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Datasheet for the decision of 1 February 2016

Case Number: T 0050/10 - 3.3.04

Application Number: 99908097.1

Publication Number: 1054894

IPC: C07K14/00, C07K16/00, C07H21/04, A61K48/00, A61K39/395, G01N33/53

Language of the proceedings: EN

Title of invention:
Breast Cancer Resistance Protein (BCRP) and the DNA which encodes it

Patent Proprietor:
University of Maryland Baltimore

Opponent:
Bayer Pharma Aktiengesellschaft

Headword:
BCRP/University of Maryland

Relevant legal provisions:
EPC Art. 54, 56, 83, 87
EPC R. 43(4)
RPBA Art. 12(1), 12(4)

Keyword:
Priority - main request (yes)
Novelty - main request (yes)
Inventive step - main request (yes)
Sufficiency of disclosure - main request (yes)

Decisions cited:
G 0002/98, R 0010/09, R 0011/11, R 0013/11

Catchword:

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Case Number: T 0050/10 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 1 February 2016

Appellant: (Opponent)	Bayer Pharma Aktiengesellschaft Müllerstrasse 178 13353 Berlin (DE)
Representative:	BIP Patents c/o Bayer Intellectual Property GmbH Alfred-Nobel-Straße 10 40789 Monheim am Rhein (DE)
Respondent: (Patent Proprietor)	University of Maryland Baltimore Office of Research and Development Suite 500 515 West Lombard Street Baltimore, MD 21201-1691 (US)
Representative:	Jones, Elizabeth Louise Dehns St Bride's House 10 Salisbury Square London EC4Y 8JD (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 10 November 2009 concerning maintenance of the European Patent No. 1054894 in amended form.**

Composition of the Board:

Chairwoman G. Alt
Members: A. Chakravarty
J. Geschwind

Summary of Facts and Submissions

I. The appeal was filed by the opponent (appellant) against the interlocutory decision of the opposition division maintaining European patent No. 1 054 894, entitled "*Breast Cancer Resistance Protein (BCRP) and the DNA which encodes it*" in amended form. The corresponding patent application was filed on 5 February 1999 claiming priority from US application 60/073 763 filed on 5 February 1998.

II. The patent had been opposed under Article 100(a) EPC, on the grounds of lack of novelty (Article 54 EPC), lack of inventive step (Article 56 EPC) and as relating to non-patentable subject-matter (Article 52 EPC in combination with Rule 29(1) EPC) and Articles 100(b) and 100(c) EPC.

III. The opposition division decided that claim 17 of the patent as granted had been amended so as to contain subject-matter extending beyond the content of the application as filed (Article 123(2) EPC). With regard to the claims of auxiliary request 1, which differed from those as granted only in the deletion of claim 17, the opposition division decided that its claims 1 to 8 and 10 to 16 enjoyed the priority date from the US application 60/073 763 and that therefore no objections under Article 54 EPC applied "*since the only document cited in this respect (D3) no longer constitute[d] prior art under Article 54(2) EPC.*" It also found that claims 1 to 3 of auxiliary request 1 met the requirements of Article 52 EPC, that claim 12 met the requirements of Article 83 and that all claims met the requirements of Articles 56 EPC.

IV. With the statement of grounds of appeal, the appellant filed document D19.

V. With the reply the patent proprietor (respondent) *inter alia* filed its previous auxiliary request 1 as its main request and objected to the admission of document D19 into the proceedings.

VI. Both parties requested oral proceedings in the event of a decision unfavourable to them.

VII. Oral proceedings were appointed for 10 November 2015.

VIII. In a communication dated 1 June 2015, the board informed the parties of its preliminary and non—binding opinion on some of the substantive and legal issues concerning the appeal. In particular, it informed the parties that it considered that the subject-matter of claim 1 of the main request validly claimed the right of priority from US application 60/073 763 and that therefore documents D3, D4 and D5 did not constitute prior art for this subject-matter. Furthermore, the board indicated that it was inclined to agree with the opposition division's finding that the subject-matter of the claims met the requirements of Article 56 EPC and that the subject-matter of claim 12 met the requirements of Article 83 EPC. Finally, the board noted that the admission of the newly filed document D19 would be decided at the oral proceedings, after hearing the parties.

IX. With a submission of 13 August 2015, the appellant withdrew the request for oral proceedings.

X. The board cancelled the oral proceedings scheduled for 10 November 2015 and indicated its intention to issue a decision in writing.

XI. The claims of the main request are as follows:

"1. Polypeptide having the sequence of SEQ ID NO: 1 (Breast Cancer Resistance Protein, BCRP) which induces resistance to cancer chemotherapeutic drugs in breast cancer cells.

2. The polypeptide of claim 1 which is about 655 amino acids in length.

3. The polypeptide of claim 1 which has a molecular mass of 72.3 kilodaltons.

4. An antibody which binds to the polypeptide of claim 1

5. The antibody of claim 4 which is monoclonal.

6. The antibody of claim 4 which is polyclonal.

7. A nucleic acid sequence which encodes the polypeptide of claim 1.

8. The nucleic acid sequence of claim 7 which is the sequence in SEQ ID NO. 2.

9. A nucleic acid comprising the nucleotide sequence of SEQ ID NO: 2.

10. An antisense probe which inhibits expression of the polypeptide of claim 1.

11. The antisense probe of claim 10 which is the complementary strand of the sequence in SEQ ID NO:7.

12. A method of determining the cause of a patient's resistance to cancer chemotherapy drugs by assaying *in vitro* for expression of the polypeptide of claim 1, whereby overexpression of the said polypeptide indicates that it is the cause.

13. Use of the antibody according to any of claims 4 to 6 for preparing a medicament for inhibiting the activity of the Breast Cancer Resistance Protein.

14. Use of the probe of claim 11 for preparing a medicament for inhibiting the activity of the Breast Cancer Resistance Protein.

15. Use of the antibody of claim 4 for preparing a medicament for enhancing a cancer patient's chemotherapy treatment.

16. Use of the probe of claim 11 for preparing a medicament for enhancing a cancer patient's chemotherapy treatment."

XII. The following documents are cited in this decision.

D1: Allikmets R. et al., Human Molecular Genetics, 5 October 1996, Volume 5, Issue 10, Pages 1649-1655.

D3: Polypeptide sequence Genbank accession no. AAC97367, 21 December 1998.

D4: Allikmets R. et al., Cancer Res., 1 December 1998, Volume 58, Issue 23, Pages 5337-5339.

D5: Miyake K. et al., Cancer Res., 1 January 1999, Volume 59, Issue 1, Pages 8-l3.

D13: Stryer L., Biochemie, 1991, Chapter 35, pages 925-933, Korr. Nachdruck.

D14: Watson D., Rekombinierte DNA, 1993, Chapter 12, pages 209-210, 2. Auflage.

D15: Stryer L., Biochemie, Korr. Nachdruck 1991, last page, Table "Der genetische Standartcode".

D19: Lee et al., Journal of Cellular Biochemistry, 15 June 1997, Volume 65, Issue 4, Pages: 513-526,

XIII. The appellant's arguments relevant to the decision can be summarised as follows:

Article 12(4) RPBA - Admissibility

Document D19

This document was cited on page 3 of the patent in the "*Background of the Invention*" and disclosed knowledge on the basis of which the skilled person *"would*

unequivocally arrive at the solution provided in claim 9. Therefore, D19 is introduced in the proceedings".

Articles 54 and 56 EPC - Novelty and Inventive step

Document D1

The subject-matter of claim 2 lacked novelty over the disclosure of document D1 because the term "about" used in the claim meant that the claim was "improperly dependent" on claim 1 and had be to considered as encompassing fragments of SEQ ID NO: 1. Document D1 disclosed such a fragment, EST 157481, designated as an ABC transporter protein which was 100% identical to SEQ ID NO: 1 over a stretch of 180 amino acids.

Documents D3 to D5

Article 87 EPC - Priority right

SEQ ID NO: 1 of the priority application and SEQ ID NO: 1 of the patent were not the same. The sequence mentioned in the patent was shorter, lacking 8 amino acids at the N-terminus compared to the sequence disclosed in the priority document.

The disclosure on page 21, lines 19-22 of the priority document that "*Analysis of the cDNA [...] indicated the presence in SEQ ID NO: 1 of a long [open reading frame] (ORF) that began at position 239, and ended with the stop codon TAA at positions 2204-6*" was not a direct and unambiguous disclosure of SEQ ID NO: 1 mentioned in the patent because, although this ORF encoded a protein with a 655 amino acid length, the existence of other long ORFs was not excluded.

Furthermore, throughout the priority document the invention was disclosed as pertaining to a Breast Cancer Resistance Protein (BCRP) of 663 amino acids in length, with only one passage referring to an ORF encoding a 655 amino acid long protein, which was not even disclosed as a BCRP variant. Thus, the skilled person would have understood that the priority application disclosed a protein having the sequence shown in figure 2A, which had a length of 663 amino acids. The single disclosure of an ORF at one single position in the priority document, in contradiction to the remaining disclosure of the whole document, could not be regarded as a direct and unambiguous disclosure.

Since the polypeptide of SEQ ID NO: 1 was not entitled to priority, documents D3 to D5 were prior art for this subject-matter.

The subject-matter of claims 1 to 3 lacked novelty with respect to the disclosure of document D3.

The subject-matter of claims 4, 5 and 6 lacked inventive step over document D3 in combination with document D13.

The subject-matter of claims 7 and 8 lacked inventive step over document D3 in combination with document D15.

The subject-matter of claims 10 lacked inventive step over document D3 in combination with document D14.
The subject-matter of claims 11, 13 and 14 lacked inventive step over document D3 alone.

Finally, the subject-matter of claims 12, 15 and 16 lacked inventive step over document D5 in combination with document D3.

Article 83 EPC - Disclosure of the invention

Claim 12 related to a "*Method of diagnosing a patient's resistance to chemotherapy manifested by overexpression of BCRP*". However, in paragraph [0031] of the patent it was disclosed that the degree of resistance did not correlate with the level of expression. On this basis it must be concluded that there was no disclosure in the patent which would allow the person skilled in the art carry out the method as claimed because there was no guidance about which level of drug resistance was caused by the overexpression of the breast cancer resistance gene (BCRP).

XIV. The respondent's arguments relevant to the decision can be summarised as follows:

Article 12(4) RPBA - Admissibility

Document D19

Document D19 should not be admitted into the appeal proceedings. According to decision T 1002/92, the admittance of new documents at the appeal stage should be allowed only very exceptionally if that material is *prima facie* highly relevant. Document D19 document was not *prima facie* relevant and moreover represented an attempt to revisit the issue of inventive step of the subject-matter of claim 9 after the appellant had failed to achieve revocation of the claim based on the document that had been used before the opposition division.

Articles 54 and 56 EPC - Novelty and Inventive step

Document D1

The disclosure of document D1 did not anticipate the subject-matter of claim 2. By virtue of its dependency on claim 1, all subject-matter of claim 2 included the full sequence of SEQ ID NO. 1. Thus claim 2 did not encompass fragments of SEQ ID NO: 1. Furthermore, EST157481 had only 98% identity over the region of overlap to the sequence represented by SEQ ID NO: 1. A 180 amino acid long fragment having 100% identity to parts of SEQ ID NO: 1 was not disclosed as a separate entity in document D1.

Documents D3 to D5

Article 87 EPC - Priority right

The priority document on page 21, lines 17-22 disclosed an open reading frame (ORF) beginning at position 239 and ending at the codon 2204-6. This ORF encoded 655 amino acids which were shown in translation from the nucleic acid in Figure 2A. There was therefore a literal, direct and unambiguous disclosure of the 655 amino acid protein designated SEQ ID NO: 1 in the patent.

Claims 1 to 8 and 12 to 16 were thus all entitled to priority. Since documents D3 to D5 post-dated the validly claimed priority date, the objections of lack of novelty and inventive step set in relation to these claims on the basis of these documents could not succeed.

Article 83 EPC - Disclosure of the invention

In the objections under Article 83 EPC, raised against the subject-matter of claim 12, the appellant had misinterpreted paragraph [0031] of the patent which allegedly disclosed that the degree of resistance to chemotherapy did not correlate to the level of expression of BCRP. In fact, the passage indicated that for two groups of cells, both of which exhibited drug resistance (albeit different levels of drug resistance), BCRP mRNA levels were the same. Thus, overexpression of BCRP was correlated with drug resistance in both cell lines.

Moreover, the method of claim 12 did not require that the level of overexpression be measured but merely required that overexpression of the polypeptide was indicative of the cause of resistance to chemotherapy. This was confirmed in paragraph [0031] of the patent which disclosed that the level of resistance varied between the tested cell lines but in both cases was linked to overexpression of BCRP.

XV. The requests of the parties were as follows:

The appellant requested that the decision of the opposition division be set aside and that the patent be revoked.

The respondent requested that the appeal be dismissed, i.e. that the patent be maintained in the form allowed by the opposition division.

Reasons for the Decision

Article 12(4) RPBA - Admissibility

Document D19

1. In the statement of grounds of appeal, the appellant introduced a line of argument of lack of inventive step of the subject-matter of claim 9 based on document D19 which had not been raised in the proceedings before the opposition division (see Section XIII.). The appellant indicated that the document had been cited on page 3 of the patent in the section "*Background of the Invention*" and therefore the document was known to the respondent. Its disclosure allowed the skilled person to *"unequivocally arrive at the solution provided in claim 9"*. Thus, the appellant regarded the document as highly relevant.

2. Article 12(1) RPBA provides, *inter alia*, that the appeal proceedings shall be based on the statement of grounds of appeal. By virtue of Article 12(4) RPBA the board has the power to hold inadmissible facts, evidence or requests which were filed with the statement of grounds of appeal if they "could have been presented [...] in the first instance proceedings".

3. The appellant had been informed by the board's communication that the admission of document D19 was an issue, but has provided no further comments on the matter in writing and also withdrew the request for oral proceedings.

4. The board is of the opinion that document D19 and the line of argument based on it could and should have been presented during opposition proceedings for the same

reasons given by the appellant in favour of its admission, namely that, at the time of the opposition proceedings, the appellant was aware of the existence of the document and considered it as highly relevant.

5. In view of this and also taking into consideration that the purpose of appeal proceedings is mainly to review the decision of the department of first instance (see decisions R 10/09, reasons 3.2, R 11/11, reasons 9 and R 13/11, reasons 16), the board, has decided not to admit document D19 into the proceedings.

Articles 54 and 56 EPC- Novelty and Inventive Step

Document D1

6. The appellant argued that EST 157481 disclosed in document D1 was an ABC transporter protein which was 100% identical to a polypeptide having SEQ ID NO: 1 over a stretch of 180 amino acids. It therefore should be considered to be a fragment of SEQ ID NO: 1. The subject-matter of claim 2 included fragments of polypeptides having SEQ ID NO: 1 because the term "*about*", used in the claim, meant that the claim was "*improperly dependent*" on claim 1.

7. However, in the board's view, the skilled person reading claim 2 would consider it to relate to subject-matter including all the features of the subject-matter of claim 1 and therefore to be dependent on that claim (Rule 43(4) EPC). Since the subject-matter of claim 1 is a "*Polypeptide having the sequence of SEQ ID NO: 1*", the subject-matter of claim 2 is considered to be any polypeptide containing the entire amino acid sequence SEQ ID NO: 1. Thus, the skilled person would not

consider that fragments of the polypeptide of claim 1 were subject-matter of claim 2.

8. In view of the above, the appellant's argument cannot succeed. The board is satisfied that the subject-matter of claim 2 is novel with respect to the disclosure of document D1.

Documents D3 to D5

Article 87 EPC - Priority right

9. There is a dispute between the parties about whether the subject-matter of claim 1 can validly claim a right of priority from the earlier application US 60/073 763 filed on 5 February 1998.

10. According to Article 87 EPC a European patent application may validly claim the right of priority from a previous first application if both relate to "the same invention". The concept of "the same invention" expressed in Article 87 EPC has been interpreted by the Enlarged Board of Appeal in decision G 2/98 (OJ EPO 2001, 413, point 9 of the reasons) as meaning subject-matter which the person skilled in the art can derive directly and unambiguously, using common general knowledge, from the previous application as a whole.

11. In the present case, the issue is thus whether the 655 amino acid polypeptide having the sequence of SEQ ID NO: 1, that is the subject-matter of claim 1, can be directly and unambiguously derived from application US 60/073 763.

12. The board notes that the application US 60/073 763 does not contain a discrete sequence identical to SEQ ID NO: 1 of the patent. However in Example 6 there is a disclosure of a "*cDNA insert [...] 2418 bp in length as in Figure 2C or SEQ ID NO: 2 [with] a long ORF that began at position 239 and ended with the stop codon TAA at position 2204-06.*" (see page 21, lines 17 to 22). Translation of this ORF yields a protein of 655 amino acids which is identical to SEQ ID NO: 1 as mentioned in the patent - it being part of the basic technical knowledge of the skilled person that translation of a nucleic acid sequence into the corresponding amino acid leads to a defined amino acid sequence. Furthermore, the translated amino acid sequence of this region is included in the longer sequence shown in Figure 2A of the priority application. Thus, the board is satisfied that, given the information about the positions of the start and stop codons of the ORF concerned, the skilled person can derive the polypeptide having SEQ ID NO: 1 as claimed, directly and unambiguously, using common general knowledge, from application US 60/073 763 as a whole.

13. It follows from this that the subject-matter of claim 1 and of the dependent claims 2 to 8 and 10 to 16 validly claims the priority date from application US 60/073763, this date being 5 February 1998.

14. Since documents D3 to D5 are all published after that date, all objections of lack of novelty and lack of inventive step made on the basis of these documents must fail.

15. Hence, the board is satisfied that the requirements of Articles 54 and 56 EPC are fulfilled.

Disclosure of the invention - Article 83 EPC

16. The appellant considered that the patent did not disclose the method of claim 12 for determining the cause of a patient's resistance to cancer chemotherapy drugs by assaying *in vitro* for expression of the polypeptide of claim 1, in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. In particular, the appellant considered that paragraph [0031] of the patent disclosed that the degree of resistance to the drug did not correlate with the level of expression of the Breast Cancer Resistance Protein (BCRP). In the absence of such a correlation, the method could not be carried out as claimed.

17. However, the board, in agreement with the opposition division and with the respondent, considers that the disclosure at paragraph [0031] of the patent demonstrates that, although the two groups of cells examined exhibit different levels of drug resistance, both are in fact drug resistant. Thus, the patent discloses to the skilled person that expression of BCRP in a cell is correlated to resistance to cancer chemotherapy.

18. The board is therefore satisfied that the patent meets the requirements of Article 83 EPC with respect to the subject-matter of claim 12.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

The Registrar: The Chairwoman:

P. Cremona G. Alt

Decision electronically authenticated