antibodies and those representing the closest prior art is, *inter alia*, phenotyping for HPA-5b.

The objective technical problem

8. The difference between the antibodies disclosed in document D8, representing the closest prior art and those of claim 1 is that the former are polyclonal and the latter are monoclonal.

9. The technical effects of this difference are that the need to obtain sera from patients is obviated, thus avoiding the problems associated with the use of serum derived polyclonal antibodies, such as their scarcity, contamination with alloantibodies against HLA class I antigens and the need to carry out extensive absorption and purification protocols, as well as improved quality, avoiding quality batch-to-batch variation due to the fluctuations of antibody titers in donor sera, see paragraph [0004] of the application.

10. Accordingly, the technical problem underlying the invention can be formulated as provision of an improved means for detecting HPA-5b.

Obviousness

11. The question to be answered is therefore whether the skilled person, faced with the above formulated technical problem and starting from the polyclonal anti-HPA-5b antisera disclosed in document D8, representing the closest prior art, would have considered it obvious to provide the claimed HPA-5b specific mAb.

12. It was not disputed that the skilled person would have sought to produce HPA-5b specific mAbs as a solution to the technical problem set out above. However, it was argued that the skilled person knew that the method disclosed in document D2 could not be used for producing an anti-HPA-5b mAb in view of the difficulty of purifying enough GPIa/GPIIa, which would allow the detection of antibodies, due to its low expression on platelets.

13. In the board's view, the skilled person seeking to produce anti-HPA-5b mAbs, would not have been bound to turn only to the phage display technique used in document D2 to screen for the desired antibodies. Instead they would have been able to turn to any established techniques for providing antigens and screening for the desired antibodies. One such established technique was indeed the phage display technology described in document D2. This technique requires the availability of the relevant purified antigen; in document D2 this was GPIIb/IIIa (see in page 4431, right column, "Selection of phage library").

14. In relation to the appellant's submissions concerning the scarcity of the HPA-5b antigen (GPIa/GPIIa), the board notes that the only information concerning its level of expression on platelets, and hence its potential availability or scarcity, is contained in document D5. This document relates to the "*The Br^a/Br^b alloantigen system on human platelets*"* and discloses that "*approximately 2,000 anti-Br^a binding sites are present on homozygous platelets and 1,000 on heterozygous platelets*" (see abstract).

* Note Br^a/Br^b is a synonym for HPA-5.

15. The board has seen no evidence to the effect that the level of expression on platelets reported in document D5 meant that the skilled person knew that phage display technique would be unsuitable to screen for HPA-5b due to a scarcity of suitable antigen, nor has the board seen any evidence that the HPA-5b antigen cannot in fact be obtained in the same way as the HPA-1a antigen.

16. Furthermore, phage display was not the only system known to the skilled person for screening for anti-HPA antibodies. Document D5 itself discloses a MAIPA assay for immobilising the HPA-5 bearing GPIa/IIIa complex (see page 2219, left column). In fact, it is exactly this MAIPA system that was used in the application to test for the presence of anti-HPA-5b antibodies (see abstract and paragraph [0051]). The board has heard no argument why the skilled person could or would not have turned to this system to provide the relevant antigen and screen for the desired antibody.

17. In view of the above, the answer to the question posed in paragraph 11. is that, in the board's view, it was obvious for the skilled person, at the relevant date of the application, seeking to solve the technical problem to provide the claimed anti-HPA-5b mAb. The board has seen no evidence showing that the skilled person would have been unable to apply conventional techniques to produce these antibodies. Thus, the subject-matter of claim 1 lacks an inventive step.

18. No claim request meets the requirements of the EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated