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Datasheet for the decision of 23 February 2012

Case Number: T 1031/09 - 3.3.08

Application Number: 99914382.9

Publication Number: 1071815

IPC: C12Q 1/68, C12Q 1/48, C12N 15/54

Language of the proceedings: EN

Title of invention:
Assay for methylation in the GST-Pi gene

Applicant:
Commonwealth Scientific and Industrial Research Organisation

Opponent:
-

Headword:
GST-Pi gene/COMMONWEALTH

Relevant legal provisions:
EPC Art. 83, 84, 123(2)

Keyword:
"Main request: compliance with Articles 83, 84 and 123(2) EPC (yes)"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1031/09 - 3.3.08

D E C I S I O N
of the Technical Board of Appeal 3.3.08
of 23 February 2012

Appellant: (Applicant)
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 11 December 2008 refusing European patent application No. 99914382.9 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: M. Wieser
Members: T. J. H. Mennessier
R. Moufang

Summary of Facts and Submissions

I. The applicant (appellant) lodged an appeal against the decision of the Examining Division, whereby the European patent application No. 99 914 382.9 with publication number 1 071 815 was refused. The application, entitled "*Assay for methylation in the GST-Pi gene*", originated from an international application published as WO 99/55905.

II. The set of claims 1 to 29 filed with the letter of 29 September 2008 was refused for reasons of lack of clarity and conciseness (Article 84 EPC), and of insufficiency of disclosure (Article 83 EPC).

III. The statement setting out the grounds of appeal was filed on 14 April 2009. It was accompanied by a new set of claims (1 to 24) to replace the set of claims of 29 September 2008. Oral proceedings were requested as an auxiliary measure.

IV. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal attached to the summons to the oral proceedings, the Board expressed its preliminary and non-binding views. It was remarked that the Examining Division had not decided on novelty and inventive step, with the consequence that, should a request be considered to comply with the requirements of Articles 83 and 84 EPC, it was to be expected that the case would be remitted to the first instance for further prosecution for the assessment of novelty and inventive step.

V. In reply to the Board's communication, the appellant filed further submissions with a letter dated 30 December 2011. The submissions were accompanied by a main request and an auxiliary request to replace the previous requests. The appellant argued that the examining division had decided on novelty and that therefore the decision of the Board should include an assessment of this criterion.

VI. In a telephone conversation held on 16 January 2012, the Board drew the appellant's attention to the fact that the mere remark made in respect of unity of invention, at point 3 of the decision under appeal that "*the concept underlying the invention as defined by the set of claims L3 (i.e. comprising a limitation to the methylation analysis in the transcribed region of the GSTP1 gene) could be considered as new*" did not equate with an assessment of novelty of the claimed invention. The Board also pointed out some defects of the main request as regards the requirements of Article 84 EPC, in particular in view of the provisions of Rule 43(2) EPC (see point 11 of the Board's communication).

VII. On 23 January 2012, in response to the telephone conversation of 16 January 2012, the appellant filed additional submissions together with a new main request to replace the main request of 30 December 2011.

VIII. In response to two further telephone conversations held on 1 and 9 February 2012 respectively, the appellant filed on 9 February 2012 a new main request. The request for oral proceedings was conditionally withdrawn.

IX. On 9 February 2012, the Board faxed a communication informing the appellant that the oral proceedings scheduled for 14 February 2012 were cancelled.

X. The main request consisted of 24 claims of which claim 1 read as follows:

"1. A diagnostic or prognostic assay for prostate cancer in a subject, said prostate cancer characterized by abnormal methylation of cytosine at a site or sites within the human glutathione-S-transferase (GST) Pi gene, wherein said assay comprises the steps of:
(i) isolating DNA from said subject, and
(ii) determining the presence of abnormal methylation of cytosine at a site or sites within the region of the human GST-Pi gene defined by (and inclusive of) CpG sites +1 to +53."

Claims 2 to 6 were dependent on claim 1. In claim 7, which also was dependent on claim 1, step (ii) of the assay was further defined as involving an amplification step. Claims 8 to 23 were directed to particular embodiments of claim 7 (and thus of claim 1).

Claim 24 was directed to a particular nucleotide primer or probe.

XI. The following document is referred to in the present decision:

(D7) D. S. Millar et al., Oncogene, Vol. 18, 1999, pages 1313 to 1324

XII. The submissions made by the appellant in writing, insofar as they are relevant to the present decision, may be summarised as follows:

Claims 1 and 7 of the main request referred to the region of GST-Pi gene defined by (and inclusive of) CpG sites +1 to +53. Figure 1 of the published application (WO 99/55905), which showed the organisation and nucleotide sequence of the human GST-Pi gene, did not indicate CpG site +11. However, this site was located within the base stretch at positions 1314 to 1317 which was not represented in Figure 1 but could have been easily identified by the skilled person looking at the nucleotide sequence published before the relevant filing date by GenBank under the accession number M24485, as indicated on page 12, line 18 of WO 99/55905. It had to be assumed that the complete sequence of GST-Pi, including CpG site +11, could be easily retrieved therefrom.

The application contained comprehensive experimental data showing that the exons of the GST-Pi gene were differentially methylated in cancer tissue. Additional data attached to the statement of grounds of appeal confirmed this observation, showing that CpG sites +1 to +33 were all hypomethylated in prostate cancer. Furthermore, it was generally known that CpG positions located with CpG rich regions (CpG islands) often showed a uniform methylation status. As CpG sites +1 to +33 and +53 were co-methylated in the GST-Pi gene, it could be assumed that also the remaining CpG sites +34 to +52 were equivalently methylated as shown in the post-published document D7.

The invention relied on the observation that the CpG positions in the GST-Pi exons 1 to 3 could serve as a diagnostic cancer marker. Designing assays which covered one or more CpG sites, selecting the best performing assay and applying said assay to analyse clinical samples was only routine work for the skilled person.

Thus, CpG sites +1 to +53 as referred to in the main request were clearly identified and their use as cancer markers was sufficiently disclosed.

XIII. The appellant requests that the decision under appeal be set aside and the case be remitted to the first instance for further prosecution on the basis of the main request filed under cover of the letter of 9 February 2012.

Reasons for the Decision

Main request

Compliance with Article 123(2) EPC

1. The question to be answered is whether the subject-matter of each of the claims is disclosed in the application as filed (see WO 99/55905).

1.1 The subject-matter of claim 1 is disclosed in claim 34 as filed.

1.2 The subject-matter of claims 2, 3, 4, 5 and 6 is disclosed in claims 35, 37, 38, 39 and 40 as filed, respectively.

1.3 The assay of claim 7 finds a basis in claims 1, 4, 19 and 25 as filed.

1.4 Claim 1 as filed (see WO 99/55905) is directed to a diagnostic or prognostic assay for a disease which is characterised by abnormal methylation of cytosine at a site or at sites within the human glutathione-S-transferase (GST) Pi gene. The assay comprises three steps. Firstly, the DNA is isolated from the subject concerned. Secondly, the DNA is exposed to reactants and conditions for the amplification of a target region of the GST-Pi gene (and/or its regulatory flanking sequences) which includes a site or sites at which abnormal cytosine methylation characteristic of **the disease or condition** occurs, the amplification being selective in that it only amplifies the target region of the said site or sites. Thirdly, the presence of amplified DNA is determined.

1.5 Dependent claim 4 as filed in addition refers to the feature that, prior to the amplifying step, the isolated DNA is treated such that unmethylated cytosines are converted to uracil or another nucleotide capable of forming a base pair with adenine while methylated cytosines are unchanged or are converted to a nucleotide capable of forming a base pair with guanine.

1.6 Dependent claim 19 as filed adds the feature that the disease is a prostate cancer.

1.7 Finally, dependent claim 25 as filed contains the additional feature that the target region of the GST-Pi gene is defined by (and inclusive of) CpG sites +1 to +53. Thus, a combination of claim 1 with dependent claims 4, 19 and 25 as filed describes exactly the assay of present claim 7.

1.8 The subject-matter of each of claims 8 to 17 is disclosed in claim 25 as filed in combination with claims 5 to 14 as filed, respectively.

1.9 The subject-matter of each of claims 18, 19 and 20 is disclosed in claim 25 as filed in combination with claims 15, 16 and 24 as filed, respectively.

1.10 The subject-matter of claims 21, 22 and 23 is disclosed in claims 26, 27 and 29 as filed, respectively.

2. The subject-matter of claim 24 is disclosed in claim 45 as filed.

3. The Board comes to the conclusion that the subject-matter of claims 1 to 24 is disclosed in the application as filed. Therefore, the requirements of Article 123(2) EPC are met.

Compliance with Article 84 EPC

4. In the decision under appeal, clarity of the claims was challenged for the reason that the position of CpG site +11 in the GST-Pi gene was not specified in any of

the nucleotide sequences contained in the application, in particular not in Figure 1.

5. Indeed, Figure 1 which shows four regions spanning the human GST-Pi gene, in which the individual CpG sites present therein are numbered according to their position relative to the start site of transcription, fails to indicate the position of CpG sites +11 and +12.

6. In its letter of 14 April 2009, the appellant has indicated that CpG site +11 was located within the nucleotide stretch CCCG not represented in Figure 1 linking the region ending with nucleotide 1313 and the region beginning with nucleotide 1318.

7. At the filing date the nucleotide sequence of the GST-Pi gene was publicly available from GenBank accession number M24485 (see page 12, lines 17 to 18 in the application). This has not been contested by the Examining Division in its decision. The Board considers that a person skilled in the art at the filing date, when examining in parallel the GenBank data and Figure 1 would have been in a position to identify CpG sites +11 and +12. In fact these are the only two CpG's present in the sequence of the gene comprised between CpG sites +10 and +13 as shown in Figure 1.

8. In consequence, the Board concludes that the claims of the main request meet the clarity requirement of Article 84 EPC.

9. In accordance with the provisions of Rule 43(2) EPC, the application, as now amended with claims 1 to 24 of the main request, contains only one independent claim

in each of the claim categories, namely process claim 1 and product claim 24. All other claims are dependent claims. Therefore, also the conciseness requirement of Article 84 EPC is met.

Compliance with Article 83 EPC

10. The application reports of the determination of the methylation status of CpG sites +1 to +10 and +13 to +33 (see page 5/17 of the drawings) in DNA isolated from prostate cancer tissue or cell lines and from normal prostate or other tissues. The results are disclosed in the table referred to as Figure 3A of the application.

11. As correctly observed by the Examining Division in its decision, neither Figure 3A nor any other part of the application provides experimental results with regard to CpG sites +11, +12, and +34 to +53.

12. Nevertheless, it can reasonably be assumed that a skilled person, following the instructions contained in the application, would be in a position to prepare appropriate materials (primers) to carry out the claimed assays for whatever CpG site(s) without undue burden. In respect of the primers needed to carry out an assay involving an amplification step, the Examining Division has contended that none of the primers described in the application appears to be selective for the amplification of a DNA fragment containing only one CpG site. Contrary to this, the Board is of the opinion that a skilled person working in the technical field of molecular biology, guided by the disclosure in the application, would be able to design such primers

and to appropriately apply them by using its technical background and general knowledge.

13. With these appropriate primers in hand, the skilled person is considered to be able to determine the methylation status of any of CpG sites +1 to +53 by routine experimentation.

14. The Board concludes that the invention as claimed in the main request is sufficiently disclosed as required in Article 83 EPC.

Conclusion

15. As substantial requirements of the EPC have not been assessed in the decision under appeal, the case is remitted to the first instance for further prosecution under the provisions of Article 111(1) EPC in accordance with the appellant's request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Examining Division for further prosecution, including an assessment of novelty and inventive step, on the basis of claims 1 to 24 of the main request filed under cover of the letter of 9 February 2012.

The Registrar | The Chairman

A. Wolinski | M. Wieser