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Datasheet for the decision of 10 March 2023

Case Number: T 0784/22 - 3.3.08

Application Number: 19171630.7

Publication Number: 3536807

IPC: C12Q1/6886, C12Q1/6869

Language of the proceedings: EN

Title of invention:
Non-invasive determination of methylome of tumor from plasma

Applicant:
The Chinese University Of Hong Kong

Headword:
tumor methylome/CHINESE UNIVERSITY

Relevant legal provisions:
EPC Art. 84, 111(1)
RPBA 2020 Art. 11

Keyword:
Claims - support in the description (yes)
Remittal to the department of first instance (yes)

Decisions cited:
T 1434/06, T 1205/13

Catchword:

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Case Number: T 0784/22 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 10 March 2023

Appellant: (Applicant)	The Chinese University Of Hong Kong Knowledge Transfer Office Room 301 Pi Ch'iu Building Shatin New Territories Hong Kong (CN)
Representative:	J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 17 August 2021 refusing European patent application No. 19171630.7 pursuant to Article 97(2) EPC**

Composition of the Board:

Chair	T. Sommerfeld
Members:	B. Claes
	R. Winkelhofer

Summary of Facts and Submissions

I. The appeal of the applicant (appellant) lies from the decision of the examining division refusing European patent application No. 19 171 630.7 (application as filed) entitled "*Non-invasive determination of methylome of fetus or tumor from plasma*". The application is a second generation divisional application based on European patent application No. 13 838 770.9 which had been filed under the PCT as an international patent application and was published as WO 2014/043763 (grandparent application).

II. The examining division considered sets of claims of a main and three auxiliary request and held *inter alia* that claim 1 of the third auxiliary request, filed during the oral proceedings, did comply with the requirements of Article 123(2) EPC but did not fulfil the requirements of Article 84 EPC.

III. With the statement of grounds of appeal, the appellant re-submitted former third auxiliary request as the main request and filed three auxiliary requests.

Claim 1 of the main request reads:

"1. A method of analyzing a plasma sample of a human organism, the plasma sample comprising cell-free DNA originating from normal cells and potentially from cells associated with cancer, the method comprising:

analyzing a plurality of cell-free DNA molecules from the plasma sample, wherein analyzing a cell-free DNA molecule includes:

determining a location of the cell-free DNA molecule in a genome of the human organism by

mapping, via sequence reads, the cell-free DNA molecule to a part of a human genome; and

determining whether the cell-free DNA molecule is methylated at one or more CpG sites of a plurality of CpG sites organized into a plurality of CpG islands, each CpG island including more than one CpG site;

determining a respective number of cell-free DNA molecules at each of the plurality of CpG islands that are methylated;

calculating a first methylation level based on the respective numbers of cell-free DNA molecules that are methylated at the plurality of CpG islands;

comparing the first methylation level to a first cutoff value indicative of whether cancer is present; and

determining a classification of whether cancer is present based on the comparison."

IV. The appellant requests that the decision under appeal be set aside and amended such that a patent be granted on the basis of the set of claims of the main request or the auxiliary requests filed with the grounds of appeal.

Reasons for the Decision

1. In the statement setting out the grounds of appeal, the appellant conditionally requests oral proceedings. However, this request does not apply to the decision taken by the board which can thus be handed down in written proceedings. The appellant is not adversely affected by this decision to remit the case for further prosecution, so oral proceedings before the board do

not need to be appointed (see Case Law of the Board of Appeal of the European Patent Office, 10th edn. 2022 (CLBA), III.C.4.5 and e.g. decisions T 1434/06, Reasons, point 3; and T 1205/13, Reasons, point 3).

2. The description and drawings of the application as filed are identical to those of the grandparent application (see section I.) except for the inclusion of claim-like clauses at the end of the description. References in this decision to the description of the application use the paragraph numbers of the grandparent application.

Main request - Article 84 EPC - claim 1

3. The claimed invention (see section III.) is a non-invasive method for determining a methylation pattern (methylome) of DNA in a human plasma sample containing a mixture of cell-free DNA fragments from genomes of tumour and normal cells. The method allows detecting the presence of cancer in a human organism by determining methylation of CpG dinucleotides in so-called CpG islands present in DNA of human plasma. Cancer DNA is associated with changed DNA methylation reflected in the CpG methylation profile of plasma from individuals with cancer. Determining methylation across a plurality of CpG islands provides integration of multiple CpG sites into a single metric which is indicative of the presence of cancer in the individual. The claimed method specifies that DNA molecules are analysed by determining whether it is methylated at one or more CpG sites of a plurality of CpG sites organised into a plurality of CpG islands. A respective number of DNA molecules methylated at each CpG island is then determined and used to calculate a first methylation level.

4. The examining division based the decision that the former third auxiliary request, now the main request, was not allowable solely on the fact that claim 1 did not comply with the requirements of Article 84 EPC. The reasons provided in the decision under appeal (see page 9 of the decision under appeal under the heading "*CLARITY and SUPPORT (Art. 84 EPC)*") may be summarised in four parts.

- i) The application provided that the disclosed method required determining plasma DNA methylation densities and not "*determining the absolute number of CpG islands*" as recited in the claim.

- ii) The statistical relevance of the claimed method for diagnosing cancer was questionable ("*some doubts arise*") if the number of CpG islands for which methylation is determined was low, e.g. two.

- iii) Because a given CpG island in the patient's sample could be either hypermethylated or demethylated versus the CpG island in the healthy sample, the wrong conclusion could be reached when the number of assessed CpG islands was too small.

- iv) The outcome of the claimed analysis was not ascertained as being a meaningful result for deciding whether or not a patient had cancer.

5. The board does not concur with these conclusions.

Part i) of the reasons

6. The examining division held that the claim "*relates to determining the number of methylated CpG islands*

(absolute number)". However, the claim in fact specifies "determining a respective number of cell-free DNA molecules at each of the plurality of CpG islands that are methylated" and "calculating a first methylation level based on the respective numbers of cell-free DNA molecules that are methylated at the plurality of CpG islands". Accordingly, the "number" in the claim is the number of methylated DNA molecules and not the number of CpG islands. For this reason alone, the board does not share this part of the examining division's conclusions.

7. Article 84 EPC provides that claims must define the matter for which protection is sought and lays down the principles governing the content and wording of the claims, i.e. they should be clear and concise and be supported by the description. It is an established principle in the case law of the boards that a claim which does not include a feature described in the application (based on the proper interpretation of the description) as an essential feature of the invention is not supported by the description (see CLBA, II.A.5.1 and the decisions referred to there).

8. Although some disclosed examples in the application describe methods in which methylation density is determined, the board agrees with the appellant that the disclosure of the application does not qualify determining plasma DNA methylation densities as an essential feature of the invention and, also, is not limited to methods based on the methylation density. In fact, the contrary can be concluded from the description, e.g. in the final sentence in paragraph [0071] ("*The methylation index, methylation density and proportion of methylated cytosines are examples of 'methylation levels'*", emphasis added) and paragraph

[0367] ("*At block 3530, it is determined whether each of the CpG islands is hypermethylated. For example, for the analysis for CpG island hypermethylation of a tested case, the methylation density of each CpG island was compared with corresponding data of a reference group. The methylation density (an example of a methylation level) can be compared to one or more cutoff values to determine whether a particular island is hypermethylated*", emphasis added). Both these passages describe methylation density merely as one means of assessing the methylation level as is to be calculated in the claimed method based on the respective numbers of cell-free DNA molecules methylated at the plurality of CpG islands.

9. In addition, Figure 28 discloses a flow chart of a method of analysing a biological sample of an organism that may potentially include DNA from cells associated with cancer "*to determine a classification of a level of cancer according to embodiments of the present invention*" (see paragraph [0311]). Paragraph [0313] clarifies that: "*At block 2820* [of Figure 28], *a respective number of DNA molecules that are methylated at the site is determined for each of a plurality of sites. In one embodiment, the sites are CpG sites, and may be only certain CpG sites, as selected using one or more criteria mentioned herein. The number of DNA molecules that are methylated is equivalent to determining the number that are unmethylated once normalization is performed using a total number of DNA molecules analyzed at a particular site, e.g., a total number of sequence reads. For example, an increase in the CpG methylation density of a region is equivalent to a decrease in the density of unmethylated CpGs of the same region*" (emphasis added). Here again

methylation density is disclosed as an example means of assessing the methylation level.

10. Also based on these considerations, the board cannot concur with part i) of the reasons provided by the examining division.

Parts ii) and iii) of the reasons

11. These parts of the reasons relate to sufficiency of disclosure of all aspects of the claimed invention in the application which is to be assessed under Article 83 EPC and not under Article 84 EPC.

12. The board agrees with the appellant that it is a key insight of the invention as disclosed and described in the application that methylation of CpG islands in a plasma DNA sample can be used in the calculation of a first methylation level providing an indication of the presence of cancer in a patient and that this can be implemented in different ways. For example, large-scale processing of DNA molecules is used, so that large numbers of molecules, and hence large sections of the genome, are analysed. This way, a large number of CpG islands is analysed, providing statistical significance to the result.

13. In fact, the explicit disclosure in paragraph [0313] of the application: "*and may be only certain CpG sites, as selected using one or more criteria mentioned herein*" (see point9. above) disqualifies large-scale processing of DNA molecules for analysing large numbers of CpG islands as an essential feature of the disclosed invention. Furthermore, particular CpG islands used in the calculation of the first methylation level can be identified and selected upfront as providing an

unambiguous distinction between healthy individuals and patients with cancer in view of particular selection criteria for CpG islands disclosed in paragraph [0365] of the application: "*As an example, for illustration purpose, the following criteria are used for the identification of the useful CpG islands: i. The mean methylation density for the CpG island in the reference group (e.g. healthy subjects) <5%*
ii. The coefficient of variation for the analysis of methylation density in plasma for the reference group (e.g. healthy subjects) <30%.
These parameters can be adjusted for a specific application. From our dataset, 454 CpG islands in the genome fulfilled these criteria". Thus, as supported by the application, the claim encompasses implementations where a small number of CpG islands can be used.

14. Thus, the board can equally not concur with part ii) of the reasons of the examining division that the claim does not comply with the requirements of Article 84 EPC.

15. As to part iii) of the examining division's reasons, the application in fact discloses that a given CpG island in a patient's sample could be either hypermethylated or hypomethylated versus the CpG island in the healthy sample (see e.g. paragraph [0362]). Accordingly, given the teaching of the application, it is well within the ability of the skilled person to select an implementation of the claimed method appropriate to a given task to generate a first methylation level that can be compared to a first cut-off value indicative of whether cancer is present in a sample and hence to determine a classification of whether cancer is present.

16. In addition, it cannot be seen why a small number (and possibly even two) of highly distinguished CpG islands may not be of sufficient statistical relevance to indicate the presence of cancer in an individual.

17. The skilled person, relying on the guidance provided in the disclosure of the application, can select an appropriate number of islands for the particular implementation used to provide appropriate statistical relevance for diagnosing cancer.

18. Accordingly, also part iii) of the examining division's reasons cannot lead to a conclusion that the claim does not comply with the requirements of Article 84 EPC either.

Part iv) of the reasons

19. This part of the reasons merely constitutes a general reflection by the examining division based on parts i) to iii) of the reasons, without itself providing any substantive argument. This part can therefore equally not lead to a conclusion that the claim does not comply with the requirements of Article 84 EPC.

Conclusion

20. In view of the above considerations, the examining division's decision that claim 1 of the current main request (then third auxiliary request) does not comply with the requirements of Article 84 EPC cannot be upheld.

Remittal (Article 111(1) EPC and Article 11 RPBA)

21. Pursuant to Article 111(1) EPC, the board may either exercise any power within the competence of the department responsible for the decision appealed or remit the case to that department for further prosecution.

22. It is the primary function of appeal proceedings to give a judicial decision on the correctness of the decision under appeal (Article 12(2) RPBA; see also CLBA, section V.A.1.1, second paragraph and the decisions referred to there).

23. With respect to the main request, the examining division took a reasoned decision only on the requirements of Articles 84 and 123(2) EPC, and the board has reviewed the decision under Article 84 EPC (see points 4. to 19. above). Other requirements for patentability have not been examined yet. Not remitting the case to the examining division would therefore require the board to carry out an in-depth examination of the application rather than review the contested decision in a judicial manner, which is the primary purpose of appeal proceedings.

24. In view of these considerations, there are special reasons within the meaning of Article 11 RPBA for remitting the case for further prosecution.

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.

The Registrar: The Chair:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated